Influence of diet and fluid on bioavailability of theophylline

The influence of various test meals, and of fluid volumes, on the bioavailability of theophylline from a solid dosage form has been studied in healthy male volunteers. Absorption of drug was faster after dosing immediately following a high protein meal than after a high fat or a high carbohydrate meal. Absorption from a solution was faster than from a solid dosage form in all treatments; areas under serum level time curves after dosing were also significantly higher up to 12 hr. Areas up to 12 hr after dosing also tended to be higher after the high protein meal and after dosing with 500 ml water on an empty stomach than after other solid dose treatments.

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The absorption of theophylline from different oral dosage forms has been the subject of considerable interest.[1, 15, 17] Enteral absorption has been demonstrated from tablets and an elixir,[3] but availability of active compound from tablets containing phenobarbital has been reported to be reduced due to formation of a theophylline-phenobarbital complex.[1] Enteral absorption of theophylline from aqueous solutions is increased in the presence of 5% and 10% alcohol but is decreased by higher concentrations.[9]

These and related studies have established that oral administration of solid and liquid preparations of theophylline is practical and efficient. There is no information available on the influence of food, specific dietary components, and the volume of water taken with the drug, on the rate or extent of theophylline absorption. This study was designed to examine these in man and to provide information that will facilitate maintenance of consistent drug bioavailability, and hence consistent drug effectiveness during chronic theophylline therapy.

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Subjects and methods

Subjects were 6 healthy male volunteers between 21 and 31 years of age (mean 26) and weighing between 64 and 80 kg (mean 74) who were shown by medical examination to be in good physical condition with normal blood and urine biochemistry.

Protocols. Subjects received no medication other than theophylline. Subjects fasted overnight and were allowed to eat no food, apart from test meals, until 4 hr after dosing. Subjects were not permitted to drink caffeine-containing beverages nor to eat chocolate or chocolate-containing foods from noon on the day before receiving medication until completion of a particular study. No fluid was permitted from

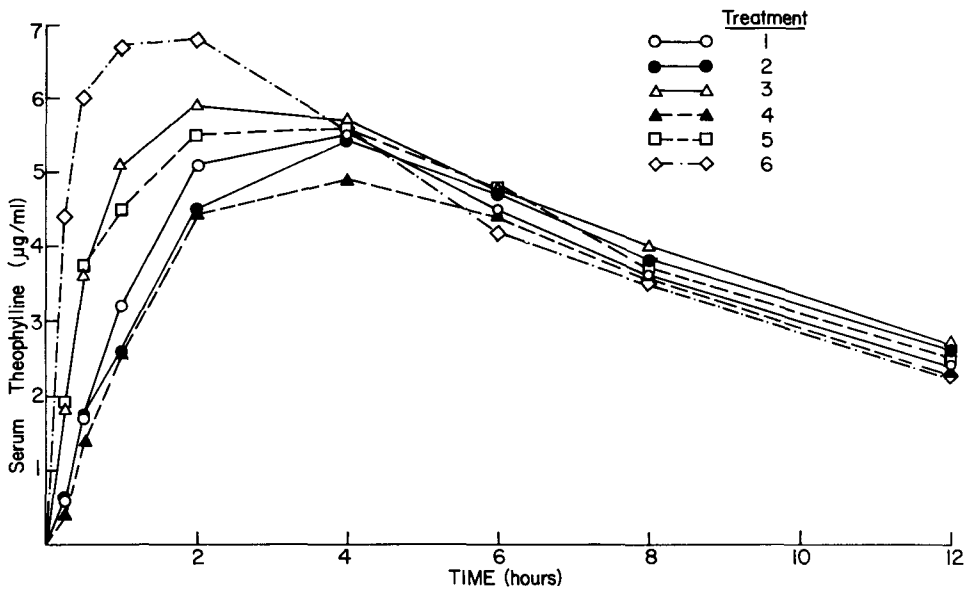

Fig. 1. Average serum levels of theophylline.

midnight before dosing until the treatment. Medication was administered at 8 A.M. and blood samples (7 to 8 ml) were collected in Vacutainers containing no anticoagulant at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hr after dosing. Serum was separated and deep frozen until assayed.

Treatments. Subjects received single doses of 260 mg theophylline as 2 × 130 mg (Tedral)* tablets. Each tablet contained 130 mg theophylline, 8 mg phenobarbital, and 24 mg ephedrine hydrochloride. Medication was administered as the following treatments.

Treatment 1. Two tablets with 20 ml of water immediately followed a standard high carbohydrate meal consisting of cornflakes with raisins, milk and sugar, grape juice, toast with butter, caffeine-free beverage with cream. The meal contained approximately 9% protein, 11% fat, and 80% carbohydrate.

