In terms of percent of administered dose, the maximum excretion rate was highest for Product 10 (11.7%/hr) and lowest for Product 5 (1.0%/hr). The latter value was significantly lower than that observed after Product 7 (2.8%/hr). The times of the maximum excretion rate (T_{max}) were 1.6, 1.9, 2.3, and 2.9 hr for the nonenteric-coated Products 1, 3, 10, and 2, respectively. These times were significantly lower than those found for the other products. Products 5 and 7 yielded significantly longer T_{max} values of 17.1 and 12.6 hr, respectively.

Subject and Week Effects—Each urinary excretion parameter also was statistically analyzed to determine the significance of differences observed among subjects and administration sequences (weeks). Since Subject 6 began the study several weeks after the other nine subjects and took the medication at 4-day intervals, the analysis of weekly differences actually related to differences that could have arisen because a dose was the first, second, third, *etc.*, dose administered.

Since there were no significant weekly differences, it may be concluded that the bioavailability of a particular dose of methenamine was not influenced by the previous administration of other dosage forms of the drug. Results of the analysis of the blank (zero time) urine samples also were monitored each week to determine if they showed any progressive increase, which would have occurred if the drug had been accumulating. No such trend was found in the blank readings. Furthermore, the statistical analysis did not indicate any significant differences among subjects in the excretion of either free formaldehyde or total methenamine.

CONCLUSIONS

Methenamine compressed tablets, methenamine mandelate granules, and methenamine hippurate tablets showed the highest methenamine urinary recovery and were considered bioequivalent. The suspension dosage form exhibited adequate bioavailability but was less well absorbed than the other dosage forms. In general, the enteric-coated products exhibited delayed urinary excretion of methenamine, but Products 4, 6, 8, and 9 did not differ significantly from the nonenteric-coated products in most measurements. Two enteric-coated products (Products 5 and 7) were significantly less bioavailable than all other products tested. None of the 10 products differed significantly ($p > 0.05$) in urinary formaldehyde concentrations. However, the large intersubject variability precluded an accurate assessment of dosage form bioavailability using only free formaldehyde determinations.

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Effect of Antacid on Bioavailability of Theophylline from Rapid and Timed-Release Drug Products

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Abstract □ Magnesium aluminum hydroxide suspension (an antacid) was given concurrently with either theophylline anhydrous tablets or theophylline anhydrous timed-release capsules to 13 volunteers using a four-way crossover design. Serum theophylline was measured by reversed-phase high-pressure liquid chromatography. The serum level–time curves were individually fitted to an oral absorption one-compartment open model. The pharmacokinetic parameters (mean ± *SD*) K_A, K, AUC, and F/V for theophylline from the rapid release theophylline anhydrous tablets were 2.1 ± 1.3 hr^{-1}, 0.15 ± 0.06 hr^{-1}, 89.2 ± 30 μg hr/ml, and 0.0023 ± 0.002 kg/ml, respectively; from the anhydrous timed-release capsules, they were 0.27 ± 0.08 hr^{-1}, 0.20 ± 0.07 hr^{-1}, 79.0 ± 27 μg hr/ml, and 0.0030 ± 0.0007 kg/ml, respectively. The concurrent administration of 15 ml of antacid (magnesium aluminum hydroxide suspension) with the theophylline products did not significantly affect any of these pharmacokinetic parameters. The extent of theophylline bioavailability from all drug products was consistent and similar as shown by the F/V and AUC values.

Keyphrases □ Theophylline—effect of antacid on bioavailability, tablets and timed-release capsules □ Antacids—effects on theophylline bioavailability, tablets and timed-release capsules □ Pharmacokinetics—effect of antacid on theophylline, tablets and timed-release capsules □ Dosage forms—tablets and timed-release capsules, effect of antacid on theophylline bioavailability

Theophylline is used extensively in the treatment of various respiratory diseases (1–4). When taken in the recommended dosage, it relieves or prevents symptoms associated with asthma, bronchitis, and emphysema. The amount of relief produced is directly related to the serum drug concentration. Side effects (nausea, vomiting, headache, and restlessness) are usually associated with high blood theophylline levels (>20 μg/ml), although some individuals may experience side effects at lower levels (1–4).

