The clinical significance of food-induced changes in the absorption of theophylline from Uniphyl tablets

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To determine the effects of food on the absorption of theophylline from Uniphyl tablets (a once-daily sustained-release theophylline formulation), we performed a crossover evaluation in 20 adults with asthma. After 5 days of continuous dosing (at 6 PM), all patients received their regular Uniphyl dose under specified fasting conditions, and serum theophylline concentrations were measured sequentially during the following 24 hours. The patients' next Uniphyl dose was administered immediately after ingestion of a standardized high-fat meal, and theophylline concentrations were again measured during 24 hours. Five days later, the procedure was repeated in the opposite order. The patients' mean daily theophylline dose was 890.0 ± 229.2 mg. We found relatively minor, but in some cases statistically significant, differences in pharmacokinetic parameters between food and fasting administration. When Uniphyl was administered with food, bioavailability was increased by 10% ($p < 0.01$), the time of maximum concentration occurred 3 hours later ($p < 0.01$), and the minimum or "trough" theophylline concentration was 0.7 mg/L greater ($p < 0.01$), as compared to administration while patients were fasting. There was no evidence of "dose dumping" after either food or fasting administration of Uniphyl, and there was no significant difference in the maximum theophylline concentration attained between the two dosing conditions. There was no evidence of a difference in therapeutic efficacy between the two dosing conditions. All patients tolerated the drug well throughout the trial. (J ALLERGY CLIN IMMUNOL 1988;82:155-64.)

Several factors, including age, coexistent disease, drugs, diet, smoking habits, time of dosing, and even posture have been demonstrated to exert some influence on theophylline kinetics.[1-3] Although the effects of these factors influence theophylline-dose selection, individual variability in theophylline kinetics remains the principal component of interpatient differences in theophylline requirements.[4] Recently, some significant effects of food on the rate and extent of theophylline absorption from some sustained-release formulations have been observed.[5, 6] Any such effects would have greater clinical impact with formulations designed for once-daily dosing, since the dose for an entire day of theophylline is taken at one time.

Abbreviations used

AUC:	Area under the serum concentration versus time curve
Cl:	Theophylline clearance
CV:	Coefficient of variation
C_{max}:	Maximum theophylline concentration
C_{min}:	Minimum theophylline concentration
T_{max}:	Time of maximum theophylline concentration (hours after dose)
T_{min}:	Time of minimum theophylline concentration (hours after dose)
$t_{1/2}$:	Half-life of elimination
ANCOVA:	Analysis of covariance
ANOVA:	Analysis of variance
Ke:	Elimination rate constant

Rall[7] reports that "food slows, but does not reduce theophylline absorption," which is likely true for all immediate-release products. Sustained-release formulations, because of differences in their release mechanisms, may be affected in different ways by

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TABLE I. Standardized meal

	Protein (gm)	Cho (gm)	Fat (gm)	Calories
28 gm white roll	3	18	1	93
7.5 gm butter			7	63
Green salad	1	2		12
30 ml oil and vinegar			14	126
180 gm sirloin steak	44		51	635
180 gm baked potato	6	42		192
7.5 gm butter			7	63
30 ml mushroom sauce		5	9	101
132 gm green beans	2	7		36
⅙ of 9-inch apple pie	3	61	18	418
125 ml ice cream	3	17	8	152
125 ml dry wine		10		200
Total	62	162	115	2091

Cho = carbohydrates.

food intake. The two leading twice-daily sustained-release formulations in Canada (Theo-Dur; Key Pharmaceuticals, Inc., Miami, Fla., and Phyllocontin; Purdue Frederick Co., Toronto, Canada, and Norwalk, Conn.) have been demonstrated to have equal bioavailability,[8, 9] and neither appears to be significantly affected by food or fasting administration. In a single-dose study, the only effect of food on these two formulations was a slight reduction in the rate of absorption, resulting in a longer interval to T_{max}.[10] When Theolair-SR (Riker Laboratories, Inc., St. Paul, Minn.) was administered with food,[11] both the AUC and C_{max} were reduced by 11%. Two encapsulated theophylline-bead formulations demonstrated significant, but opposite, effects of food. Bioavailability of a twice-daily bead formulation (Theo-Dur Sprinkle; Key Pharmaceuticals, Inc.) was reduced by 50% when it was administered with solid food.[6, 12] The reverse was noted with a once-daily formulation (Theo-24; Searle Laboratories, Chicago, Ill.) in which administration with a high-fat breakfast resulted in a dramatic increase in the rate of absorption and a 60% increase in bioavailability.[5] In a single-dose study, the bioavailability of Uniphyl was reported to be significantly reduced when it was taken in the morning after an overnight fast.[6]