Treatment 2. Two tablets with 20 ml of water immediately followed a standard high fat meal consisting of eggs scrambled with cream and butter, pork sausages, milk, toast with butter, caffeine-free beverage with cream. The meal contained approximately 28% protein, 50% fat, and 22% carbohydrate.

Treatment 3. Two tablets with 20 ml of water immediately followed a standard high protein meal consisting of lean broiled steak, toast with jelly, skimmed milk, caffeine-free beverage with cream. The meal contained approximately 53% protein, 11% fat, and 36% carbohydrate.

Treatment 4. Two tablets with 20 ml of water were taken on an empty stomach.

Treatment 5. Two tablets with 500 ml of water were taken on an empty stomach.

Treatment 6. Two tablets dissolved in 500 ml of water were taken on an empty stomach.

In all treatments except Treatment 6, tablets were swallowed whole. Treatments were administered at least 7 days apart. Problems associated with test meal preparation made treatment randomization impractical, and all subjects received the same treatment at the same time. Test meals were prepared in the University of Wisconsin Hospitals cafeteria and were standardized as closely as possible regarding total weight and fluid volume.

Assay of serum samples. Serum was assayed for theophylline by a modification[11] of the method of Schack and Waxler.[16] Serum (1.5 ml), 0.1N hydrochloric acid (0.3 ml) and chloroform containing 5% by volume isopropyl alcohol (15 ml) were combined in a 50 ml conical centrifuge tube and shaken for 20 min. After cen-

*Tedral tablets were kindly supplied by Warner Chilcott Co.

Table I. *Average serum concentrations of theophylline (±1 SD*) obtained from all treatments*

	Serum theophylline concentration (μg/ml)							
Treatment	*0.25 hr*	*0.5 hr*	*1 hr*	*2 hr*	*4 hr*	*6 hr*	*8 hr*	*12 hr*
1	0.6 ± 0.7	1.7 ± 1.5	3.2 ± 1.8	5.1 ± 1.1	5.5 ± 0.8	4.5 ± 1.0	3.6 ± 1.1	2.4 ± 0.9
2	0.6 ± 1.1	1.7 ± 1.6	2.6 ± 2.2	4.5 ± 1.6	5.4 ± 0.9	4.7 ± 0.9	3.8 ± 0.9	2.6 ± 0.6
3	1.8 ± 0.7	3.6 ± 0.9	5.1 ± 1.2	5.9 ± 1.0	5.5 ± 1.2	4.7 ± 1.0	4.0 ± 1.0	2.7 ± 0.8
4	0.4 ± 0.5	1.4 ± 1.0	2.6 ± 1.4	4.5 ± 1.9	4.9 ± 1.6	4.4 ± 1.1	3.6 ± 1.2	2.3 ± 0.9
5	1.9 ± 1.5	3.7 ± 1.6	4.5 ± 1.5	5.5 ± 1.4	5.6 ± 1.0	4.7 ± 1.0	3.9 ± 1.2	2.5 ± 0.7
6	4.4 ± 0.8	6.0 ± 0.6	6.7 ± 0.6	6.8 ± 0.9	5.6 ± 0.9	4.2 ± 1.0	3.5 ± 1.0	2.3 ± 0.9
Paired t test† among treatments	6 > 1-5 3 > 1,4	6 > 1-5 3,5 > 1,2,4	6 > 1-5 5 > 4 3> 1,2,4	6 > 1-5 3 > 1,2,4	NSD‡	2 > 6	3 > 1,6	3 > 1,6

*Standard deviation.

†Significant at $p < 0.05$.

‡No significant differences.

trifuging, exactly 10 ml of the chloroform phase was transferred into a 15 ml conical centrifuge tube containing 0.1N sodium hydroxide (2 ml). The tube was shaken for 10 min and centrifuged. The concentration of theophylline in the aqueous phase was then determined in the usual way[16] in a Cary 16 spectrophotometer using semi-micro cells of 1 cm pathlength. The extraction efficiency was 83 ± 2% over a serum theophylline concentration range of 1 to 10 μg/ml. Circulating ephedrine does not interfere with the theophylline assay. Phenobarbital does interfere, but not at the very low doses used in this study.

