ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 660–664
0066-4804/91/040660-05$02.00/0

Vol. 35, No. 4

Lack of Interaction between Lomefloxacin and Caffeine in Normal Volunteers

DANIEL P. HEALY,[1]†* JANNA R. SCHOENLE,[1]‡ JENNIFER STOTKA,[2] AND RON E. POLK[1,2]

Antibiotic Research Unit, Department of Pharmacy and Pharmaceutics, School of Pharmacy,[1] and Division of Infectious Diseases, Department of Medicine,[2] Medical College of Virginia/Virginia Commonwealth University, Box 581, MCV Station, Richmond, Virginia 23298-0581

Received 25 July 1990/Accepted 21 January 1991

Sixteen healthy, nonsmoking adult males participated in a randomized, double-blind, placebo-controlled, two-way crossover study to evaluate the influence of chronic lomefloxacin administration on the disposition of caffeine and its major metabolite, paraxanthine, at steady-state conditions. Lomefloxacin (400 mg) or placebo was administered orally once daily for 5 days to xanthine-free volunteers after an overnight fast. Caffeine (200 mg orally) was administered simultaneously with lomefloxacin on days 3 through 5. After a 2-day washout period, subjects were crossed over to the alternate 5-day regimen with caffeine, which was again given on the final 3 days. Blood samples for caffeine, paraxanthine, and lomefloxacin concentration determinations were serially collected for 48 h following the last dose of each regimen. All compounds were analyzed by high-performance liquid chromatography. For the placebo versus lomefloxacin-containing treatments, maximum caffeine concentrations in plasma (4.35 ± 0.63 versus 4.07 ± 0.56 μg/ml), areas under the concentration-time curve from time zero to 24 h at steady state (30.3 ± 6.9 versus 29.7 ± 6.6 μg · h/ml), and elimination half-lives of caffeine (4.8 ± 1.1 versus 4.8 ± 1.2 h) were not significantly different. In addition, there were no significant changes in the disposition parameters of paraxanthine as a result of lomefloxacin administration. The frequencies of central nervous system-related effects for the two treatments were not statistically different. We conclude that lomefloxacin has no significant effect on the disposition of caffeine in young healthy volunteers.

Several quinolone antibiotics, including enoxacin, ciprofloxacin, and pefloxacin, have been reported to interfere with the clearance of methylxanthine compounds such as theophylline and caffeine, leading to elevated concentrations of the xanthine in serum (1, 9, 10, 17, 19, 23, 29, 33, 34) and, in the case of theophylline, central nervous system (CNS) toxicity (13, 20, 30, 32). However, other quinolones such as norfloxacin, ofloxacin, and fleroxacin appear to have minimal or no effect on methylxanthine disposition (3, 5, 6, 9, 11, 16, 21, 25, 34).

Lomefloxacin is an investigational difluoroquinolone that has a broad antimicrobial spectrum. Following oral administration, lomefloxacin is rapidly absorbed into the blood, widely distributed into peripheral tissues, and excreted into urine, primarily as the parent compound. It has a relatively long serum half-life ($t_{1/2}$) of 6 to 8 h in volunteers with normal renal function (8). Recent studies have shown that lomefloxacin does not significantly interfere with theophylline kinetics (12, 15, 27). However, its effect on caffeine clearance has not been studied previously. The purpose of this study was to determine whether multiple oral doses of lomefloxacin alter the disposition of caffeine and its major metabolite, paraxanthine, at steady-state conditions in healthy volunteers.

(Results of this study were presented at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 24 October 1990 [10a].)

* Corresponding author.
† Present address: Anti-Infectives Research Laboratory, College of Pharmacy, University of Cincinnati Medical Center, 3223 Eden Avenue, Cincinnati, OH 45267.
‡ Present address: Department of Pharmacy, University of Virginia, Charlottesville, VA 22903.

MATERIALS AND METHODS

Volunteers. Sixteen healthy adult males participated in this study after internal review board approval and written informed consent were obtained. The mean (± standard deviation) age was 27.1 ± 3.1 years, and the weight was 76.7 ± 6.8 kg. Volunteers were excluded on the basis of the following criteria: prior hypersensitivity to quinolones, smoking, the use of medication for chronic illness, body weight deviating by more than 15% from ideal weight, and abnormalities on physical examination, electrocardiogram, or prestudy laboratory tests. Each volunteer was given a list of xanthine-containing products and instructed to abstain from such items, alcohol, and all other drugs beginning 2 days prior to study participation. A xanthine-free diet was maintained throughout the study.

Drug administration and sample collection. Subjects reported to the Medical College of Virginia's Biopharmaceutics Center each morning for the 2-week study period. After an overnight fast, subjects randomly received a single daily dose of either lomefloxacin (400 mg; two 200-mg capsules; lot 8568RCT, G. D. Searle & Co., Skokie, Ill.) or identical-appearing placebo capsules for 5 consecutive days. Caffeine (200 mg; two 100-mg NO-DOZ tablets; lot ND9Y1B; Bristol-Myers Co., New York, N.Y.) was simultaneously administered with the last three doses of each lomefloxacin or placebo treatment. After a 2-day washout period, subjects were begun on the alternate 5-day regimen with caffeine, which was again administered on the final 3 days. Subjects ingested lomefloxacin, placebo, and caffeine doses with 180 ml of distilled water. Following administration of the final dose of each regimen, subjects were required to continue fasting for 4 h.

