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Interaction between Oral Ciprofloxacin and Caffeine in Normal Volunteers

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The influence of multiple doses of ciprofloxacin on the disposition of caffeine and its major metabolite, paraxanthine, was investigated in healthy volunteers. Ten xanthine-free, fasting males were given 100 mg of caffeine orally 24 h before being given ciprofloxacin and again with the third dose of ciprofloxacin (750 mg administered every 12 h). Blood samples were serially collected after both doses of caffeine and after the first and last doses of ciprofloxacin. Ciprofloxacin significantly increased the half-life of caffeine (from 5.2 ± 1.2 to 8.2 ± 2.5 h) and the area under the caffeine concentration-time curve (from 16.3 ± 6.6 to 25.9 ± 7.8 μg · h/ml) while decreasing the total body clearance (from 106 ± 41.6 to 58.2 ± 28.8 ml/min per 1.73 m^2). In addition, the rate of conversion of caffeine to paraxanthine was significantly delayed. There was no significant linear correlation between the urinary recovery of oxociprofloxacin at 0 to 12 h and the change in the area under the caffeine concentration-time curve. There was also a small but statistically significant increase in the area under the ciprofloxacin concentration-time curve during simultaneous administration of caffeine. We concluded that ciprofloxacin causes a significant increase in the half-life of caffeine and in the area under the caffeine concentration-time curve by reducing total body clearance. This interaction is due at least in part to a delay in the conversion of caffeine to paraxanthine. The clinical significance of these observations remains to be determined. Lastly, caffeine may alter the kinetics of ciprofloxacin, a possibility which should be more fully explored.

Several of the new fluoroquinolones, including ciprofloxacin, have been reported to interfere with the clearance of theophylline, leading to elevated concentrations of theophylline in serum and central nervous system (CNS) toxicity (2, 14, 16, 19, 22; F. P. V. Maesen, J. P. Teengs, C. Baur, and B. I. Davies, Letter, Lancet ii:530, 1984). Caffeine, a methylxanthine, is similar in structure to theophylline and is widely consumed in the form of caffeinated beverages. Both compounds induce the same concentration-related symptoms of CNS toxicity, which include nervousness, insomnia, headache, lightheadedness, dizziness, tremors, and in some cases, convulsions (17). Since caffeine and ciprofloxacin are likely to be used concomitantly in many patients, the major purpose of this study was to determine whether multiple oral doses of ciprofloxacin alter the disposition of caffeine and its major metabolite, paraxanthine, in normal volunteers. A secondary aim was to determine whether caffeine significantly alters the pharmacokinetic profile of ciprofloxacin.

(Results of this study were presented in part at the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, N.Y., 4 to 7 October 1987.)

MATERIALS AND METHODS

Volunteers. Ten healthy, nonsmoking, male volunteers with normal renal and hepatic functions participated in this investigation. Subjects were admitted to the Antibiotic Research Unit of the Biopharmaceutics and Pharmacokinetics Center, School of Pharmacy, after internal review board approval and informed written consent were obtained. The mean ± standard deviation age, weight, and serum creatinine of the subjects were 26.7 ± 1.6 years, 76.3 ± 8.6 kg, and 1.0 ± 0.1 mg/dl, respectively. Exclusion criteria included prior hypersensitivity to any drug and the use of medication for chronic illness. Each volunteer was given a list of xanthine-containing products and instructed to abstain from all such items, alcohol, and all other drugs beginning 3.5 days prior to participation in the study. A xanthine-free diet was maintained throughout the study. Subjects fasted for 12 h before and 4 h after both doses of caffeine and after the first and last doses of ciprofloxacin.

