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CIMETIDINE INHIBITS THEOPHYLLINE CLEARANCE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A STUDY USING STABLE ISOTOPE METHODOLOGY DURING MULTIPLE ORAL DOSE ADMINISTRATION

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1 The effect of concurrent cimetidine administration on the disposition of theophylline was investigated in eight male patients (56–78 years) with chronic obstructive pulmonary disease (COPD).

2 The patients, who were taking oral theophylline preparations chronically (384–1020 mg/day), received a [^{15}N], [^{13}C]-labelled analogue of theophylline (10 mg i.v.) before and during cimetidine treatment (1200 mg/day p.o.).

3 During cimetidine treatment trough levels of theophylline increased 34% (6.4 ± 0.8 to 8.6 ± 1.0 μg/ml, $P < 0.05$), half-life increased 48% (6.5 ± 0.6 to 9.6 ± 0.8 h, $P < 0.001$), and total plasma clearance decreased 33% (3.88 ± 0.46 to 2.59 ± 0.33 l/h, $P < 0.001$), without a significant change in volume of distribution or protein binding.

4 The effect of cimetidine on plasma levels of theophylline was maximal within 72 h. Levels returned to control values within 48 h after its discontinuation.

5 Although there was no correlation with mean plasma concentrations of cimetidine, the change in clearance of theophylline correlated with initial clearance values ($r = 0.72$).

6 Cimetidine reduced the plasma clearance of theophylline in patients with COPD to an extent similar to that reported in healthy volunteers.

Introduction

Cimetidine, a potent H_2-receptor antagonist, is widely used in the treatment of peptic ulcer disease and related gastrointestinal disorders. Studies in both man and experimental animals have demonstrated that it is also a potent inhibitor of the hepatic metabolism of a variety of other drugs, including antipyrine (Serlin *et al.*, 1979; Klotz & Reimann, 1980; Roberts *et al.*, 1981), aminopyrine (Pelkonen & Puurunen, 1980), chlordiazepoxide (Desmond *et al.*, 1980), diazepam (Klotz & Reiman, 1980), propranolol (Feely *et al.*, 1981), and warfarin (Serlin *et al.*, 1979). The metabolism of both caffeine (Broughton & Rogers, 1981) and theophylline (Roberts *et al.*, 1981; Jackson *et al.*, 1981; Reitberg *et al.*, 1981) is also inhibited. Since previous studies of the theophylline-cimetidine interaction were not conducted during multiple oral dose administration of both drugs, the applicability of these observations to patients has been questioned (Ambrose & Harralson, 1981).

Accordingly, we undertook a study in patients with chronic obstructive pulmonary disease (COPD) who were regularly taking an oral theophylline preparation. To fully characterize the effect of cimetidine on the pharmacokinetics of theophylline without interruption of the usual oral dosage form, a stable isotope labelled analogue of theophylline was administered intravenously as a tracer dose in the presence and absence of concomitant cimetidine administration. In addition to confirming a marked inhibition of the clearance of theophylline by cimetidine, this study also provides information on the time course of inhibition and recovery and suggests that patients

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who eliminate theophylline most rapidly may be the most susceptible to inhibition of its metabolism by cimetidine.

Methods

Patients

The study group consisted of eight patients with clinically stable chronic obstructive pulmonary disease (COPD) (Table 1). The patients ranged in age from 56 to 78 years. All were taking an oral theophylline preparation and none had cor pulmonale, congestive heart failure, liver disease or renal insufficiency. Except for patient 5, all were non-smokers. The protocol was approved by the Human Subjects Committees of the University of Washington and the Boise Veterans Administration Medical Centre.

Protocol

All patients abstained from alcohol and from foods or beverages containing methylxanthines for 2 weeks prior to the study. Usual medications were continued without interruption. The dose interval for theophylline in all patients was fixed at either 8 or 12 h, depending upon the specific preparation the patient was taking. On the first day of the study at 09.00 h after an overnight fast and following an initial blood sample for measurement of the trough level and plasma protein binding of theophylline, the patient received a rapid intravenous injection of 1,3-[^{15}N], 2-[^{13}C]-theophylline (10 mg) obtained from KOR Isotopes (Cambridge, Massachusetts) simultaneous with his usual oral theophylline dosage form. Blood samples (10 ml) were obtained at 2.5, 10, 15, 30, 45 min and 1, 1.5, 2, 4, 6, 8, 12, 23 and 24 h and plasma was stored at −20°C until analysis. In patients 1–7 cimetidine was begun after the 24 h blood sample and continued for 7 days at which time the pharmacokinetic protocol was repeated. In patient 8, who had been taking cimetidine for several months prior to the study, the drug was continued through the first pharmacokinetic study and then discontinued for 7 days prior to repeat study. Cimetidine was given orally as 400 mg every 8 h and to patients 1, 2, 3 and 7 or 300 mg every 6 h to patients 4, 5, 6 and 8. In all patients plasma samples were obtained at 09.00 h on the inter-study days for trough levels of theophylline and cimetidine. Additionally, in patients 5, 6, and 7 plasma samples were obtained for 6 days following the discontinuation of cimetidine at the end of the second pharmacokinetic study.

