Effects of cimetidine on caffeine disposition in smokers and nonsmokers

The absorption, distribution, and elimination of caffeine, 2 mg/kg by mouth, were evaluated in six smokers and six nonsmokers before and on the fourth day of administration of cimetidine, 300 mg by mouth every 6 hr. Caffeine absorption, assessed by the maximal serum caffeine concentration (C_{max}) and the time to reach C_{max} (t_{max}), was very rapid relative to elimination. The total body clearance (TBC) of caffeine was higher (2.49 ± 0.35 and 1.59 ± 0.19 ml/kg/min, $P < 0.05$) and the elimination half-life (t½) shorter (190 ± 15 and 276 ± 30 min, $P < 0.05$) in smokers than nonsmokers, but C_{max}, t_{max}, and the apparent volume of distribution (Vd,app) did not differ ($P > 0.05$). Cimetidine decreased the TBC of caffeine by 31% (to 1.73 ± 0.28 ml/kg/min, $P < 0.05$) and by 42% (to 0.92 ± 0.11 ml/kg/min, $P < 0.01$) in smokers and nonsmokers. The increases in t½ were 45% (to 276 ± 25 min, $P < 0.05$) and 96% (to 542 ± 123 min, $P < 0.05$). C_{max}, t_{max}, and Vd,app were unaffected by cimetidine. Caffeine induced similar slight increases in blood pressure and pulse rate in smokers and nonsmokers both before and during cimetidine dosing.

David C. May, M.D., Ph.D.,* Charles H. Jarboe, Ph.D., Adrian B. VanBakel, M.D., and Walter M. Williams, M.D., Ph.D. *Louisville, Ky.*

Department of Pharmacology and Toxicology and Department of Medicine, University of Louisville School of Medicine

Cimetidine is used in the treatment of duodenal ulcer, pathologic hypersecretory states such as the Zollinger-Ellison syndrome,[11] and many other conditions.[6, 27] In 1980 it was the fifteenth most frequently prescribed drug in the United States.[32] Cimetidine impairs the elimination of several drugs, including antipyrine,[25, 28] chlordiazepoxide,[9] diazepam,[18] propranolol,[10] warfarin,[28, 29] and theophylline,[16, 25] resulting in cumulation to toxic blood levels in some cases.[5] It is not known whether elimination of other methylxanthines is similarly affected by cimetidine. In the rat ^{14}C-caffeine demethylation, as assessed by expired ^{14}C-carbon dioxide measurements, was inhibited by large doses of cimetidine.[8] Such interaction, if it were to occur in man, would be of clinical importance because of the widespread use of both drugs and the potential cardiovascular[26] and nervous system toxicity of caffeine.[23] The present investigation was therefore undertaken to determine the effects of cimetidine in the usual clinical

Supported, in part, by the Therapeutics and Toxicology Laboratory, University of Louisville.

Presented, in part, at the 66th Annual Meeting of the Federation of American Societies for Experimental Biology, New Orleans, April, 1982.

Received for publication Dec. 10, 1981.

Accepted for publication Jan. 8, 1982.

Reprint requests to: W. M. Williams, Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY 40292.

*Present address: Department of Internal Medicine, University of Texas Health Science Center at Dallas, Dallas, TX 75235.

0009-9236/82/050656+06$00.60/0

dosage on the absorption, distribution, and elimination of caffeine. Studies were performed on both cigarette smokers and nonsmokers because of differences in caffeine elimination in the two groups.[20]

Methods

Our subjects were 12 healthy men between the ages of 21 and 50 yr. Six subjects were smokers who had consumed 20 or more cigarettes daily for at least 2 yr and six were nonsmokers. No subject had taken any medication within 2 wk of the study. The subjects were instructed to abstain from methylxanthine-containing food and beverages for 24 hr before and during each determination of caffeine kinetics.