Magnesium aluminum hydroxide suspension is a commonly used antacid for the symptomatic relief of hyperacidity, gastritis, and heartburn. However, antacids affect the bioavailability of various drugs (5–8). The object of this investigation was to determine the effect of concurrent antacid therapy on the rate and extent of theophylline absorption from theophylline anhydrous tablets and theophylline anhydrous timed-release capsules.

EXPERIMENTAL

Reagents and Chemicals—All reagents and chemicals including theophylline anhydrous[1], sodium acetate[1], 7-(β-hydroxypropyl)theophylline[1], β-hydroxyethyltheophylline[1], 8-chlorotheophylline[1], theo-

[1] Sigma Chemical Co., St. Louis, Mo.

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Table I—Patient Data and Doses of Theophylline for Each Drug Product

Volunteer	Age, years	Height, m	Weight, kg	Product A, mg	Product A, mg/kg	Product B, mg	Product B, mg/kg	Product C, mg	Product C, mg/kg	Product D, mg	Product D, mg/kg
1	18	1.72	83.4	400	4.796	435	5.216	400	4.796	435	5.216
2	18	1.82	99.8	500	5.010	500	5.010	500	5.010	500	5.010
3[a]	18	1.82	71.8	—	—	375	5.223	350	4.875	375	5.223
4	19	1.80	71.1	350	4.923	375	5.274	350	4.923	375	5.274
5	18	1.80	64.1	300	4.680	310	4.836	300	4.680	310	4.836
6	23	1.82	91.4	450	4.923	435	4.759	450	4.923	435	4.759
7	25	1.78	74.5	350	4.698	375	4.034	350	4.698	375	5.034
8	26	1.78	81.8	400	4.890	435	5.318	400	4.890	435	4.318
9	24	1.78	79.5	400	5.031	375	4.717	400	5.031	375	4.717
10	22	1.87	82.7	400	4.837	435	5.260	400	4.837	435	5.260
11	19	1.87	93.2	450	4.828	435	4.667	450	4.828	435	4.667
12	23	1.70	60.9	300	4.926	310	5.090	300	4.296	310	5.090
13[b]	18	1.72	65.7	350	5.327	—	—	—	—	—	—
14	19	1.75	62.7	300	4.785	310	4.944	300	4.785	310	4.944
Mean	20.7		77.3		4.896		5.027		4.867		5.027
SD	3.0		12.1		0.167		0.227		0.109		0.227

[a] Volunteer withdrew from study after receiving Treatments B–D. [b] Volunteer withdrew from study after receiving Treatment A only.

bromine[2], caffeine[3], and acetonitrile[4] were of USP, NF, or analytical grade and were used as received. Normal serum samples[5] were obtained from healthy students. All other reagents and solvents were purchased from commercial sources and used without further purification.

Design—Fourteen male volunteers (18–26 years old), weighing an average of 77 kg, were judged healthy by physical examination. The volunteers refrained from all other medications, smoking, and theophylline-containing beverages such as coffee, tea, chocolate, and cola prior to and during the study. Each volunteer fasted overnight prior to and for 4 hr after receiving the theophylline formulation.

The following drug products were given to each volunteer in a four-way crossover Latin-square design with a 1-week interval between treatments: Product A, theophylline anhydrous tablets[6]; Product B, theophylline anhydrous timed-release capsules[7]; Product C, theophylline anhydrous tablets[6] with 15 ml of magnesium aluminum hydroxide suspension[8]; and Product D, theophylline anhydrous timed-release capsules[7] with 15 ml of magnesium aluminum hydroxide suspension[8].

All doses of theophylline were based on 5 mg/kg, and each drug product was given with 240 ml of water. Both serum and urine samples were obtained at zero time and periodically after medication. Serum samples were assayed for theophylline, and urine samples were tested for pH.

Theophylline Assay—Serum samples were assayed for theophylline concentrations by reversed-phase high-pressure liquid chromatography (HPLC) (9) with β-hydroxyethyltheophylline as the internal standard.