Analytical methods

The stable isotope methodology used in this study has been previously described in detail (Vestal *et al.*, 1982). In brief, standards and study samples (1 ml plasma) to which d_6-theophylline (KOR Isotopes) had been added as an internal standard were extracted with organic solvent and purified by high pressure liquid chromatography (h.p.l.c.). The fraction of column effluent containing theophylline and the two stable isotope labelled analogues was collected and prepared for mass spectral (MS) analysis which employed a direct insertion solid probe technique with monitoring of ion currents at m/z 180, 183 and 186. Quantification of unknown plasma samples from peak-height ratios of the ion currents at m/z 180 and 183 compared to those at m/z 186 was accomplished from standard curves. The unbound fraction of theophylline in plasma was determined in triplicate by direct h.p.l.c. assay of total and free concentrations after equilibrium dialysis of 1 ml aliquots of plasma against phosphate buffer (pH 7.4) for 16 h at 37°C (Vestal *et al.*, 1983). Cimetidine plasma levels were also determined by an h.p.l.c. method (Ziemniak *et al.*, 1981). The presence of cimetidine was not found to interfere with the MS analysis of theophylline.

The h.p.l.c. system (Micromeritics Instrument Corp., Norcross, Georgia) consisted of a Model 730 Universal Injector, a Model 752 Gradient Programmer, a Model 750 Solvent Delivery System, equipped with a Rheodyne 10μ LiChrosorb Diol column (4.6 mm i.d. × 25 cm) obtained from Brownlee Laboratories (Santa Clara, California), and a Model 786 Detector. The solid probe MS analysis was performed with a Model 3200 F quadrupole mass spectrometer (Finnigan Corporation, Sunnyvale, California) equipped with a programmable multiple ion monitor to accomplish selected ion monitoring in the electron impact mode.

Pharmacokinetic analysis

Data were obtained for the plasma concentrations of both theophylline administered orally and the stable isotope enriched species administered intravenously. Data analysis was performed according to standard methods (Gibaldi & Perrier, 1982) with the aid of a curve fitting program developed for non-linear regression analysis of pharmacokinetic data (Koeppe & Hamann, 1980). Data for intravenous administration were fitted mathematically to a two-compartment linear open model to determine the hybrid first order rate constants for the initial distribution and terminal elimination phases, α and β respectively. Area under the curve for the intravenous tracer from time zero to infinity (AUC_{iv}) and area under the oral theophylline curve for the dose interval (AUC_{oral}) was obtained by the trapezoidal rule. Bioavailability (F) was estimated from the ratio of AUC_{oral} and AUC_{iv} corrected for the difference in dose:

$$F = \frac{(AUC_{oral})\ (Dose_{iv})}{(AUC_{iv})\ (Dose_{oral})} \qquad (1)$$

Table 1 Clinical data on study patients with chronic obstructive pulmonary disease (COPD)