Caffeine and sodium benzoate injection was diluted with water to a caffeine concentration of 10 mg/ml for use in the study. After an overnight fast, 2 mg/kg body weight caffeine was taken by mouth; this was followed by 150 ml of water. Blood samples (1 ml) were drawn, through an indwelling intravenous catheter, into anticoagulant-free tubes immediately before and at 10, 15, 20, 25, 30, 35, 40, and 50 min and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr after caffeine. The catheter was filled with a sterile heparin-containing saline solution between blood collections. Blood pressure and pulse rate were recorded before caffeine, hourly for the first 4 hr after caffeine, and every 2 hr thereafter. Six subjects remained at rest in a sitting position throughout the study; the other six performed normal work, interrupted only by the blood sampling and hemodynamic measurements. Smokers had free access to cigarettes and all subjects had meals at approximately 5 and 11 hr after caffeine dosing. Clotted blood samples were centrifuged and the serum stored at 4° until caffeine analysis, which was within a week. (It has been determined that caffeine is stable under these conditions.) A second caffeine kinetic determination was performed by the same procedure on the fourth day of cimetidine dosing (300 mg by mouth every 6 hr).

The analytic method used to quantify caffeine was based on a modification of the high-pressure liquid chromatographic method of Thompson et al.[31] The analyses were performed with a duPont Model 848 liquid chromatograph

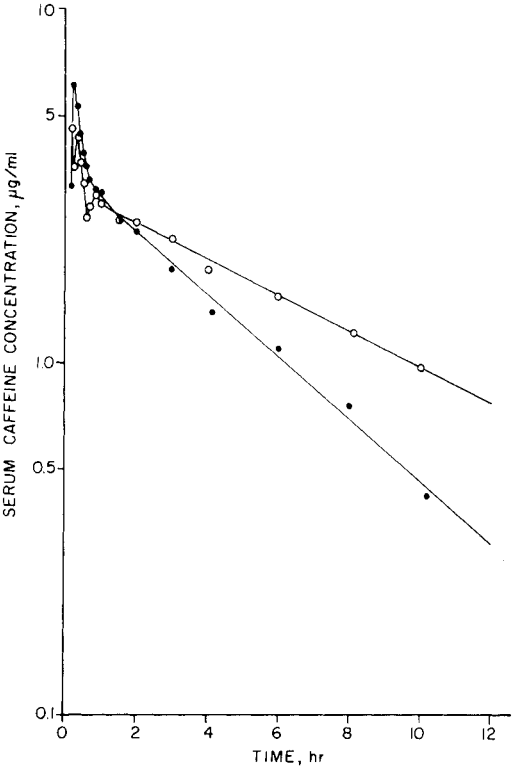

Fig. 1. Serum caffeine concentrations in subject 1 before (●) and during (○) cimetidine dosing.

equipped with a 10-μl rotating valve sample loop injector (Rheodyne), a 100 cm × 2.1 mm (inner diameter) cation-exchange column (Zipax^R SCX, duPont), and a variable wavelength detector set at 273 nm. The mobile phase, an aqueous (Burdick and Jackson) solution of HNO_3 (1.0 mM) and $NaClO_4$ (0.5 mM), was delivered at 2000 psi and ambient temperature. This chromatographic system will cleanly resolve a mixture of dyphylline, theophylline, theobromine, β-hydroxypropyltheophylline, and caffeine. Samples were prepared by organic solvent extraction. To 200 μl of serum was added 2.0 ml of isopropanol/chloroform (1:20) containing β-hydroxypropyltheophylline internal standard. The sample was extracted for 60 sec by vortex and the organic phase was separated by filtration through Whatman PS-1 paper. The organic phase was evaporated to dryness at 50° in a dry air stream. The residue was redissolved in 100 μl of mobile phase and an aliquot was injected onto the chromato-

Table I. *Effect of cimetidine on caffeine disposition in smokers*

Subject No.	C_{max} (μg/ml)		t_{max} (min)		Vd, app (ml/kg)		t½ (min)		TBC (ml/kg/min)	
	Control	Cimet.	Control	Cimet.	Control	Cimet.	Control	Cimet.	Control	Cimet.
1	4.66	5.00	15	12	597	622	208	356	1.97	1.18
2	2.32	2.42	30	50	804	889	173	227	3.22	2.76
3	2.58	4.23	30	18	726	714	131	246	3.84	2.00
4	4.66	6.60	20	15	573	572	239	240	1.66	1.66
5	3.30	4.10	48	22	623	653	191	233	2.24	1.96
6	—	—	—	—	561	411	196	354	1.98	0.80
Mean	3.50	4.47	29	23	647	644	190	276	2.49	1.73
(±SEM)	(0.50)	(0.68)	(6)	(7)	(40)	(65)	(15)	(25)	(0.35)	(0.28)
P	NS		NS		NS		<0.05		<0.05	