Evening dosing with Uniphyl tablets (Purdue Frederick Co.) has been demonstrated to significantly attenuate the early morning deterioration in pulmonary function and symptoms of the patient with asthma compared to a reference twice-daily theophylline[13, 14] or Uniphyl administered in the morning.[15] Because of the apparent advantage of evening dosing, it is likely that this medication will frequently be taken with, or shortly after, the evening meal. Accordingly, we conducted a comparison of the serum theophylline concentrations attained with once-daily Uniphyl when it is administered in the evening under fasting conditions and after a standardized, high-fat evening meal. The high-fat meal was selected because it was a high-fat breakfast that was reported to cause "dose dumping" with another once-daily theophylline formulation.[5]

MATERIAL AND METHODS

Patients

Twenty-one adults (12 were male and nine were female) with chronic reversible airway obstruction, requiring continuous bronchodilator therapy, entered the study. Five patients participated in Ottawa and 16, in Kelowna, Canada. All were patients with asthma and had demonstrated an increase in FEV_1 of 15% or more after inhaled salbutamol. Patients with clinically significant cardiac, hepatic, or renal disease were excluded, as were pregnant patients and nursing mothers. All patients had previously participated in one of two double-blind clinical investigations with Uniphyl tablets and were receiving the drug, on a once-daily regimen, as their ongoing theophylline medication. The study was approved by the Research Ethics Committees of the Kelowna General Hospital and Ottawa Civic Hospital, and by the Bureau of Human Prescription Drugs, Health and Welfare, Canada. All patients gave written informed consent before entry into the study.

Drugs

Uniphyl, 400 mg of ultrasustained-release theophylline tablets (Purdue Frederick), was the only theophylline formulation allowed during the food versus fasting study. The tablets were selected at random from regular production lots 1L6 (Kelowna patients) and 1P5 (Ottawa patients) of Uniphyl marketed in the United States. Each patient's daily theophylline dose was that which had been previously determined to produce predose serum theophylline levels of 7.0 mg/L or more. This daily dose remained constant throughout the study.

Other bronchodilator drugs that had been part of a patient's regular therapy were continued at stable dosages throughout the trial. Drugs reported to affect theophylline clearance (allopurinol, cimetidine, erythromycin, and metoclopramide) were not allowed during the trial or within the preceding 3 weeks.

Procedure

At least 3 days before beginning the study, patients were instructed to switch the timing of their daily Uniphyl dose to 6 PM. On study day 1, patients were instructed to eat their lunch before 12 noon and then begin fasting. Later that afternoon, patients reported to the clinical investigation unit and, at 6 PM, a blood sample for theophylline analysis was obtained, and the patients then took their Uniphyl dose with 8 oz of water. Patients remained fasting until 5 hours after dose (11 PM), at which time a buffet of cold cuts,

bread, salad, and soft drinks was served. Patients then slept and were allowed breakfast on awakening the following morning. Beginning at 12 noon that afternoon (i.e., 18 hours after dose), patients again fasted, as this led to the next dosing interval. At 5 PM (23 hours after dose), patients reported to a local restaurant that had agreed to prepare a specific standardized meal (Table I). Patients consumed the meal between 5 PM and 5:45 PM; then they returned to the clinical investigation unit by 6 PM. At 6 PM, a blood sample was obtained and they again took their Uniphyl dose with 8 oz of water, beginning study day 2 (i.e., dosing approximately 15 minutes after ingestion of the meal). The patients had no additional food until 11 PM, at which time they had a light snack and then returned to their normal diet the following morning.

During both 24-hour postdose periods (study day 1 and day 2), blood samples were obtained at 0, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dose. On completion of study day 2, patients were discharged and instructed to continue taking their Uniphyl at 6 PM. Five days later, the procedure was repeated in the opposite order, that is, dosing with food (study day 8) preceded dosing while the patient was fasting (study day 9).

After completion of study day 9, patients had their theophylline $t_{1/2}$ determined. After a 48-hour theophylline washout and an overnight fast, each patient received a dose of a rapidly absorbed liquid aminophylline (Palaron [Somophyllin]; Fisons) equivalent to approximately 50% of their daily theophylline dose during the food versus fasting study. This dose ratio was selected to minimize the differences in peak serum theophylline concentrations attained with the liquid aminophylline formulation and Uniphyl, thus reducing the potentially confounding effects of the dose-dependent elimination of theophylline on comparisons between AUCs.[16] Blood samples were obtained at 0, ½, 1, 1½, 2, 2½, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after dose. The liquid aminophylline was administered with 8 oz of water, and patients remained fasting for 4 hours after dosing.