Patient	Age (years)	Weight (kg)	Diagnoses	Concurrent medications	Oral theophylline preparation		
					Name	Usual dose	Adjusted dose for study
1	61	75.4	COPD Glaucoma Osteoarthritis	Terbutaline Orciprenaline (inhaled) Beclomethasone (inhaled) Pilocarpine (eyedrops)	Aminophylline (Aminophyllin ®)	500 mg four times daily	400 mg every 8 h (340 mg)*
2	75	99.7	COPD Hypertension Obesity Osteoarthritis Constipation	Hydrochlorothiazide Dioctyl sodium sulphosuccinate Metamucil	Aminophylline (Aminophyllin ®)	200 mg three times daily	200 mg every 8 h (170 mg)
3	61	75.4	COPD Glaucoma	Orciprenaline (inhaled) Beclomethasone (inhaled) Pilocarpine (eyedrops)	Aminophylline (Aminophyllin ®)	200 mg four times daily	200 mg every 8 h (170 mg)
4	56	57.2	COPD Rheumatoid arthritis	Aspirin	Theophylline (Theo-dur®)	300 mg twice daily	300 mg every 12 h
5	78	59.0	COPD Osteoarthritis Diverticulosis	Orciprenaline (inhaled) Guaifenesin Dioctyl sodium sulphosuccinate Mylanta	Theophylline (Theo-dur ®)	200 mg twice daily	200 mg every 12 h
6	65	87.3	COPD Pansinusitis Hyperuricemia	Orciprenaline (inhaled) Beclomethasone (inhaled) Prednisone	Theophylline (Theo-dur ®)	300 mg twice daily	300 mg every 12 h
7	72	65.3	COPD Coronary artery disease Hyperuricaemia Osteoarthritis	Orciprenaline (inhaled)	Oxtriphylline (Choledyl ®)	200 mg four times daily	200 mg every 8 h (128 mg)
8	62	76.4	COPD (asthma) Hiatal hernia Cataracts	Cimetidine Orciprenaline (inhaled) Beclomethasone (inhaled) Prednisone	Theophylline (Theo-dur ®)	500 mg twice daily	500 mg every 12 h

*Values in parenthesis indicates equivalent dose of anhydrous theophylline.

The half-life was computed according to the relationship:

$$t_{1/2} = \frac{\ln 2}{\beta} \quad (2)$$

Total plasma clearance was calculated from the intravenous data according to the model-independent relationship:

$$CL = \frac{Dose_{iv}}{AUC_{iv}} \quad (3)$$

A noncompartmental estimate of the volume of distribution at steady-state (V_{ss}) was determined from the intravenous data (Benet & Galeazzi, 1979). The apparent volume of distribution (V_β) was also calculated from the ratio of CL and β.

Statistical analysis

Statistical analysis employed the Student's *t*-test for paired data (two-tailed probabilities), the Pearson product moment correlation and a one-factor analysis of variance with repeated measures ('two-way' ANOVA) for the daily plasma levels (Goldstein, 1964; Winer, 1971). Dunnett's test was used to compare daily trough plasma levels of theophylline with the value obtained in the first day of the study (Winer, 1971). Data in the figures and tables are expressed as the mean ± s.e. mean.

Results

In patients 1–7 the addition of cimetidine increased the mean trough plasma concentration of orally administered theophylline 34% (from 6.4 ± 0.8 μg/ml on Day 1 to 8.6 ± 1.0 μg/ml on Day 8, $P < 0.05$). In patient 8 who had been taking cimetidine 1200 mg/day regularly prior to entry into the study, the trough plasma theophylline level decreased from 19.3 to 13.3 μg/ml by the sixth day following withdrawal of cimetidine. The mean plasma concentration of theophylline (Table 2) was higher at the end of the cimetidine treatment period than during the control period ($P < 0.01$). The effect of cimetidine was maximal 72 h after starting the drug (Figure 1). In three patients a decline to pretreatment plasma levels occurred within 48 h after stopping cimetidine treatment. Analysis of variance confirmed a significant change in plasma levels over time in association with the administration of cimetidine. In patient 8 baseline trough plasma levels were achieved 96 h after withdrawal of cimetidine.

Plasma concentrations of oral theophylline and the intravenous theophylline tracer are shown for patients 1 and 5 in Figure 2. The value of the intravenous tracer for the estimation of pharmacokinetic parameters is emphasized by the relatively constant plasma levels of theophylline in the patient taking the extended release preparation. The clearance of theophylline (Table 3) as determined from the data for the labelled analogue was reduced in the presence of cimetidine from 3.88 ± 0.46 to 2.59 ± 0.33 l/h, a decrease of 33% ($P < 0.001$), without a change in V_{ss} or protein binding. Similarly, V_β was unchanged during the cimetidine treatment period (33.5 ± 2.1 l) compared to the control period (33.7 ± 1.5 l). The elimination rate constant (β) decreased 32% with a corresponding increase in half-life from 6.5 ± 0.6 to 9.6 ± 0.8 h ($P < 0.001$). Bioavailability calculations produced values exceeding 100% in 13 out of 16 observations. In addition, the apparent bioavailability of theophylline was 9% less with cimetidine treatment than during the control period ($P < 0.05$). Mean plasma concentrations of cimetidine (Table 2) ranged from 0.8 to 1.5 μg/ml, but did not correlate with the change in theophylline clearance. There was, however, a positive correlation ($r = 0.72$) between the control value of theophylline clearance and the change in clearance measured during cimetidine treatment.