NS = not significant (P > 0.05).

graphic column. The peak height ratio of caffeine to internal standard was then calculated, and the sample caffeine concentration determined from a standard curve. Standard curves were constructed daily using caffeine solutions made in serum.

The caffeine elimination rate constant (k) and half-life (t½) were determined by linear regression analysis of the logarithm serum caffeine concentration-time relationship over the 2- to 12-hr period. Total body clearance (TBC) of caffeine was calculated as dose divided by area under the serum caffeine concentration-time curve (AUC). AUC from t = 0 to t = 12 hr was calculated by means of the trapezoidal rule and AUC from t = 12 hr to t = ∞ was estimated as the concentration at 12 hr ÷ k.[12] The apparent volume of distribution (Vd,app) was calculated as TBC ÷ k. For two subjects in whom complete absorption-phase blood samples were not obtained, Vd,app was calculated as dose ÷ C_0, where C_0 is the serum caffeine concentration extrapolated to time zero, and TBC was calculated as k × Vd,app. Mean TBC and Vd,app values obtained by this method were within 10% of those obtained by the AUC method; the latter are reported in the results. These calculations are based on the assumption of rapid and complete gastrointestinal absorption of caffeine, which is supported by experimental evidence.[2] The maximum serum caffeine concentration (C_{max}) and time to reach C_{max} (t_{max}) were determined by visual inspection of the logarithm serum concentration-time curve.

For statistical comparisons between the smoker and nonsmoker groups, Student's t test for independent samples, using a pooled estimate of common variance, was employed. Student's t test for paired samples was used for intragroup comparisons of control and postcimetidine values.[30]

Results

The logarithm of serum caffeine concentration-time profile for a typical subject is shown in Fig. 1 and the kinetic values for caffeine disposition in each subject are summarized in Tables I and II. In each subject the serum caffeine concentration increased within minutes to a maximal value, then slowly declined over a period of several hours, indicating that absorption was very rapid relative to elimination. Serum disappearance of caffeine followed apparent first-order kinetics over the concentration range employed.

The TBC of caffeine was higher (2.49 ± 0.35 and 1.59 ± 0.19 ml/kg/min, $P < 0.05$) and the elimination t½ shorter (190 ± 15 and 276 ± 30 min, $P < 0.05$) in smokers than in nonsmokers. There was, however, some overlap of these values in the two groups. There was no difference between the groups ($P > 0.05$) in Vd,app, C_{max}, or t_{max}.

The administration of cimetidine resulted in a slowing of caffeine elimination in 11 of the 12 subjects. Caffeine TBC fell by 31% (to 1.73 ± 0.28 ml/kg/min, $P < 0.05$) and 42% (to 0.92 ± 0.11 ml/kg/min, $P < 0.01$) in smokers and nonsmokers. The increases in elimination

Table II. *Effect of cimetidine on caffeine disposition in nonsmokers*

Subject No.	C_{max} (μg/ml)		t_{max} (min)		Vd, app (ml/kg)		t½ (min)		TBC (ml/kg/min)	
	Control	Cimet.	Control	Cimet.	Control	Cimet.	Control	Cimet.	Control	Cimet.
7	3.75	3.80	35	30	680	682	255	454	1.84	1.02
8	3.50	4.60	75	18	530	496	251	428	1.48	0.79
9	3.50	2.60	30	30	514	792	423	1124	0.82	0.49
10	3.05	3.70	48	25	628	458	221	240	1.95	1.33
11	2.70	3.15	43	28	750	620	246	492	2.10	0.87
12	—	—	—	—	506	796	259	514	1.35	1.07
Mean	3.30	3.57	46	26	601	641	276	542	1.59	0.92
(±SEM)	(0.19)	(0.34)	(8)	(2)	(41)	(59)	(30)	(123)	(0.19)	(0.11)
P	NS		NS		NS		<0.05		<0.01	

NS = not significant (P > 0.05).

t½ were 45% (to 276 ± 25 min, P < 0.05) and 96% (to 542 ± 123 min, P < 0.05). There was no change (P > 0.05) in Vd,app, C_{max}, or t_{max} in cimetidine-treated smokers or nonsmokers.