Theophylline analyses

Theophylline analyses were performed by the Departments of Biochemistry at the study centers. Both centers used an immunoassay technique, TDX (Abbott, Chicago, Ill.), in Kelowna, and EMIT (Syva Co., Palo Alto, Calif.), in Ottawa. Both institutions calibrated the assays over the range of 1.0 to 30.0 mg/L. CVs at theophylline concentrations <5.0 mg/L, 10.0 mg/L, and 20.0 mg/L are 5.0%, 3.7%, and 3.8%, respectively. Samples were analyzed on completion of each collection period (i.e., days 1 and 2 and days 8 and 9, and the liquid aminophylline dosing). Each sample was identified only with the patient's name and time of collection. The laboratory personnel had no knowledge of the specifics of the study.

Data reduction and statistical analysis

After Uniphyl dosing under fasting and food conditions, model-independent pharmacokinetic parameters of T_{max}, T_{min}, C_{max}, C_{min}, and AUC were determined from each serum theophylline concentration versus time profile. AUC was calculated with the trapezoidal rule from 0 to 24 hours after dose. These parameters were analyzed by ANOVA for repeated measures during the two dosing conditions (fasting versus food) and the order of administration of the dosing conditions. Tests for differences between the two dosing conditions and order of administration were Student's t tests with standard errors derived from the ANOVA. An 0.05 level of significance was used for all such tests.

ANCOVA for repeated measures was used to compare the mean serum concentration versus time profiles for dosing conditions and order of administration. In this analysis, the predose (0 hour) concentration was used as a covariate so that the food and fasting profiles were compared after adjustment for differences in 0 hour theophylline concentrations. Comparisons between the food and fasting mean concentrations at each blood sampling time were Student's t tests with the standard error determined from the ANCOVA. Because of the large number of such comparisons (10 postdose blood sampling times), a nominal significance level of 0.005 was used to elicit an overall error rate of 0.05 ($10 \times 0.005 = 0.05$).

After liquid aminophylline dosing, each patient's theophylline Ke was calculated, with least-squares regression, as the slope of the elimination phase of the semilogarithmic serum theophylline concentration versus time profile. The $t_{1/2}$ was calculated from Ke with the equation:

$$t_{1/2} = \frac{0.693}{Ke}$$

AUC was calculated from 0 to 24 hours with the trapezoidal rule. AUC from 0 hours to infinity was calculated by dividing the 24-hour serum theophylline concentration by Ke and adding this value to the AUC (0 to 24 hours). Clearance was calculated by dividing the dose administered (in terms of anhydrous theophylline) by the AUC (0 to ∞). The relative bioavailability of Uniphyl was calculated, after adjusting the liquid aminophylline AUC to account for differences in theophylline doses administered, with the equation:

$$\text{Uniphyl bioavailability} = \frac{\text{Uniphyl AUC (0 - 24 hr)}}{\text{Liquid aminophylline AUC (0-}\infty\text{), adjusted}} \times 100\%$$

Comparisons between the AUCs and relative bioavailability during Uniphyl and liquid aminophylline were by Student's paired t tests with the adjusted liquid aminophylline AUC values.

RESULTS

Food versus fasting Uniphyl dosing at steady state

Twenty-one patients entered the study. There were no dropouts; however, one patient's data were excluded from analysis because he changed his daily theophylline dose during the study. The characteristics and concomitant medications for the 20 patients included in the analysis are listed in Table II.

The mean serum concentration versus time profiles during food and fasting administrations of Uniphyl

TABLE II. Patient characteristics and concomitant medications

Patient	Sex	Age (yr)	Weight (kg)	Smoking history			Concomitant medications			
				N	R	C	IBA	IS	OS	IIB
1	M	73	81		√		√	√		√
2	F	67	54		√		√			
3	M	48	73	√			√	√		
4	F	51	53		√		√	√	√	√
5	M	59	72		√		√			
6	M	74	76		√		√	√	√	
7	M	60	84		√		√	√		
8	M	67	64		√		√	√		
9	M	66	64		√		√	√	√	√
10	M	36	78			√	√			
11	F	46	72	√			√	√	√	
12	M	36	82		√		√	√		
13	F	47	72		√		√	√		
14	M	28	76		√		√	√		
15	F	21	59		√		√	√		
16	M	32	54	√			√	√	√	
17	F	20	64		√		√			
18	F	56	57	√			√	√	√	√
19	F	31	63	√			√	√		
20	F	29	61	√			√	√	√	√
Mean ± SD		47.3 ± 17.4	67.9 ± 9.9							

N = never; R = reformed (>6 months); C = current; IBA = inhaled β-agonist; IS = inhaled steroid; OS = oral steroid; IIB = inhaled ipratropium bromide.

are illustrated in Fig. 1. Administration of Uniphyl with food resulted in a slight reduction in the rate of absorption and an increase in the period during which the rate of absorption exceeded the rate of elimination. This increased the time at which T_{max} occurred. Overall, mean ± SD T_{max} to food was 11.4 ± 3.7 hours after dose, whereas mean T_{max} to fasting was 8.6 ± 4.5 hours after dose. This difference was statistically significant ($p < 0.01$). When the mean plasma concentrations were analyzed by ANCOVA to adjust for differences in the 0 hour levels, the differences between the two mean profiles were significant from 10 through 24 hours after dose.