Interpretation of results. Individual serum theophylline levels were successfully fitted to the pharmacokinetic one-compartment open model with first order absorption and elimination. With this model serum concentrations of theophylline, C, at any time after dosing are described by Equation 1[19] where F is the fraction of the dose D that is absorbed, V is the distribution volume of theophylline in the body, and k and K are first order rate constants for absorption and elimination, respectively. Individual data sets were fitted to Equation 1 by iterative least-squares methods with the use of the program NREG on a Univac digital computer at the Madison Academic Computer Center. In some cases a lag time, t_0, had to be introduced into the equation in order to obtain a satisfactory fit. Pharmacokinetic analysis also included calculation of half-times of absorption (ln 2/k), biological half-lives (ln 2/K), areas under serum level versus time curves from time zero to infinity (FD/VK) and also from time zero to 4 and 12 hr after dosing, by trapezoidal rule.

$$C = \frac{FD}{V}\left(\frac{k}{k-K}\right)\left(e^{-Kt} - e^{-kt}\right) \qquad (1)$$

It is recognized that analysis of theophylline data by this model is an oversimplification as the kinetics of theophylline have been shown to obey two-compartment model kinetics after intravenous dosing.[12] With oral dosing, however, the relatively slow absorption of theophylline obscures the early drug distribution phase and precludes interpretation by the more complex model.

Statistical analysis included comparison of serum levels at each sampling time and also the pharmacokinetic parameters obtained from each treatment by paired t test.

Results

Mean serum concentrations of theophylline resulting from various treatments are given in Table I and the data are summarized graphically in Fig. 1. Averaged results from the pharmacokinetic analysis are given in Table II.

From Table I and Fig. 1 it is clear that there were significant differences in serum theophylline levels due to treatments only during the first 2 hr after dosing, serum levels obtained from the solution being significantly higher than

Table II. *Values of pharmacokinetic parameters (±1 SD)*

Parameter	Treatment 1	2	3	4
k (hr^{-1})	0.8 ± 0.4	0.6 ± 0.4	1.3 ± 0.5	1.0 ± 1.1
t½ (abs) (hr)	1.2 ± 0.6	1.5 ± 0.8	0.6 ± 0.2	1.1 ± 0.5
K (hr^{-1})	0.12 ± 0.04	0.10 ± 0.02	0.10 ± 0.02	0.12 ± 0.04
t½ (elim) (hr)	6.4 ± 2.1	6.8 ± 1.0	7.0 ± 1.5	6.4 ± 1.8
FD/V (μg/ml)	7.8 ± 0.9	8.1 ± 1.9	7.9 ± 1.4	7.5 ± 2.0
Area* $0 \rightarrow \infty$ (μg.hr/ml)	75.0 ± 31.4	80.0 ± 24.5	79.6 ± 23.7	68.8 ± 23.8
Area† $0 \rightarrow 4$ (μg.hr/ml)	16.1 ± 3.7	14.5 ± 4.9	19.7 ± 3.1	14.1 ± 5.7
Area† $0 \rightarrow 12$ (μg.hr/ml)	46.6 ± 11.1	46.2 ± 12.0	52.2 ± 10.4	41.7 ± 16.5
V‡ (% body wt)	44.9 ± 3.7	45.5 ± 7.7	45.8 ± 4.4	49.9 ± 11.2
t_0 (hr)	0.04 ± 0.10	0.08 ± 0.13	0.0	0.0
r^2§	0.99 ± 0.01	0.98 ± 0.03	0.99 ± 0.01	0.98 ± 0.02
Peak height (μg/ml)	5.6 ± 0.8	5.5 ± 1.1	6.0 ± 1.0	5.1 ± 1.6
Time of peak height (hr)	3.3 ± 1.0	3.7 ± 0.8	2.3 ± 1.0	3.5 ± 1.5

*Obtained from FD/VK.
†Obtained by trapezoidal rule.
‡Units of (l/kg) × 100.
§$(\Sigma obs^2 - \Sigma dev^2)/\Sigma obs^2$.

those from other treatments. Serum levels were also higher after the high protein meal than after the other test meals and when the drug was given with only 20 ml of water on an empty stomach. Serum levels tended to be higher after dosing with 500 ml of water on an empty stomach than after the carbohydrate and fat meals and after limited water intake, but the differences were not always significant.

From 6 hr after dosing, serum levels from Treatment 6 tended to be low, but there were no significant trends. In fact, the serum theophylline time profiles after this time are remarkably similar for all treatments and declined monoexponentially in all cases, indicating that gastrointestinal absorption is completed within 6 hr. It is noteworthy that the scatter in individual data is inversely related to the rates of theophylline absorption.