In the six subjects (three smokers and three nonsmokers) who remained at rest throughout the period of blood sampling, caffeine consistently produced slight rises in blood pressure and pulse rate (Fig. 2), which reached maximal values within 1 to 4 hr of caffeine dosing. Only the increase in systolic pressure was significant in smokers and nonsmokers, however. At 8 hr, blood pressure and pulse had nearly returned to control levels. The pattern of hemodynamic changes was not appreciably changed during cimetidine dosing.

Discussion

Our data demonstrate that caffeine elimination is stimulated by cigarette smoking and inhibited by cimetidine. These effects presumably reflect altered caffeine metabolism since the drug is eliminated almost entirely by this mechanism.[2, 7]

The TBC of caffeine was about 60% greater in smokers than nonsmokers, whereas absorption (C_{max} and t_{max}) and distribution were similar in the two groups. These findings, based on serum caffeine measurements, are in close agreement with those of Parsons and Neims[20] who found enhanced salivary clearance of caffeine in smokers. The actual caffeine clearance values from the two studies vary by less than 10%. Smoking has a similar stimulatory effect on the elimination of theophylline.[15, 17, 21] This effect of smoking has been attributed to enhanced activity of microsomal aryl hydrocarbon hydroxylase (AHH), which utilizes cytochrome P-448 as the terminal oxidase. In the rat,[1] 3-methylcholanthrene, an inducer of AHH, is a much more effective stimulant of caffeine metabolism than is phenobarbital, an inducer of microsomal cytochrome P-450 systems.[4]

Cimetidine in the usual clinical dosage for 3 days induced a 30% to 40% reduction in caffeine TBC in both smokers and nonsmokers. The absolute or percent decrease in TBC did not correlate with the initial value, making it impossible to predict the degree of impairment in a given patient. There was, however, a direct linear correlation between the prolongation in elimination t½ (r = 0.86, P < 0.001), or percent prolongation (r = 0.60, P < 0.05), and the initial t½, raising the possibility that the greatest impairment of caffeine elimination is in subjects whose elimination is slow initially. It is not known whether treatment for a longer duration or at higher dosage would further reduce caffeine elimination, although the latter is suggested by the demonstration of dose-related decreases in ^{14}C-carbon dioxide expiration after ^{14}C-caffeine dosing in cimetidine-treated rats.

Cimetidine can decrease drug elimination by at least two different actions: (1) the direct inhibition of microsomal enzyme metabolism demonstrated by in vitro binding and in metabolic studies[22, 24] and (2) the reduction of hepatic blood flow, as shown by cimetidine-induced decreases in indocyanine green and propranolol clearance.[10] The relative contribu-