Table 2 Mean plasma concentrations of theophylline and cimetidine

Patient	*Theophylline (μg/ml)* Control	Cimetidine	*Cimetidine (μg/ml)*
1	7.1	11.6	0.8
2	8.2	10.0	1.4
3	8.5	8.4	1.1
4	6.2	6.6	1.4
5	4.2	7.9	1.5
6	8.4	14.2	0.9
7	8.9	10.9	1.5
8	13.6	19.6	1.2
Mean	8.1	11.2	1.2
s.e. mean	0.95	4.16	0.10
Statistical significance*	$P < 0.01$		

*Paired Student's *t*-test (two-tailed probabilities).

Discussion

In these patients cimetidine markedly inhibited the clearance of theophylline and resulted in an increase in steady state mean plasma levels of nearly 40%. Since the volume of distribution was unchanged, this change in clearance (33% decrease) was reflected in a corresponding 32% decrease in the elimination rate constant, and an increase of 48% in half-life. These observations in patients under multiple dose conditions confirm and extend the previously reported studies in healthy volunteers who received

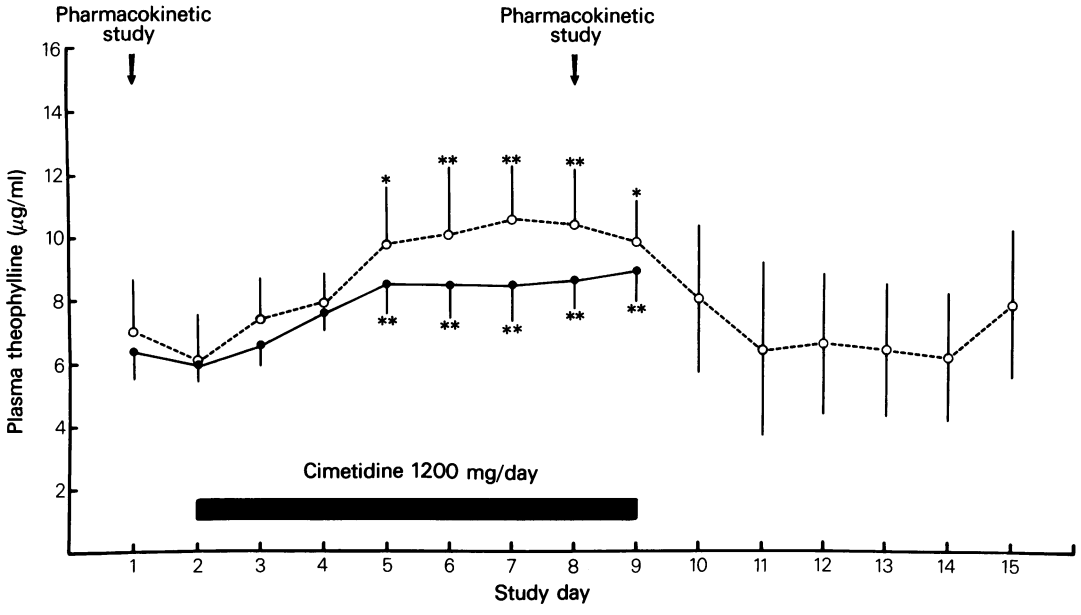

Figure 1 Plasma theophylline levels (mean ± s.e. mean) obtained at 09.00 h are shown for patients 1–7 (●). In association with cimetidine treatment there was a significant change in plasma levels with time ($F_{8,48} = 7.450$, $P < 0.001$). Values on days 5–9 were significantly different from the value on day 1 ($P < 0.01$). In addition, mean values for patients 5–7 (○) are shown separately to demonstrate the time course following the discontinuation of cimetidine. Associated with the addition of cimetidine to the regimen, there was also a significant change in plasma levels with time in this subset of patients ($F_{14,28} = 6.134$, $P < 0.001$) and again values on days 5–9 were significantly different from the values on day 1.
$^{*}P < 0.05$, $^{**}P < 0.01$ compared with value on day 1.

single oral or intravenous doses of theophylline before and during cimetidine treatment at daily doses of 1000–1200 mg for 3–8 days (Roberts *et al.*, 1981; Jackson *et al.*, 1981; Reitberg *et al.*, 1981). The average decrease in plasma clearance of theophylline ranged from 21 to 39% in these studies.