Drug administration and sample collection. On the morning of study day 1, subjects received 100 mg of caffeine (No-Doz tablet, lot 6F114; Bristol-Myers Co., New York, N.Y.) with 180 ml of water. Blood samples were collected before drug administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, and 24 h after dosing. Twenty-four hours after caffeine dose 1 and following an overnight fast, subjects were started on oral ciprofloxacin (Cipro, lot MK-13-69; Miles Laboratories, Inc., West Haven, Conn.) at a dosage of one 750-mg tablet every 12 h, for a total of three doses. Each dose was administered with 180 ml of water. Serial blood samples were collected over the first dosing interval at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 h following ciprofloxacin administration. A second 100-mg dose of caffeine was given simultaneously with the last dose of ciprofloxacin, and blood for measurement of caffeine, paraxanthine, and ciprofloxacin concentrations was obtained over the ensuing 24 h as described above. Specimens were allowed to clot for approximately 45 min before centrifugation. Serum was separated and stored at −70°C until analysis. Urine for measurement of oxociprofloxacin concentration was collected for a 12-h period (after a predose void) following coadministration of ciprofloxacin and caffeine.

Caffeine and paraxanthine assay. All samples were assayed for caffeine and paraxanthine concentrations within 2 weeks of collection by a reversed-phase, high-performance liquid

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TABLE 1. Pharmacokinetic parameters for caffeine before and after three doses of ciprofloxacin (750 mg every 12 h)

Parameter[a]	Mean ± SD			P
	Before ciprofloxacin	After ciprofloxacin	% Change[b]	
C_{max} (μg/ml)	2.1 ± 0.5	2.3 ± 0.4	15 ± 37	NS[c]
T_{max} (h)	1.2 ± 0.4	1.4 ± 0.6	25 ± 66	NS
k_{el} (h^{-1})	0.139 ± 0.026	0.095 ± 0.037	−32 ± 23	0.0003
$t_{1/2}$ (h)	5.2 ± 1.2	8.2 ± 2.5	61 ± 47	0.004
V (liters/kg)	0.67 ± 0.19	0.62 ± 0.16	−2 ± 26	NS
$AUC_{0-\infty}$ (μg · h/ml)	16.3 ± 6.6	25.9 ± 7.8	67 ± 36	<0.001
TBC (ml/min per 1.73 m^2)	106 ± 41.6	58.2 ± 28.8	−38 ± 12	<0.001

[a] C_{max}, Maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; V, volume of distribution; TBC, total body clearance.
[b] Calculated as the mean percent change from data for individual subjects (see text).
[c] NS, Not statistically significant ($P > 0.05$).

TABLE 2. Pharmacokinetic parameters for paraxanthine before and after three doses of ciprofloxacin (750 mg every 12 h)

Parameter[a]	Mean ± SD			P
	Before ciprofloxacin	After ciprofloxacin	% Change[b]	
C_{max} (μg/ml)	0.6 ± 0.2	0.6 ± 0.2	−10 ± 21	NS[c]
T_{max} (h)	6.2 ± 1.7	10.4 ± 2.7	81 ± 67	0.002
AUC_{0-10} (μg · h/ml)	4.6 ± 1.3	2.5 ± 0.8	−43 ± 17	<0.001

[a] C_{max}, Maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum.
[b] Calculated as the mean percent change from data for individual subjects (see text).
[c] NS, Not statistically significant ($P > 0.05$).

chromatographic (HPLC) technique developed in our laboratory. A filtered, degassed mobile phase containing HPLC-grade methanol (Fisher Scientific Co., Medford, Mass.) and deionized, double-distilled water (25:75 [vol/vol]) was pumped through a 5-μm, reversed-phase C_{18} column (150 by 4.6 mm) (Econosphere; Alltech Associates, Inc., Applied Science Div., State College, Pa.) at a flow rate of 1 ml/min by an HPLC pump (model 302; Gilson Medical Electronics, Middleton, Wis.). The effluent was monitored at a UV detector (HM Holochrome; Gilson) set at 273 nm with a sensitivity of 0.02 absorbance unit (full scale). The signal was recorded, and the peak area ratios of caffeine and paraxanthine to an internal standard (β-hydroxyethyltheophylline) were determined with a data integrator (Sigma 10; The Perkin-Elmer Corp., Norwalk, Conn.). These ratios were linearly correlated with drug concentrations in known standards.