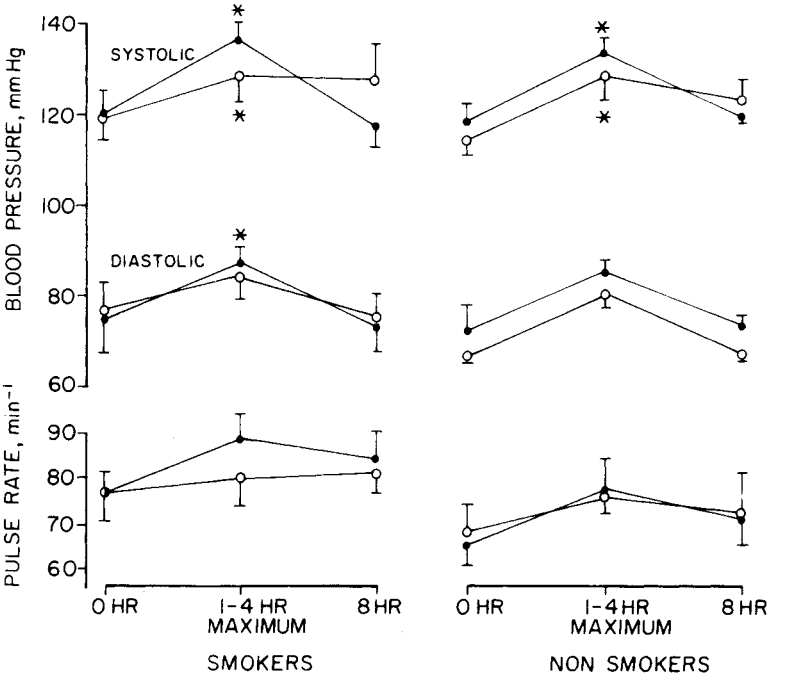

Fig. 2. Caffeine-associated changes in blood pressure and pulse rate before (•) and during (○) cimetidine. Data are plotted as mean ± SEM (n = 3). *P < 0.05 with respect to precaffeine value.

tions of these mechanisms to the impairment of caffeine elimination are uncertain, but since the clearance of methylxanthines is not highly flow dependent,[3] one would predict that the decrease in clearance is due predominantly to a cimetidine action at the microsomal level. Other types of kinetic drug interactions involving cimetidine, such as altered gastrointestinal absorption due to the increase in gastric pH caused by inhibition of gastric acid secretion,[11] are theoretically possible. For weak organic acids, this pH change would promote ionization and could result in impaired absorption, whereas for weak organic bases ionization would be retarded and absorption could be enhanced.[13, 14] However, an increase in pH should not alter the absorption of weak bases, such as caffeine, that undergo rapid and complete absorption under normal physiologic conditions.[2] This is supported by the findings that the C_{max} and t_{max} values for caffeine were not changed by treatment with cimetidine. Another possible interaction, based on the renal tubular secretion of cimetidine,[19] is the impaired urinary excretion of other organic bases. Again, such an interaction is unlikely with caffeine, since only about 1% of the dose is excreted unchanged in the urine.[2, 7]

Although the caffeine interactions reported here must be extremely common, their precise pharmacologic significance is uncertain, largely because the diverse long- and short-term effects of caffeine and its numerous metabolites are not completely understood. Parsons and Neims[20] suggested that faster elimination of caffeine in smokers leads to increased coffee consumption, but in the present study there was no correlation between coffee consumption and either smoking or caffeine clearance.

A single morning dose of caffeine, equivalent to about two cups of brewed coffee,[23] induced similar modest increases in blood pressure and pulse rate in smokers and nonsmokers both before and during cimetidine dosing and these were consistent with C_{max} values. However, in the event of multiple dosing, as would occur in persons drinking coffee throughout the day, greater than usual cumulation of caffeine would be expected, possibly resulting in cardiovascular or nervous system toxicity.