The trough plasma levels of theophylline reached an apparent plateau within 72 h after starting cimetidine (Figure 1). The mean half-life in these patients during cimetidine was 9.3 h. Although the prolonged time course after withdrawal of cimetidine in patient 8 is unexplained, in patients 5, 6 and 7 trough plasma levels reached a new plateau within 72 h after starting cimetidine and returned to control levels within 48 h after its withdrawal (Figure 1). In those three patients the mean half-life was 6.5 h before cimetidine and 10.5 h during cimetidine. Thus, the time course for the effect of cimetidine seems to be primarily determined by the half-life of theophylline under control and treatment conditions and suggests that the biochemical effects of cimetidine are rapidly reversible.

Although the exact mechanism of its inhibitory effect on microsomal drug metabolism has not been fully characterized and *in vitro* studies with theophylline are not available, cimetidine undoubtedly inhibits the clearance of theophylline by an effect on hepatic microsomal drug oxidation (Pelkonen & Puurunen, 1980). Since 10% or less of theophylline is excreted unchanged by the kidney, inhibition of renal excretion could not account for the large changes that we and others have observed. The imidazole ring in cimetidine appears to be critical for its inhibitory properties. (Wilkinson *et al.*, 1972), but whether its effects are specific to one or more forms of cytochrome P-450 and P-448 is uncertain.

The data on the bioavailability of theophylline were unexpected. Except for selected formulations several studies have shown that bioavailability is virtually complete after a single oral dose compared to a single intravenous dose (Fixley *et al.*, 1977; Weinberger *et al.*, 1978; Dederich *et al.*, 1981), but studies under steady state conditions have not been performed. It should be noted that values exceeding the administered dose have been reported (Fixley *et al.*, 1977; Weinberger *et al.*, 1978) and that the intrasubject variation in absorption of sustained release preparations of theophylline may be quite marked (Dederich *et al.*, 1981). Since the calculation of bioavailability used in this study assumes a constant AUC for each dose interval, such variation in absorption might account for our results. For the same