Pharmacokinetic parameters are listed in Table III. Since there were no significant differences in any parameter within the two food (i.e., day 2 versus day 8) or fasting (day 1 versus day 9) administration days, parameters listed for each patient during Uniphyl administration represent the average of the two values obtained for each dosing condition. In order to reflect intrapatient variation within each dosing condition, the CV is listed, in parentheses, after each averaged value for AUC, C_{max}, and C_{min}.

Administration of Uniphyl with food resulted in a 10% increase in bioavailability, as evidenced by an overall mean AUC to food of 313.0 ± 85.5 mg/L/hr, compared to a mean AUC to fasting of 284.0 ± 93.2 mg/L/hr. The standard deviations reported in this article differ slightly from those in Table III, since the text values were calculated with all 40 values measured for each parameter (20 patients times two values for each dosing condition). The standard deviations listed in Table III were calculated with the 20 averaged values for each parameter. However, all statistical comparisons between food and fasting administration were performed with the full (nonaveraged) data. Inspection of the CVs and standard errors reveal that both intra- and interpatient variation in AUC was lower when Uniphyl was administered with food, although the differences did not reach statistical significance.

The overall mean C_{max} attained did not differ significantly between food (17.4 ± 4.5 mg/L) and fasting (16.5 ± 4.5 mg/L) administration. The effect of food on maximum theophylline concentrations was further assessed by subtracting each patient's greatest C_{max} fasting from his or her greatest C_{max} food. The resulting mean increase in C_{max} was 1.0 mg/L (range 4.8 mg/L to −6.1 mg/L). In comparison, the mean intrapatient difference in C_{max} on the 2 fasting days,

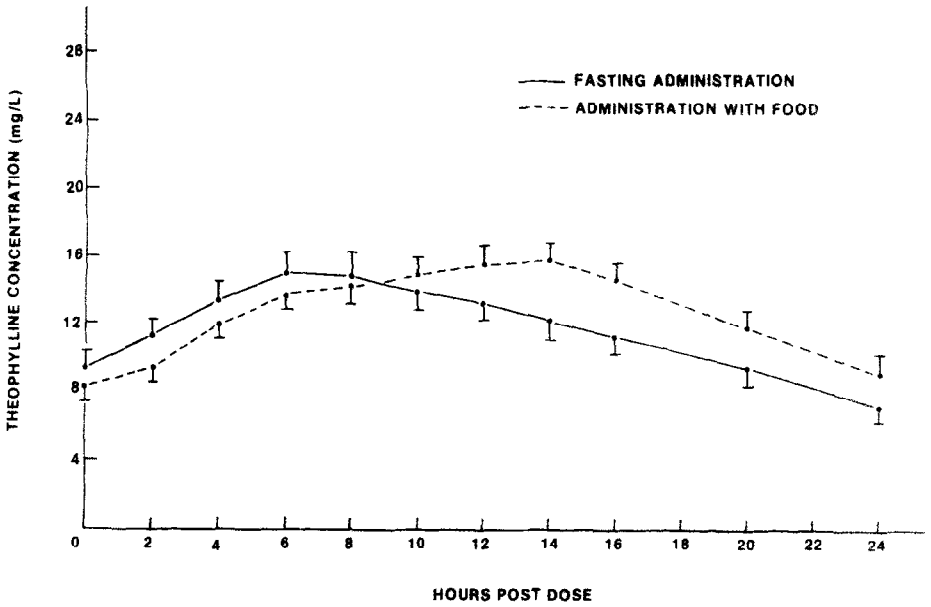

FIG. 1. Mean ± SEM steady-state serum theophylline levels in 20 patients with asthma after administration of Uniphyl while they were fasting and with food.

a measure of individual variation outside the influence of food, was 3.7 mg/L. The mean intrapatient difference in C_{max} on the 2 food administration days was also 3.7 mg/L.