Peak serum levels of theophylline were significantly higher after Treatment 6 than after other treatments, and also after the high protein meal compared to other test meals. Although the times of peak serum levels were considerably shorter after Treatment 6, significant differences were obtained only between this treatment and Treatments 1 and 2. Although the absorption rate constant was significantly higher from Treatment 6 than from other treatments, and was higher after the protein meal compared to the other test meals, most other pharmacokinetic parameters, except for the trapezoidal areas, were essentially the same for all treatments. The biological half-life of 5.9 to 7.0 hr is similar to previously reported values.[12]

The close similarity of the areas under serum

		Paired t test
5	*6*	
1.3 ± 0.8	2.9 ± 0.4	6 > 1-5 3 > 1, 2
0.8 ± 0.5	0.3 ± 0.04	1-5 > 6 1, 2 > 3
0.12 ± 0.02	0.13 ± 0.03	NSD
6.1 ± 0.8	5.9 ± 1.7	NSD
8.1 ± 1.6	8.3 ± 0.9	NSD
72.0 ± 18.2	71.2 ± 24.8	NSD
20.3 ± 3.8	23.7 ± 3.0	6 > 1-5 5, 3 > 1, 2, 4
51.7 ± 11.9	52.7 ± 10.3	6 > 1, 2, 4 5 > 2, 4 3 > 1, 2
44.8 ± 5.9	43.1 ± 7.4	NSD
0.0	0.0	
0.99 ± 0.01	0.99 ± 0.01	
6.0 ± 1.1	6.9 ± 0.9	6 > 1-5 3 > 1, 2
2.8 ± 1.3	1.4 ± 0.6	1, 2 > 6

level curves indicate that the overall absorption of theophylline is the same for all treatments, although slower absorption from some treatments is reflected in significantly reduced areas under serum level curves during the first 4 and 12 hr after dosing. The distribution volumes were calculated on the assumption of quantitative absorption of drug into the systemic circulation (F = 1). The calculated values are similar to those obtained after oral doses of aminophylline,[4] suggesting similar absorption characteristics for the two drug forms.

Discussion

Although phenobarbital has been reported to decrease the bioavailability of theophylline by complexing,[1] unpublished data from this laboratory indicate that, with the theophylline tablets used in our study, this is not the case. In a controlled study in man, the bioavailability of theophylline was not significantly different in subjects given Tedral tablets and tablets containing only theophylline.

The extent to which food influences the absorption of a drug taken orally will depend on interactions between the drug and particular food components, the food mass creating a physical barrier between the drug and the gastrointestinal epithelium, the digestive capacity of the intestinal secretions, changes in gastric emptying rate, intestinal motility, and the dissolution rate of the drug in the gastrointestinal fluids. Reports on the influence of food on enteral absorption are fragmentary, and no distinct cause-effect relationship has evolved. The inhibitory effect of foods, particularly those containing large amounts of divalent cations, on tetracycline absorption is well documented.[7, 14] Reduction in absorption efficiency of lincomycin,[18] penicillin,[8] dicloxacillin,[2] and some sulfonamides[10] by food has also been demonstrated.

Some studies have indicated that a meal immediately preceding oral drug administration may enhance its absorption. The absorption of riboflavin and riboflavin-5′-phosphate is increased after a breakfast of cornflakes and milk,[5] and the absorption of griseofulvin is increased after some fatty meals.[6] The influence of food, as well as other factors, on drug absorption from the gastrointestinal tract has recently been reviewed by Prescott.[13]

In our study the enteral absorption of theophylline from a solid dosage form was not significantly influenced by the test meals used, although the high fat meal tended to yield lower serum levels of drug shortly after dosing. Foodstuffs in general, and fatty meals in particular, tend to decrease the gastric emptying rate and should increase the residence time of drug in the stomach. Theophylline is a weak acid of pK_a 8.8 and is essentially nonionized while in the stomach and the proximal small intestine. If one assumes that the nonionized form of the drug is preferentially absorbed, then delay in stomach emptying might not be expected to have a marked effect on absorption. Interactions between drug and particular food compo-

nents and also food bulk appear to have a negligible effect on enteral theophylline absorption from a solid dosage form.

Comparison of the data from Treatments 4 and 5 indicate the influence of the volume of fluid administered with the medication on the rate of theophylline absorption. Although the only pharmacokinetic parameters of these treatments that differed are the areas under serum level curves from zero to 4 and zero to 12 hr, it appears reasonable to suggest that more consistent theophylline absorption rates will be obtained if the drug is administered with fairly large volumes of water.

The increased absorption rate in Treatment 6 indicates that theophylline absorption is related to dissolution. Nevertheless, overall absorption was independent of dissolution characteristics. Our results indicate that the rate and extent of absorption of theophylline from a solid dosage form is not markedly influenced by the presence of food and that consistent circulating drug levels can be obtained with a solid oral dosage form.

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