The high-pressure liquid chromatograph[9] was fitted with a UV (254 nm) absorbance detector and strip-chart recorder[10]. Samples were chromatographed on a reversed-phase HPLC column, 30 cm × 4 mm i.d., packed with 10-μm octadecyltrichlorosilane-coated silica beads[11]. The mobile phase was prepared by mixing 930 ml of a 10-mmole sodium acetate buffer (pH 4.0) with 70 ml of acetonitrile. The mobile phase was degassed and filtered[12] prior to use.

All determinations were performed at ambient temperature with a solvent flow rate of 2 ml/min. The detector sensitivity scale was 0.005, and the chart speed was 0.25 cm/min. Pressure was maintained at ~2200 psi. All sample injections were 10 μl.

A standard theophylline concentration curve was prepared daily by processing pooled serum samples spiked with known concentrations of theophylline concurrently with the unknown serum samples. A statistical least-squares fitting procedure was employed for calculating the standard curve by comparing the peak height ratio of theophylline to β-hydroxyethyltheophylline to the spiked serum theophylline concentrations. Assay sensitivity was ~0.5 μg/ml, which is adequate for measuring the expected serum theophylline concentrations. This HPLC procedure was validated using control human serum samples containing known concentrations of theophylline, which were unknown to the operator (r 0.972).

Table II—Effect of Antacid on Theophylline Pharmacokinetics from Rapid and Timed-Release Drug Products

Parameter	Product A	Product B	Product C	Product D
K_A, hr^{-1}	2.10[a] (1.31)	0.27[b] (0.08)	2.41 (1.77)	0.24[b] (0.06)
K, hr^{-1}	0.15 (0.06)	0.20 (0.07)	0.16 (0.07)	0.17 (0.06)
F/V, kg/ml	0.0023 (0.0003)	0.0030 (0.0007)	0.0025 (0.0004)	0.0024 (0.0005)
AUC, μg hr/ml	89.2 (30.4)	79.0 (27.4)	87.3 (28.5)	76.2 (32.5)
t_{max}[c], hr	1.66 (0.67)	4.45[b] (0.92)	1.73 (0.91)	5.04[b,d] (0.89)
C_{max}[c], μg/ml	9.07 (1.32)	6.18[b] (1.37)	9.04 (1.53)	5.24[b,d] (1.44)

[a] Each value represents the mean for 13 volunteers with the standard deviation in parentheses. [b] $p < 0.01$ compared to Product A. [c] Obtained by calculation. [d] $p < 0.01$ compared to Product B.

RESULTS

The patient data and doses of theophylline appear in Table I. The serum theophylline concentration–time curves obtained from each patient were fitted to an oral absorption one-compartment open model using a least-squares regression analysis program[13]. Preliminary parameter

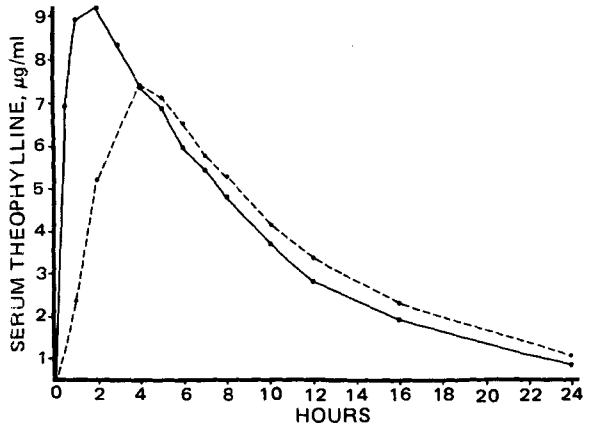

Figure 1—*Comparison of mean theophylline level–time curves in volunteers after receiving either Product A, theophylline anhydrous tablets (●—), or Product B, theophylline anhydrous time-release capsules (○---); n = 13.*

[2] Merck & Co., Rahway, N.J.
[3] Mallinckrodt, St. Louis, Mo.
[4] J. T. Baker Chemical Co., Phillipsburg, N.J.
[5] Lane Health Center, Northeastern University, Boston, Mass.
[6] Slo-Phyllin, Dooner Laboratories, Haverhill, Mass.
[7] Slo-Phyllin Gyrocaps, Dooner Laboratories, Haverhill, Mass.
[8] Maalox, William H. Rorer, Fort Washington, Pa.
[9] ALC GPC model 204, Waters Associates, Milford, Mass.
[10] Fisher Recordall Series 500, Fisher Scientific Co., Fair Lawn, N.J.
[11] μBondapak C_{18}, Waters Associates, Milford, Mass.
[12] Millipore filtering system (type GS), Millipore Corp., Bedford, Mass.
[13] C. M. Metzler, The Upjohn Co., Kalamazoo, MI 49001, personal communication.