The overall mean C_{min} differed between food and fasting administration. C_{min} food was 7.7 ± 3.1 mg/L, whereas C_{min} fasting was 7.0 ± 3.0 mg/L ($p < 0.01$). The mean interpatient difference in C_{min} on the 2 fasting and 2 food days was 1.68 ± 1.26 mg/L and 1.85 ± 1.64 mg/L, respectively. There was no significant difference in the magnitude of peak-to-trough differences in serum theophylline levels between the two dosing conditions. The mean C_{max} to C_{min} was 9.7 ± 2.1 mg/L during administration with food and 9.5 ± 2.2 mg/L during fasting administration. Converting the difference between C_{max} and C_{min} to percent fluctuation ($[C_{max}-C_{min}]/C_{min}$) produced a mean fluctuation of 146.4 ± 76.4% during food administration and 162.3 ± 81.4% during fasting administration. This difference is not statistically significant.

Single dose liquid aminophylline

Eighteen of the 20 patients who completed the food versus fasting study returned to receive the single dose of liquid aminophylline. The two remaining patients declined because they did not want to perform the required 48-hour theophylline washout. The mean dose of liquid aminophylline administered (in terms of anhydrous theophylline) was 416.7 ± 98.5 mg, which is slightly <50% of the once-daily Uniphyl dose. Four patients received >1000 mg/day of Uniphyl, and doses were selected in consideration of expected tolerance. In only one case was a dose of liquid formulation >500 mg considered appropriate.

The patients' mean theophylline $t_{1/2}$ was 7.1 ± 1.8 hours (range: 4.1 to 11.8 hours), and their mean clearance was 0.043 ± 0.015 L/hr/kg (range, 0.022 to 0.075 L/hr/kg). The mean AUC (0 to ∞) for the liquid aminophylline (adjusted to the daily theophylline dose taken during Uniphyl dosing) was 320.8 ± 97.1 mg/L/hr. In these 18 patients, the mean Uniphyl AUC to food was 319.4 ± 80.4 mg/L, whereas the mean Uniphyl AUC to fasting was 291.5 ± 86.8 mg/L/hr. When the difference was compared by Student's paired *t* tests, the difference between the Uniphyl AUC to food and Uniphyl AUC to fasting was significant ($p < 0.05$), but the difference between the dose adjusted AUC from liquid aminophylline and the Uniphyl AUC to food or Uniphyl AUC to fasting did not reach statistical significance ($p = 0.65$ and 0.07, respectively). This is also reflected in the mean bioavailability calculations. Assuming 100% bioavailability for the liquid aminophylline formulation, the mean bioavailability of Uniphyl administered during fasting was 93.9%, which increased to 103.2% when Uniphyl was administered with food. Again, the difference between Uniphyl bioavailability to food and bioavailability to fasting was significant ($p < 0.05$), but neither was significantly different from 100% bioavailability assigned to liquid aminophylline. The mean C_{max} from the liquid aminophylline (14.8

TABLE III. Pharmacokinetic parameters after oral doses of liquid aminophylline and Uniphyl tablets

	Liquid aminophylline					Uniphyl		
							AUC (CV) (mg/L/hr [%])	
Patient	$t_{1/2}$ (hr)	Cl (L/hr/Kg)	Dose (mg)	C_{max} (mg/L)	AUC* (mg/L/hr)	Daily dose (mg)	Fasting	Food
1	7.3	0.041	500	15.0	303.0	1000	280.7 (7.7)	317.8 (2.7)
2	9.1	0.022	300	16.0	449.2	600	331.8 (6.5)	402.4 (24.3)
3	7.1	0.034	300	10.0	295.8	800	295.8 (17.0)	398.8 (17.3)
4	4.8	0.049	400	16.5	293.0	800	354.7 (21.7)	353.8 (36.0)
5	4.6	0.066	400	11.5	206.7	1000	325.8 (5.0)	258.7 (5.2)
6	8.3	0.028	500	18.0	555.8	1200	491.5 (2.3)	498.7 (1.0)
7	8.5	0.030	500	16.5	447.4	1200	404.7 (21.4)	375.0 (3.1)
8	7.7	0.031	300	12.5	335.2	800	249.7 (1.0)	300.6 (5.7)
9	7.3	0.045	500	19.5	286.7	800	253.6 (41.2)	223.4 (27.5)
10	7.3	0.040	500	13.5	389.8	1200	294.7 (11.6)	350.0 (4.2)
11	7.9	0.026	300	12.8	404.3	800	364.3 (18.4)	351.4 (1.2)
12	6.3	0.058	500	10.5	225.8	1000	247.3 (14.8)	319.0 (20.0)
13	7.7	0.039	400	13.1	263.0	800	281.3 (8.0)	310.0 (12.6)
14	4.1	0.063	600	17.0	292.4	1400	193.1 (0.9)	259.9 (21.1)
15	4.8	0.075	500	14.0	193.4	1000	214.6 (54.7)	247.1 (19.5)
16						800	214.3 (36.1)	241.2 (8.2)
17	6.2	0.044	300	12.4	202.8	600	161.9 (18.6)	178.2 (0.1)
18	6.7	0.032	300	16.0	339.6	600	143.4 (35.6)	212.7 (3.8)
19						600	220.5 (21.4)	268.6 (12.6)
20	11.8	0.043	400	22.7	290.4	800	355.6 (3.3)	391.3 (9.3)
Mean	7.1	0.043	416.7	14.8	320.8	890.0	284.0 (17.4)	313.0 (11.8)
SD	1.8	0.015	98.5	3.3	97.1	229.2	85.4 (14.8)	79.0 (10.2)