To 500 μl of a known standard, control, or patient specimen, 500 μl of potassium phosphate buffer solution (pH 4.5) containing 5.0 μg of the internal standard β-hydroxyethyltheophylline per ml was added; the mixture was vortexed for 15 s. To this solution, 6 ml of a methylene chloride–2-propanol mixture (4:1 [vol/vol]) was added to extract the compounds of interest. This mixture was vortexed for 30 s and then centrifuged for 12 min at 3,000 × g. The lower organic layer was transferred to a clean glass culture tube and evaporated to dryness under nitrogen. The residue was reconstituted with 250 μl of the mobile phase, and 20 μl was injected onto the column. The retention times for paraxanthine, β-hydroxyethyltheophylline, and caffeine were 5.7, 6.6, and 11.2 min, respectively.

The limits of detection were 0.1 μg/ml for caffeine and 0.05 μg/ml for paraxanthine; this represents a signal-to-noise ratio of 3. Linearity of caffeine/internal standard and paraxanthine/internal standard peak area ratios was demonstrated, with concentrations in serum in the range of 0.1 to 5.0 and 0.05 to 2.5 μg/ml, respectively. Within-day and between-day coefficients of variation for the range of linearity were less than 7.2%. Absolute recovery of caffeine and paraxanthine over the measured concentration range, as determined by comparison of peak area ratios between processed serum samples and aqueous solutions, was 84.9 to 96.0%.

Ciprofloxacin and oxociprofloxacin assay. The concentration of ciprofloxacin in serum was measured by using a modification of the method of Nix et al. (15). Differences included a mobile phase consisting of 13% acetonitrile and 87% phosphate buffer (pH 3.0) and the incorporation of an extraction step with methylene chloride-isopropyl alcohol (90:10). Peak area ratios of ciprofloxacin to an internal standard (difloxacin [A-56619]; Abbott Laboratories, North Chicago, Ill.) were linear over the concentration range of 0.1 to 10 μg/ml, and coefficients of variation were less than 7.8%. Absolute analytical recoveries of ciprofloxacin were 34.1% at 0.25 μg/ml and 65.2% at 5.0 μg/ml. The limit of ciprofloxacin detection was 0.07 μg/ml. Concentrations of oxociprofloxacin in urine were measured by HPLC at Miles Laboratories (Pharmaceutical Div.) by their previously published methods (12).

Analysis. Concentrations of caffeine, paraxanthine, and ciprofloxacin in serum were analyzed by using noncompartmental pharmacokinetic methods. The terminal elimination rate constants (k_{el}) for caffeine and ciprofloxacin were obtained by regression of the concentrations in the log-linear phase. The elimination half-lives ($t_{1/2}$) of caffeine and ciprofloxacin were determined on the basis of the relation $t_{1/2}$ (h) = $0.693/k_{el}$ (h^{-1}).

Areas under the concentration-time curves (AUCs) for caffeine, paraxanthine, and ciprofloxacin were calculated by using the trapezoidal rule. The areas of residual trapezoids for caffeine and ciprofloxacin were determined by dividing the last detectable concentration by k_{el}. The k_{el} for paraxanthine, and therefore the area of the residual trapezoids, could not be accurately calculated because of the limited number of samples in the log-linear phase of its elimination. The AUC for ciprofloxacin from 0 h to infinity ($AUC_{0-\infty}$) following the first 750-mg dose was compared with the AUC from 0 to 12 h (AUC_{0-12}) after dose 3. Theoretically, these two measures of area are equivalent (8; also see Discussion). Total body clearance of caffeine was calculated by dividing the dose administered (i.e., 100 mg) by the $AUC_{0-\infty}$. The absolute bioavailability of oral caffeine was assumed to be 100% (3). Volume of distribution of caffeine was calculated by dividing the dose by the product of AUC and k_{el}.