References

1. Aldridge A, Parsons WD, Neims AH: Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. Life Sci **21:**967-974, 1977.
2. Axelrod J, Reichenthal J: The fate of caffeine in man and a method for its estimation in biological material. J Pharmacol Exp Ther **107:**519-523, 1952.
3. Blaschke TF: Protein binding and kinetics of drugs in liver diseases. Clin Pharmacokinet **2:**32-44, 1977.
4. Bresnick E: Induction of the enzymes of detoxication, *in* Jakoby WB, editor: Enzymatic basis of detoxication. New York, 1980, Academic Press, Inc., vol. I, pp. 69-83.
5. Campbell MA, Plachetka JR, Jackson JE, Moon JF, Finley PR: Cimetidine decreases theophylline clearance. Ann Intern Med **95:**68-69, 1981.
6. Cocco AE, Cocco DV: A survey of cimetidine prescribing. N Engl J Med **304:**1281, 1981.
7. Cornish HH, Christman AA: A study of the metabolism of theobromine, theophylline and caffeine in man. J Biol Chem **228:**315-323, 1957.
8. Desmond PV, Patwardhan R, Parker R, Schenker S, Speeg KV Jr: Effect of cimetidine and other antihistaminics on the elimination of aminopyrine, phenacetin and caffeine. Life Sci **26:** 1261-1268, 1980.
9. Desmond PV, Patwardhan RV, Schenker S, Speeg KV Jr: Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. Ann Intern Med **93:**266-268, 1980.
10. Feely J, Wilkinson GR, Wood AJJ: Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med **304:**692-695, 1981.
11. Finkelstein W, Isselbacher KJ: Cimetidine. N Engl J Med **299:**992-996, 1978.
12. Gibaldi M, Perrier D: Pharmacokinetics. New York, 1975, Marcel Dekker, Inc., pp. 293-296.
13. Hogben CAM, Schanker LS, Tocco DJ, Brodie BB: Absorption of drugs from the stomach. II. The human. J Pharmacol Exp Ther **120:**540-545, 1957.
14. Hogben CAM, Tocco DJ, Brodie BB, Schanker LS: On the mechanism of intestinal absorption of drugs. J Pharmacol Exp Ther **125:**275-282, 1959.
15. Hunt SN, Jusko WJ, Yurchak AM: Effect of smoking on theophylline disposition. CLIN PHARMACOL THER **19:**546-551, 1976.
16. Jackson JE, Powell JR, Wandell M, Bentley J, Dorr R: Cimetidine decreases theophylline clearance. Am Rev Respir Dis **123:**615-617, 1981.
17. Jenne J, Nagasawa H, McMugh R, MacDonald F, Wyse E: Decreased theophylline half-life in cigarette smokers. Life Sci **17:**195-198, 1975.
18. Klotz U, Reimann I: Delayed clearance of diazepam due to cimetidine. N Engl J Med **302:** 1012-1014, 1980.
19. McKinney TD, Myers P, Speeg KV Jr: Cimetidine secretion by rabbit renal tubules in vitro. Am J Physiol **241:**F69-F76, 1981.
20. Parsons WD, Neims AH: Effect of smoking on caffeine clearance. CLIN PHARMACOL THER **24:** 40-45, 1978.
21. Powell JR, Thiercelin J, Vozeh S, Sansom L, Riegelman S: The influence of cigarette smoking and sex on theophylline disposition. Am Rev Respir Dis **116:**17-23, 1977.
22. Puurunen J, Pelkonen O: Cimetidine inhibits microsomal drug metabolism in the rat. Eur J Pharmacol **55:**335-336, 1979.
23. Rall TW: Central nervous system stimulants: The xanthines, *in* Gilman AG, Goodman LS, Gilman A, editors: The pharmacological basis of therapeutics, ed. 6. New York, 1980, Macmillan, Inc., pp. 592-607.
24. Rendić S, Šunjić V, Toso R, Kajfež F, Ruf HH: Interaction of cimetidine with liver microsomes. Xenobiotica **9:**555-564, 1979.
25. Roberts RK, Grice J, Wood L, Petroff V, McGuffie C: Cimetidine impairs the elimination of theophylline and antipyrine. Gastroenterology **81:**19-21, 1981.
26. Robertson D, Frolich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA: Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N Engl J Med **298:**181-186, 1978.
27. Schade RR, Donaldson RM Jr: How physicians use cimetidine: A survey of hospitalized patients and published cases. N Engl J Med **304:**1281-1284, 1981.
28. Serlin MJ, Sibeon RG, Mossman S, Breckenridge AM, Williams JRB, Atwood JL, Willougby JMT: Cimetidine: Interaction with oral anticoagulants in man. Lancet **2:**317-319, 1979.
29. Silver BA, Bell WR: Cimetidine potentiation of the hypoprothrombinemic effect of warfarin. Ann Intern Med **90:**348-349, 1979.
30. Snedecor GW, Cochran WG: Statistical methods, ed. 6. Ames, 1967, The Iowa State University Press, pp. 91-119.
31. Thompson RD, Nagasawa HT, Jenne JW: Determination of theophylline and its metabolites in human urine and serum by high-pressure liquid chromatography. J Lab Clin Med **84:**584-593, 1974.
32. 1980: Top 200 drugs. Pharmacy Times, April 1981, pp. 17-25.