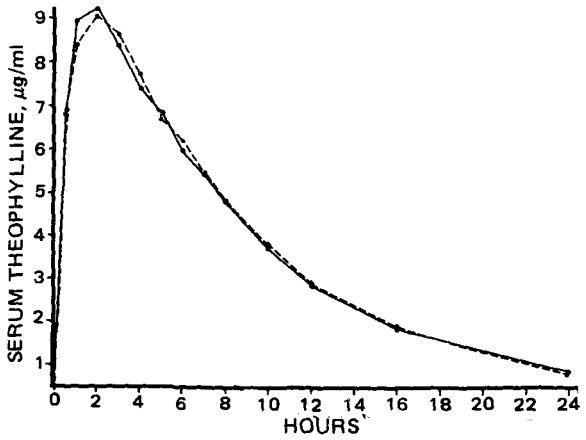

Figure 2—*Comparison of mean theophylline level–time curves in volunteers after receiving either Product A, theophylline anhydrous tablets (●—), or Product C, theophylline anhydrous tablets plus 15 ml of antacid (○- - -); n = 13.*

estimates were made using the Wagner–Nelson method (10). The one-compartment oral absorption model (Scheme I) is described by:

$$\xrightarrow{K_A} \boxed{V, C} \xrightarrow{K}$$

Scheme I

$$C = \frac{FDK_A}{(K_A - K)V}(e^{-Kt} - e^{-K_{at}}) \qquad \text{(Eq. 1)}$$

where K_A is the first-order absorption rate constant, K is the first-order elimination rate constant, D is the dose, C is the serum drug concentration, V is the volume of distribution, t is the time after drug adminstration, and F is the fraction of drug absorbed.

The time for peak serum theophylline level (t_{max}) for each subject was calculated from:

$$t_{max} = \frac{\ln(K_A/K)}{K_A - K} \qquad \text{(Eq. 2)}$$

and the maximum serum theophylline level (C_{max}) was calculated by substitution of t_{max} for t in Eq. 1. Computer estimation of theophylline pharmacokinetic parameters for each patient and each drug product was obtained. Coefficients of correlation for the theophylline anhydrous tablets and the theophylline anhydrous timed-release capsules were 0.97–0.99 and 0.96–0.99, respectively, demonstrating excellent fit of the data. The t_{max} is the time for peak serum theophylline concentration as calculated from K_A and K.

The mean pharmacokinetic parameters obtained for the theophylline anhydrous tablets and theophylline anhydrous timed-release capsules are shown in Table II. As expected, the K_A value (2.10 ± 1.31 hr^{-1}) for the theophylline bioavailability rate from the rapid release tablet was significantly larger than the K_A (0.27 ± 0.08 hr^{-1}) for theophylline bioavailability from the timed-release capsules. Furthermore, the t_{max} for rapid release theophylline anhydrous tablets (Product A) was 1.66 ± 0.67 hr, which was significantly shorter than the t_{max} of 4.45 ± 0.92 hr for the theophylline anhydrous timed-release capsules (Product B). The corresponding serum theophylline level–time curves for Products A and B are shown in Fig. 1.