Liquid aminophylline was administered under fasting conditions after a 48-hour theophylline washout. Uniphyl parameters were measured at steady state on 4 separate study days, twice with dosing under fasting conditions and twice with dosing immediately after a high-fat meal. Individual patient parameters listed for Uniphyl represent the average of the two values obtained for each dosing condition. Mean values for AUC, T_{max}, and C_{min} were significantly greater when Uniphyl was administered with food as compared to fasting. Also, the relative bioavailability of Uniphyl administered with food was significantly greater than Uniphyl administered during fasting, but neither was significantly different from the 100% bioavailability assigned to liquid aminophylline.

*AUC adjusted to the daily theophylline dose administered during Uniphyl dosing.

mg/L) was not significantly different from the mean C_{max} to food or mean C_{max} to fasting observed during administration of Uniphyl.

DISCUSSION

To avoid the potential inaccuracies associated with predictions from single-dose studies conducted in theophylline naive volunteers,[16-18] we performed our study under steady-state conditions in patients with asthma receiving individually titrated doses of Uniphyl. We found no evidence that potentially toxic changes in the pharmacokinetic behavior of the drug may occur if patients alter the time they take their Uniphyl dose in relation to meals. Food resulted in a slightly reduced rate of theophylline absorption from Uniphyl and in a prolongation of the time at which maximum theophylline concentrations were attained. This reduced rate of absorption is consistent with the findings for most other theophylline formulations and is opposite to that that would occur if food induced a rapid release of theophylline from the formulation, a phenomenon that has been termed "dose dumping."

When the difference is interpreted with reference to the knowledge that pharmacopeal standards allow a ±6% variation in content for many oral drugs,[19] including theophylline, it is our opinion that the 10% difference in bioavailability between food and fasting administration is not clinically significant. Although some patients exhibited a difference >10% between the food and fasting AUCs, we believe that it would be incorrect to attribute these larger differences solely

Uniphyl							
Relative bioavailability (%)		C_{max} (CV) (mg/L [%])		C_{min} (CV) (mg/L [%])		T_{max} (hr)	
Fasting	Food	Fasting	Food	Fasting	Food	Fasting	Food
93	105	15.0 (16.5)	16.1 (12.7)	6.6 (7.4)	8.3 (0)	11	10
74	90	17.3 (15.1)	20.3 (25.4)	8.8 (11.2)	11.6 (25.6)	8	10
100	135	17.6 (5.6)	19.9 (12.1)	11.9 (7.7)	11.9 (17.8)	22	9
121	121	21.3 (13.3)	19.4 (26.5)	6.5 (46.4)	7.9 (63.1)	7	15
158	125	19.7 (3.9)	13.5 (6.8)	7.8 (3.6)	7.6 (0)	8	9
88	90	25.6 (0.3)	27.7 (2.3)	13.1 (2.7)	13.7 (3.1)	8	11
90	84	21.4 (16.5)	20.6 (2.0)	10.1 (15.4)	10.3 (12.4)	7	11
74	90	13.7 (5.1)	16.4 (3.0)	6.0 (15.2)	6.4 (22.1)	7	10
88	78	13.4 (34.2)	14.2 (39.8)	5.0 (22.6)	4.7 (4.5)	9	8
76	90	16.7 (11.4)	19.2 (10.6)	6.2 (39.6)	8.9 (14.3)	11	13
90	87	21.1 (18.1)	20.0 (7.4)	8.7 (24.4)	9.1 (16.2)	9	14
110	141	13.4 (3.2)	15.8 (12.0)	6.8 (22.9)	7.5 (7.5)	8	16
107	118	14.7 (16.3)	18.2 (8.9)	7.4 (31.3)	6.8 (21.7)	14	15
66	89	13.7 (10.3)	16.2 (16.2)	3.8 (0)	4.5 (22.0)	6	9
111	128	13.4 (43.6)	17.7 (5.6)	4.3 (53.6)	4.7 (37.2)	7	7
		14.5 (42.3)	12.8 (8.8)	4.5 (23.3)	4.6 (19.8)	6	8
80	88	11.0 (12.9)	10.2 (15.2)	2.9 (21.6)	4.0 (22.7)	4	15
42	63	10.9 (32.4)	13.1 (2.7)	2.9 (43.9)	4.3 (17.9)	5	13
		14.1 (34.5)	14.7 (12.5)	5.1 (5.5)	6.4 (34.0)	5	10
122	135	20.8 (12.9)	22.0 (21.5)	11.4 (0)	11.1 (3.2)	11	15
93.9	103.2	16.5 (17.4)	17.4 (12.6)	7.0 (19.9)	7.7 (18.2)	8.6	11.4
25.7	23.1	4.0 (13.0)	4.0 (9.6)	3.0 (16.2)	2.9 (14.9)	4.0	2.8