The percent change in pharmacokinetic parameters was determined for each subject by subtracting the base-line value (before ciprofloxacin) from the corresponding value after ciprofloxacin, dividing by the base-line value, and multiplying by 100.

Student's t test (two tailed) for paired comparisons was used to assess the statistical significance of differences between pharmacokinetic parameters for caffeine and paraxanthine before ciprofloxacin administration and simultaneous with dose 3 of ciprofloxacin and between the AUC of ciprofloxacin before caffeine administration ($AUC_{0-\infty}$)

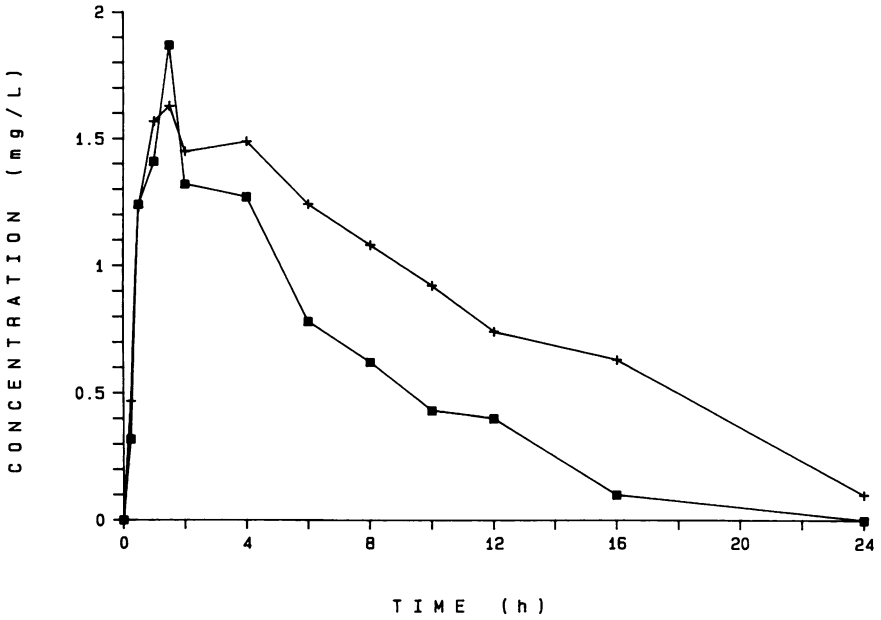

FIG. 1. Concentrations of caffeine in serum taken from a representative subject (subject 2) following a 100-mg oral dose given before ciprofloxacin administration (■) and with dose 3 of ciprofloxacin (+).

and the AUC of ciprofloxacin when given with caffeine (AUC_{0-12}). Differences were considered significant if P was <0.05.

RESULTS

Means ± standard deviations for the pharmacokinetic parameters for caffeine and paraxanthine before ciprofloxacin administration and after multiple doses are shown in Tables 1 and 2. Concentrations of the two compounds in serum are illustrated in Fig. 1 and 2 for a representative subject.

Coadministration of ciprofloxacin significantly prolonged the mean $t_{1/2}$ of caffeine from 5.2 to 8.2 h and decreased mean total body clearance from 106 to 58.2 ml/min per 1.73 m^2. This corresponded to a mean increase of 67% (range, 20 to 153%) in the $AUC_{0-\infty}$ of caffeine. For caffeine, mean values for maximum concentration in serum, time to maximum concentration in serum, and volume of distribution did not change significantly with ciprofloxacin administration.

Ciprofloxacin did not significantly alter the mean maximum concentration of paraxanthine in serum; however, the time for paraxanthine to reach maximum concentration was significantly increased from 6.2 to 10.4 h. This prolongation in the time to peak concentration was accompanied by a mean decrease in the AUC of paraxanthine of 43% during the first 10 h (Table 2).