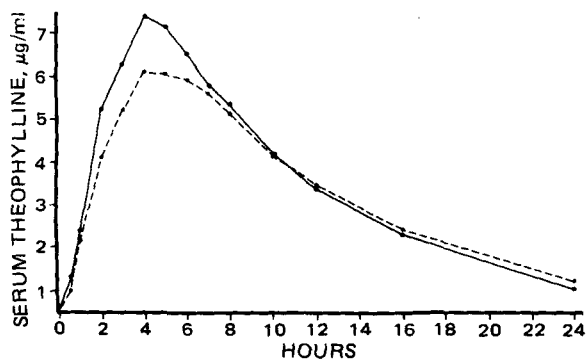

Figure 3—*Comparison of mean theophylline level–time curves in volunteers after receiving either Product B, theophylline anhydrous timed-release capsules (●—), or Product D, theophylline anhydrous timed-release capsules plus 15 ml of antacid (○- - -); n = 13.*

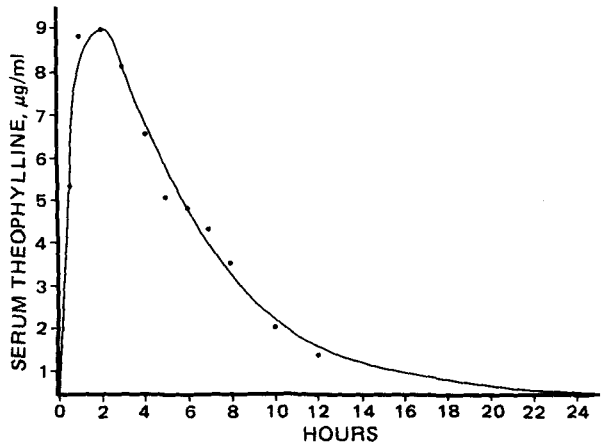

Figure 4—*Predicted serum theophylline level time–curve in Patient 1 after receiving Product A, theophylline anhydrous tablets. Experimental values are indicated.*

The medication of 15 ml of magnesium aluminum hydroxide suspension given concurrently with the theophylline products did not affect the t_{max} for the rapid release theophylline tablets (Product C) but significantly ($p < 0.05$) increased the t_{max} for the timed-release theophylline capsules (Product D) (Table II and Figs. 2 and 3). However, the apparent rate constant for absorption, K_A, for theophylline from the timed-release capsules was not affected by concurrent antacid administration.

The extent of theophylline bioavailability from both rapid release and timed-release forms was essentially similar as shown by the *AUC* values. Furthermore, there were no differences in the *F/V* values for both drug products, demonstrating that theophylline availability was similar and consistent. Moreover, the concurrent administration of 15 ml of magnesium aluminum hydroxide suspension with either the rapid release or timed-release theophylline drug products did not affect the *AUC* or *F/V* values (Table II).

The observed serum theophylline concentration–time curves and the theoretically calculated curves for each drug product in one patient are shown in Figs. 4–7. All curves from each patient demonstrated excellent correlation coefficients, indicating that the data were well described by the oral absorption one-compartment open model.

Urine pH was measured for each individual. No significant differences in urine pH due to antacid were apparent in the specimens collected during the entire 24 hr of sampling.

DISCUSSION

Theophylline pharmacokinetics after an intravenous bolus have been described as a two-compartment open model with a very rapid distribution phase (3, 11–14). The results of this study confirm previous reports that the one-compartment open model may be used to describe the oral absorption of theophylline from a rapid release tablet or a timed-release capsule (3, 13, 14).

Concurrent administration of 15 ml of magnesium aluminum hy-

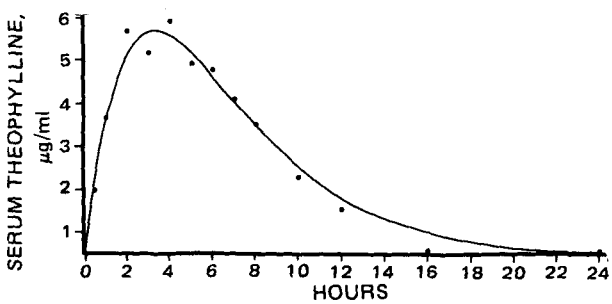

Figure 5—*Predicted serum theophylline level–time curve in Patient 1 after receiving Product B, theophylline anhydrous timed-release capsules. Experimental values are indicated.*