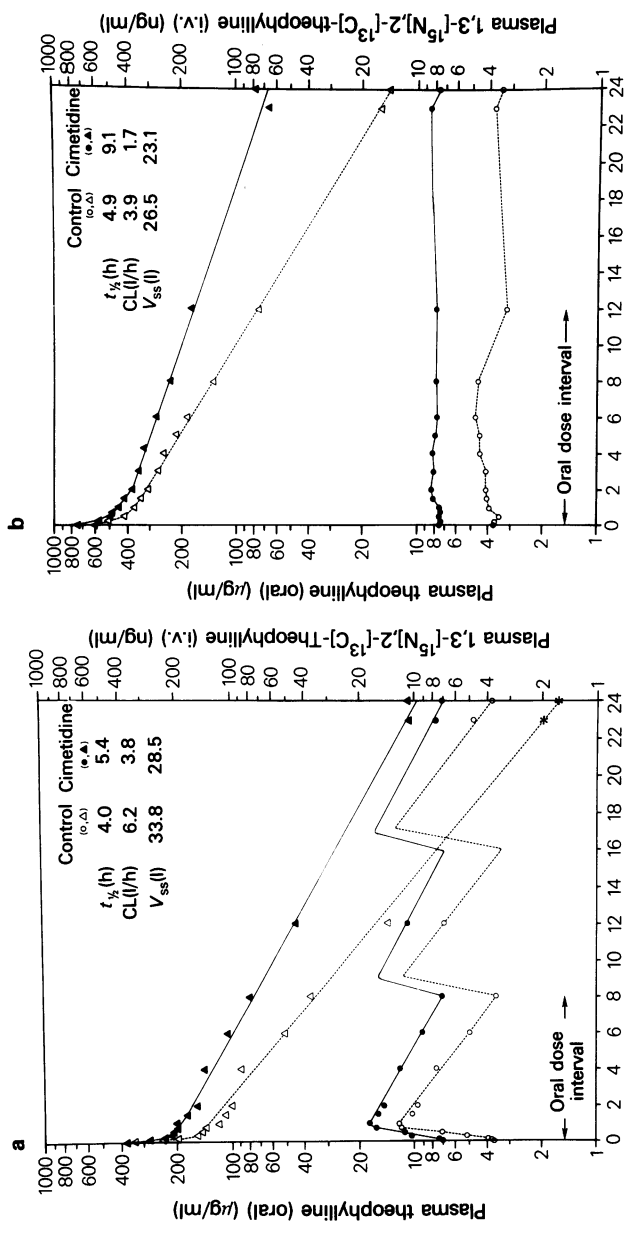

Figure 2 Plasma concentration-time profile curves for theophylline and the [^{15}N], [^{13}C]-labelled stable isotope of theotheophylline (1,3-[^{15}N],2-[^{13}C]-theophylline) in patient 1 (**a**) and patient 5 (**b**). Concentrations of the unlabelled compound are indicated by the circles (○, ●) and concentrations of the labelled compounds are indicated by the triangles (△, ▲). Open symbols (○, △) indicate values obtained before cimetidine and closed symbols (●, ▲) indicate values obtained on the seventh day of concurrent treatment with cimetidine. Patient 1 was taking aminophylline 400 mg every 8 h and patient 5 was taking Theo-dur® 200 mg every 12 h. In patient 1, values of the theophylline analogue at 23 and 24 h (*) were below the detection limits of the assay.

Table 3 Effect of cimetidine on pharmacokinetic parameters of theophylline disposition in plasma

Patient	Elimination rate constant β (h^{-1})		Half-life (h)		Volume of distribution at steady state (l)		Clearance (l/h)		Bioavailability		Unbound fraction	
	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine
1	0.175	0.129	4.0	5.4	33.8	28.5	6.16	3.77	1.02	1.03	0.70	0.72
2	0.090	0.059	7.7	11.7	35.0	38.4	3.13	2.26	1.21	1.06	0.69	0.70
3	0.087	0.071	8.0	9.8	31.1	32.1	2.80	2.35	1.12	0.93	0.75	0.63
4	0.146	0.103	4.7	6.7	37.4	37.2	5.53	4.28	1.36	1.13	0.72	0.71
5	0.142	0.076	4.9	9.1	26.5	23.1	3.92	1.72	0.98	0.84	0.58	0.60
6	0.107	0.064	6.5	10.8	33.5	32.0	3.53	2.16	1.18	1.23	0.69	0.74
7	0.087	0.59	8.0	11.7	26.6	28.6	2.50	1.72	1.39	1.17	—	—
8	0.087	0.062	8.0	11.2	39.0	40.3	3.43	2.46	1.12	1.12	0.65	0.72
Mean	0.115	0.078	6.5	9.6	32.9	32.5	3.88	2.59	1.17	1.06	0.68	0.69
s.e. mean	0.0122	0.0089	0.60	0.84	1.62	2.06	0.461	0.331	0.052	0.045	0.021	0.020
Statistical significance*	$P < 0.001$		$P < 0.001$		NS		$P < 0.001$		$P < 0.05$		NS	

*Paired Student's *t*-test (two-tailed probabilities).

reason it is interesting to consider the possibility that diurnal variation in drug disposition may complicate the use of this equation during multiple dose administration. Decourt *et al.* (1982) have recently observed differences in the pharmacokinetics of theophylline depending upon the time of dose administration. Although not statistically significant, the AUC was greater and the total plasma clearance lower when the drug was given at 09.00 h compared to 11.00 h. Simulations using the mean data of Decourt's study (1982) demonstrate an effect of diurnal variation on bioavailability estimates (unpublished observations), which is consistent with the observations in the present study. The apparent small reduction in bioavailability of theophylline with cimetidine was also unexpected and the reasons for this change are not obvious. Although small in magnitude and of no clinical importance, these two findings related to bioavailability are interesting and await confirmation in subsequent studies.

Objective measurements of airflow obstruction were not obtained. It is interesting, however, that following slight reduction of his aminophylline dose prior to the study, patient 1 noted increased dyspnea which resolved after the addition of cimetidine. Audible wheezes on physical examination were also markedly reduced. The only other patient with a significant bronchospastic component to his disease was patient 8, but he did not notice a difference between the two treatment periods. His plasma theophylline levels were well within the therapeutic range during both treatment periods (Table 2).

Because of its potent effects on theophylline metabolism, the clinician must be alert to possible toxicity when cimetidine is co-administered with theophylline. There are now several reports of patients who developed potentially toxic plasma levels of theophylline following the addition of cimetidine to their regimen (Weinberger *et al.*, 1981; Campbell *et al.*, 1981; Bauman *et al.*, 1982). The results of this study indicate that, following the addition of cimetidine, theophylline doses should be reduced by approximately one-third and plasma levels obtained in 3 days to permit further individualization of dosage. After stopping cimetidine the previous dose can be resumed after 2 or 3 days. Alternatively, ranitidine, which does not inhibit theophylline metabolism (Breen *et al.*, 1982) may be preferable in patients who require treatment with an H_2-receptor antagonist.

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