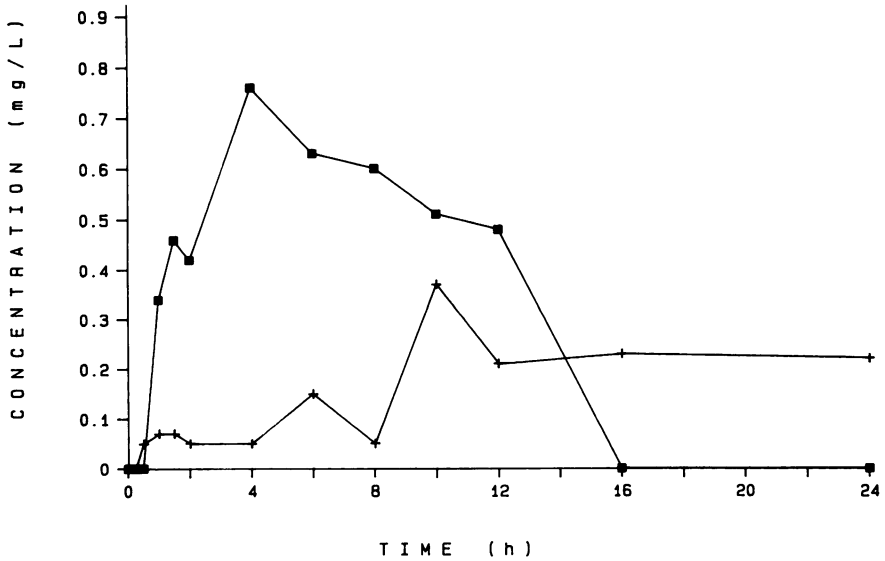

FIG. 2. Concentrations of paraxanthine in serum taken from subject 2 following a 100-mg oral dose of caffeine given before ciprofloxacin administration (■) and with dose 3 of ciprofloxacin (+).

The mean $AUC_{0-\infty}$ of ciprofloxacin following the first 750-mg dose was 16.4 μg · h/ml (range, 12.4 to 23.1 μg · h/ml), while the AUC_{0-12} at steady state was 22.4 μg · h/ml (range, 17.1 to 31.0 μg · h/ml) ($P = 0.002$). Concentrations prior to ciprofloxacin dose 3 were similar to concentrations 12 h later (0.64 ± 0.18 versus 0.67 ± 0.16 μg/ml; $P = 0.38$), indicating that steady-state conditions had been achieved.

There was no significant linear correlation between the AUC_{0-12} of ciprofloxacin after dose 3 and the change in the AUC of caffeine ($r^2 = 0.036$, $P = 0.6$) or between the urinary excretion of oxociprofloxacin (mean, 31.3 mg; range, 16.0 to 47.9 mg) and the change in the AUC of caffeine ($r^2 = 0.154$, $P = 0.26$).

Adverse reactions were reported in 6 of 10 subjects following caffeine and ciprofloxacin coadministration. Four subjects noted mild lightheadedness that occurred shortly after dosing (20 min to 1.5 h) and persisted for 40 min to 2 h. One subject reported mild nausea, and another complained of a generalized feeling of weakness shortly after dosing. Although these reactions were mild and could have been related to study conditions such as overnight fasting and depletion of blood volume due to venipuncture, no adverse effects were noted on the preceding study days when caffeine and ciprofloxacin were given separately.

DISCUSSION

The concomitant administration of various quinolones and theophylline (1,3-dimethylxanthine) has been shown to decrease the total body clearance of theophylline in both healthy volunteers and patients and in several instances has resulted in CNS toxicity (18, 22; Maesen et al., Letter). Enoxacin is the most potent inhibitor of theophylline metabolism, and it reduces the clearance of theophylline by 42 to 74% (2, 14). Ciprofloxacin and pefloxacin are intermediate in their ability to impede theophylline clearance (decrease, approximately 30% [16, 19, 22]), whereas ofloxacin, norfloxacin, and nalidixic acid have little or no effect on its disposition (4, 7, 22). Data from the present study indicate a significant interaction between ciprofloxacin and caffeine. Ciprofloxacin administered at a dosage of 750 mg every 12 h resulted in a mean decrease in total caffeine clearance of 38% and a 3-h prolongation of caffeine $t_{1/2}$ in serum. The only other published data on this interaction with caffeine were recently reported by Staib et al. (20). They also reported a 33% decrease in total caffeine clearance when ciprofloxacin was coadministered at a dosage of 250 mg every 12 h. At this lower dose they found a small (0.5-h) yet statistically significant increase in the $t_{1/2}$ or caffeine. The 3-h increase in $t_{1/2}$ in the present study may reflect a dose-dependent interaction between caffeine and ciprofloxacin, although there was no significant correlation between the AUC of ciprofloxacin and the change in caffeine clearance. Further work is needed to evaluate the possibility of dose dependence.