to the different dosing conditions, since approximately this same level of intrapatient variation was observed within the 2 fasting and 2 food administration days. In all studies, it is important to interpret differences between treatments with consideration of the day-to-day variation observed within the treatments. Substantial day-to-day variation in theophylline concentrations is also known to occur with twice-daily sustained-release theophylline formulations, even under consistent dosing conditions.[20-23] In one of these studies,[22] in which single 300 mg doses of Theo-Dur were administered on 2 separate days, intrasubject variation in both AUC and C_{max} was >20% in two of the six subjects, between 10% and 20% in two other subjects, and <10% in the remaining two subjects. This day-to-day variability, particularly in C_{max}, has important implications for the application of theophylline concentrations to dosage adjustments. Isolated serum theophylline concentrations need to be interpreted with caution, and if a substantial increase in theophylline dosage appears warranted, we recommend that it be preceded by further theophylline concentration measurements.

The single dose of liquid aminophylline was administered to our patients, primarily to characterize their theophylline elimination kinetics, and the results demonstrated that in this respect they are representative of the general population with asthma.[24] Since liquid aminophylline formulations are known to be consistently and completely absorbed,[24] the finding of no significant difference between the liquid aminophylline and Uniphyl AUCs suggests that the bioavailability of Uniphyl approaches 100%. This finding is in agreement with previous multiple-dose studies in volunteers[25] and patients with asthma[14, 26-28] that demonstrated that once-daily Uniphyl tablets were of equal bioavailability to twice-daily Theo-Dur. Our results are not consistent with those of Karim et al.[6] who, in a single-dose study, found only 53% bioavailability when Uniphyl was administered under fasting conditions. However, there are methodologic differences between the Karim et al. study and our study that

could contribute to the different findings. Karim et al. administered Uniphyl in the morning, whereas we administered the drug in the evening. This may account for some, but not likely all, of the difference, since in a previous steady-state study it has been demonstrated that the bioavailability of Uniphyl was only 9% greater when it was administered in the evening.[15] Volunteers of Karim et al. fasted overnight for a minimum of 10 hours before dosing, whereas our patients fasted in the afternoon for a minimum of 6 hours, and in both studies, fasting continued for an additional 4 or 5 hours after dosing. Thus, in both studies, there were rigid fasting conditions, although it has been argued that the "true" fasting state is attained only in the morning after an overnight fast.[29] Since there are significant therapeutic advantages to evening dosing with Uniphyl, we believe that this is when the drug should be administered. Thus, the considerations of an overnight fast preceding dosing become somewhat obscure. A major difference between the two studies is that our study was a multiple-dose study with the pharmacokinetic parameters measured at steady state, whereas that of Karim et al.[6] was a single-dose evaluation. The multiple-dose design allows for comparisons to be made at therapeutic plasma concentrations under conditions more closely resembling routine clinical use and, in the case of bioavailability calculations, avoids the need to estimate any portion of the AUC.

Controlled studies in patients with asthma have demonstrated that Uniphyl taken once daily in the evening produces clinically significant improvement in early morning FEV_1 and asthma symptoms, as compared to a reference twice-daily sustained-release theophylline.[13, 14] This may well be because evening dosing with Uniphyl elicits peak theophylline levels at the most critical time for many subjects with asthma, the early morning hours.[30, 31] We also found that administration of Uniphyl after the evening meal resulted in a relative plateau of maximal theophylline concentrations across the 4- to 10-hour period. The mean peak-to-trough theophylline concentration ratio in our study (2.5:1) is consistent with that observed with Uniphyl in the studies that demonstrated significant spirometric and symptomatic advantages over twice-daily theophylline, despite the fact that the twice-daily formulation resulted in significantly less fluctuation in theophylline concentrations. These findings do not support widely quoted views that a more constant serum theophylline concentration (i.e., minimal peak-to-trough fluctuation) necessarily results in more effective asthma control.[24]