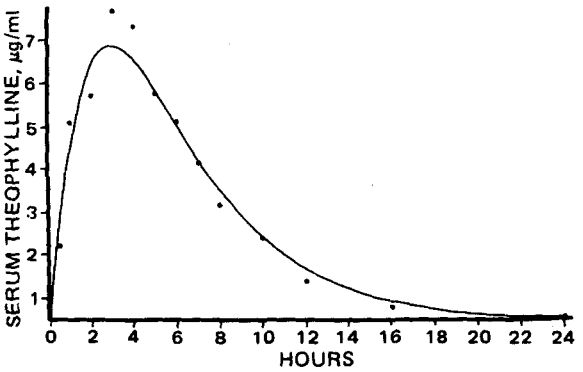

Figure 6—*Predicted serum theophylline level–time curve in Patient 1 after receiving Product C, theophylline anhydrous tablets plus 15 ml of antacid. Experimental values are indicated.*

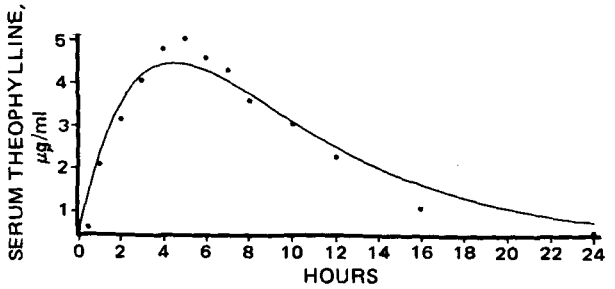

Figure 7—*Predicted serum theophylline level–time curve in Patient 1 after receiving Product D, theophylline anhydrous timed-release capsules plus 15 ml of antacid. Experimental values are indicated.*

droxide suspension with the rapid release theophylline anhydrous tablets did not affect theophylline bioavailability, as shown by the lack of any significant effect on the various pharmacokinetic parameters measured.

Antacid given with the theophylline anhydrous timed-release capsules increased the time for peak serum concentration, t_{max}, by ~13%. However, both the absorption rate constant, K_A, and the *AUC* for theophylline from the timed-release capsules were not affected by concurrent antacid administration. Therefore, the extent of theophylline bioavailability from the timed-release capsules was unaffected by antacid, and the theophylline bioavailability rate was affected only slightly.

A previous study (5) reported that 30 ml of magnesium aluminum hydroxide suspension significantly decreased the K_A for theophylline in volunteers given a single 200-mg dose of aminophylline tablets. This decrease may have been due to the fact that theophylline was given as the ethylenediamine salt (aminophylline) and in smaller doses compared to the present study. In addition, 30 ml of antacid was given compared to the 15 ml used in this study. In both studies, the elimination rate constant, K, *AUC*, and F/V values were in good agreement.

In conclusion, these data demonstrate that the concurrent administration of 15 ml of magnesium aluminum hydroxide suspension does not significantly affect the bioavailability of theophylline from theophylline anhydrous tablets or theophylline anhydrous timed-release capsules.

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Preparation and Antidiabetic Activity of New 3-Methyl-5-phenylpyrazolesulfonylurea Derivatives

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Abstract □ Two series of *p*-(3-methyl-5-phenylpyrazole-1)benzenesulfonylurea and *p*-(4-bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylurea derivatives were prepared for evaluation as hypoglycemic agents. Preliminary biological testing revealed that the new compounds possess potent antidiabetic activity.

Keyphrases □ 3-Methyl-5-phenylpyrazolesulfonylurea derivatives—preparation and evaluation for antidiabetic activity □ Structure–activity relationships—3-methyl-5-phenylpyrazolesulfonylurea derivatives and antidiabetic activity □ Antidiabetic activity—3-methyl-5-phenylpyrazolesulfonylurea derivatives synthesized and tested

Since 3,5-dimethylpyrazole and its active metabolite, 5-methylpyrazole-3-carboxylic acid, have potent hypoglycemic activity (1–5), studies have been performed on the synthesis of several new 3,5-disubstituted pyrazoles (6–8). In a continuation of previous work (8), many new substituted 3-methyl-5-phenylpyrazolesulfonylurea derivatives were prepared[1]. These compounds are analogous to, but vary in structure from, the aryl sulfonylurea derivatives.

The proposed compounds might provide valuable information concerning the structural requirements for

[1] Application for a patent was made for the compounds described in this report.

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