The precise mechanism(s) responsible for the quinolone-xanthine interactions is still unknown. 3-Demethylation of caffeine (1,3,7-trimethylxanthine) to form paraxanthine (1,7-dimethylxanthine) is the most important pathway of caffeine elimination in humans, accounting for approximately 80% of the clearance from plasma (13). Our data indicate that the interaction between caffeine and ciprofloxacin is a result of decreased metabolic conversion of caffeine to its major metabolite, paraxanthine. Paraxanthine formation was significantly less (mean reduction in AUC, 43%; range, 22 to 77%) during the first 10 h after coadministration of caffeine and ciprofloxacin than following administration of caffeine alone (Fig. 2).

Wijnands et al. (22) first proposed that differences among the quinolones in their abilities to inhibit xanthine (theophylline) metabolism might be related to the amount of oxometabolite produced. They found a significant correlation between the degree of theophylline inhibition and the recovery of urinary oxometabolite among the tested quinolones. This correlation, however, does not prove causality, and more recent data suggest that the oxometabolite is not directly responsible for the metabolic inhibition. Edwards et al. (6) showed that direct injection of oxoenoxacin had no effect on antipyrine clearance in the rat, whereas the parent compound (enoxacin) reduced clearance by 44.1%. In support of the findings by Edwards and colleagues, we found no significant correlation between the amount of oxociprofloxacin recovered in the urine and the change in the AUC of caffeine. In vitro models involving specific human isozymes will be required to evaluate the exact biochemical mechanism(s) responsible for this interaction and to delineate the structure-activity relations involved.

There are no other published data on the influence of theophylline or caffeine on quinolone kinetics. Preliminary data from the present study suggest that a reciprocal interaction exists, since the AUC of ciprofloxacin showed accumulation beyond what would be predicted on the basis of first-order kinetics. However, the accumulation kinetics of ciprofloxacin have not been rigorously evaluated, and there is some evidence that accumulation is not accurately predicted from first-dose data (9). This area deserves further investigation.

The adverse effects encountered in this study were mild and cannot be said to have resulted from coadministration of caffeine and ciprofloxacin. However, impairment of caffeine clearance by such agents as disulfiram, idrocilamide, mexiletine, and furafylline, leading to CNS toxicity, has been well described (1, 5, 11, 21). Since the average coffee drinker consumes about 300 mg of caffeine per day, with as many as 20 to 40% of coffee drinkers consuming 600 to over 1,000 mg a day (10), further investigations of the effects of long-term administration of caffeine and ciprofloxacin will be needed to determine the clinical significance of this pharmacokinetic interaction. Until those data are available, it would be prudent to instruct certain patients, such as the elderly, those on multiple medications with potential CNS effects, and those with a history of seizures, to limit their caffeine intake while receiving ciprofloxacin.

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ADDENDUM IN PROOF

Harder et al. (S. Harder, A. H. Staib, C. Beer, A. Papenburg, W. Stille, and P. M. Shah, Eur. J. Clin. Pharmacol. **35**:651–656, 1988) recently published similar findings in which ciprofloxacin (500 mg twice a day) resulted in a prolongation of the elimination half-life of paraxanthine by 1.7-fold and an increase in the time to maximum concentration of paraxanthine in serum from 4.3 to 7.7 h. These data are consistent with those from the present study.

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