The view that minimization of fluctuation in theophylline concentrations is critical is most often presented within the context of a need to maintain theophylline concentrations within a "therapeutic range" of 10 to 20 mg/L. However, there is a significant body of literature demonstrating substantial bronchodilator activity at theophylline concentrations of 5 to 10 mg/L.[32-35] In fact, some studies have demonstrated activity at concentrations <5 mg/L.[36, 37] Other clinical trials have demonstrated only minimal clinical and spirometric differences between theophylline regimens that differed significantly in the resultant peak-to-trough fluctuations.[38-41] These and other studies demonstrate that the relationship between serum theophylline concentrations and pulmonary function or asthma symptom control is not as direct as has been suggested and that the bronchodilator response to a peak theophylline concentration may persist for several hours.[37, 42] Although we believe that the relationship between theophylline concentrations and clinical effect is not as direct as is generally stated, we did observe that during both food and fasting administration of Uniphyl, there was a significant correlation ($r = 0.60$; $p < 0.01$) between $t_{1/2}$ and C_{min}. Thus, patients with more rapid elimination tended to have lower trough theophylline concentrations, particularly during fasting administration. Although all of our patients had a good clinical response to Uniphyl, only four had $t_{1/2}$ <5.0 hours. Accordingly, additional studies are needed to determine if once-daily theophylline provides the most optimum therapy in patients with rapid theophylline elimination.

In conclusion, our study has demonstrated that the release mechanism of Uniphyl tablets is not adversely affected when the drug is taken after a high-fat meal. Thus, it would appear to be safe for patients to take Uniphyl either with or without food. However, dosing after the evening meal offers the following advantages. First, evening dosing is superior to morning dosing in terms of efficacy, likely because evening dosing results in maximum theophylline concentrations at the time of most patients' greatest need for bronchodilation. Second, when Uniphyl is administered with food, bioavailability is essentially 100% and intrapatient variation in pharmacokinetic parameters is reduced. Thus, it appears that absorption is both enhanced and more consistent when Uniphyl is administered with food. Finally, linking dosing to a regular lifestyle event, such as meals, is known to improve compliance.[43]

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Analysis of bronchoalveolar lavage in allergic bronchopulmonary aspergillosis: Divergent responses of antigen-specific antibodies and total IgE

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Bronchoalveolar lavage (BAL) was performed in eight patients with allergic bronchopulmonary aspergillosis (ABPA) at a time when chest roentgeongraphy did not reveal an infiltrate, and respiratory status was stable. BAL was tolerated well by all patients with only one patient experiencing mild wheezing. BAL fluid recovery averaged 40%, and total cells/lavage were 22.3 × 10⁶ (range 3.5 to 49.5 × 10⁶). Cell viability, as determined by trypan blue exclusion, averaged 48% (range 34% to 60%). Mean values for cellular elements were macrophages, 62%; epithelial cells, 12%; lymphocytes, 16%; neutrophils (PMN), 4%; and eosinophils, 6%. Isotypic antibodies to Aspergillus fumigatus *(Af) in BAL and serum were detected by an amplified indirect ELISA. Antibodies to Af in BAL expressed as optical density/albumin (milligrams per milliliter) were compared to BAL from six nonatopic patients. IgE-Af and IgA-Af in BAL were elevated in patients with ABPA compared with six nonatopic patients. The ratios of Ig-Af in BAL to peripheral blood in patients with ABPA were 48 (range 18 to 75) for IgE-Af, 96 (range 37 to 159) for IgA-Af, and 0.94 (range 0.24 to 1.40) for IgG-Af, suggesting local production of IgE-Af and IgA-Af in the bronchoalveolar compartment. Total serum IgE correlated directly with IgE-Af in BAL ($r_s = 0.67$; $p < 0.02$). However, the ratio of total BAL IgE/albumin divided by total serum IgE/albumin was 0.93 ± 0.94, suggesting that the bronchoalveolar compartment is not the source of the significant elevations in total serum IgE in ABPA. (J ALLERGY CLIN IMMUNOL 1988;82:164-70.)*

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ABPA is a complication of asthma that results in transient infiltrates, revealed by roentgenography, proximal bronchiectasis, and, in some patients, end stage fibrotic lung disease.[1, 2]

ABPA is characterized by a spectrum of immunologic reactions to antigens of *Aspergillus* present in the bronchial tree.[3-7] Some of these reactions include immediate cutaneous reactivity to Af,[7] elevated levels of serum IgE, IgG, and IgA antibodies to Af,[5, 6] pre-