Subjects were interviewed individually by blinded investigators each morning prior to receiving their scheduled dose

of study medication. All adverse events were recorded in the subjects' study chart. Each registered complaint was given a severity rating by the subject based on standard definitions (e.g., mild, causing no limitation of usual activities; moderate, causing some limitation; and severe, inability to carry out usual activities).

Serial blood samples for caffeine, paraxanthine, and lomefloxacin concentration determinations were collected before drug administration each study day and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 32, and 48 h after dosing on the final day of each regimen. Blood samples were centrifuged within 15 min of collection, and plasma samples were stored at −35°C until analysis (about 4 weeks).

Caffeine and paraxanthine assay. Caffeine and paraxanthine concentrations in plasma were measured by validated reversed-phase high-performance liquid chromatography using UV detection by a previously described method (10). Linearities of caffeine-internal standard and paraxanthine-internal standard peak area ratios were demonstrated, with concentrations in plasma being in the range of 0.1 to 5.0 (interday coefficient of variation, <10.9%) and 0.05 to 2.5 μg/ml (interday coefficient of variation, <12.8%), respectively.

Lomefloxacin assay. Lomefloxacin concentrations were measured in our laboratory by using a reversed-phase high-performance liquid chromatography method developed by G. D. Searle & Co. (Department of Drug Metabolism). A mobile phase consisting of acetonitrile, citric acid (0.05 M), and ammonium acetate (1.0 M) (22:77:1 [vol/vol]) was pumped through a 10-μm, C-18 column (250 by 4.6 mm; Nucleosil; Alltech Associates, Inc., Applied Science Div., State College, Pa.) at a flow rate of 1.5 ml/min. The signal was recorded by fluorescence detection with excitation and emission wavelengths of 280 and 418 nm, respectively.

To 500 μl of a known standard, control, or patient specimen, 100 μl of internal standard (2.0 μg/ml; E-1608; G. D. Searle & Co.) and 400 μl of sodium phosphate buffer (0.2 M, pH 7.0) were added; the mixture was vortexed for 5 s. Lomefloxacin and the internal standard were extracted into 5.0 ml of chloroform-isoamyl alcohol (95:5 [vol/vol]) with rotation (5 min) and then centrifugation (500 × *g*, 5 min). The lower organic phase was transferred to a clean glass culture tube and evaporated to dryness under nitrogen. The residue was reconstituted with 500 μl of mobile phase, and 40 μl was injected onto the column. Retention times for lomefloxacin and E-1608 were 6.2 and 12.6 min, respectively. The limit of lomefloxacin detection was 0.01 μg/ml and the range of linearity was 0.01 to 5.0 μg/ml. Between-day coefficients of variation ranged from 4.5 to 10.7%, and relative analytical recovery was 101 to 103%.

Pharmacokinetics. The pharmacokinetic parameters of caffeine, paraxanthine, and lomefloxacin were determined by compartmental and noncompartmental methods. The maximum concentration (C_{max}) and the time of maximum concentration (T_{max}) were determined by inspection of the observed concentrations in plasma. Terminal elimination rate constants (k_{el}) were determined by nonlinear least-squares regression analysis with an unweighted, two-compartment, multiple-dose model with first-order absorption and elimination (PCNONLIN [28]). Weighting factors of $1/C$ and $1/C^2$ did not significantly reduce the weighted sum of squared residuals, compared with unweighted fits. $t_{1/2}$ was calculated by using $0.693/k_{el}$. The areas under the plasma concentration-time curve from time zero to 24 h at steady state (AUC_{0-24}s) were determined by the trapezoidal rule method. The apparent total body clearance (CL) of caffeine

TABLE 1. Pharmacokinetic parameters of caffeine, paraxanthine, and lomefloxacin at steady state for two regimens: caffeine plus placebo and caffeine plus lomefloxacin[a]

Regimen	Caffeine				Paraxanthine			Lomefloxacin			
	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24} (μg · h/ml)	CL (ml/min/1.73 m²)[b]	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24} (μg · h/ml)	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)[c]	AUC_{0-24} (μg · h/ml)
Caffeine-placebo	4.35 ± 0.63	0.78 ± 0.18	4.8 ± 1.1	30.3 ± 6.9	104 ± 21.8	1.32 ± 0.23	5.88 ± 1.54	9.2 ± 2.9	21.3 ± 4.9				
Caffeine-lomefloxacin	4.07 ± 0.56	0.98 ± 0.31	4.8 ± 1.2	29.7 ± 6.6	107 ± 20.4	1.34 ± 0.27	5.50 ± 1.15	9.2 ± 4.0	20.8 ± 4.62	3.1 ± 0.53	1.45 ± 0.65	6.3 ± 1.8	25.2 ± 3.4

[a] Pharmacokinetic parameters for caffeine and paraxanthine were not statistically different between the two regimens ($P > 0.05$). Data are means ± standard deviations.
[b] CL, Apparent total body clearance of caffeine.
[c] Determined by nonlinear least-squares regression of all datum points by using a two-compartment model. Log-linear regression of only those datum points in the terminal phase (noncompartmental) resulted in a $t_{1/2}$ of 8.6 ± 0.84 h.

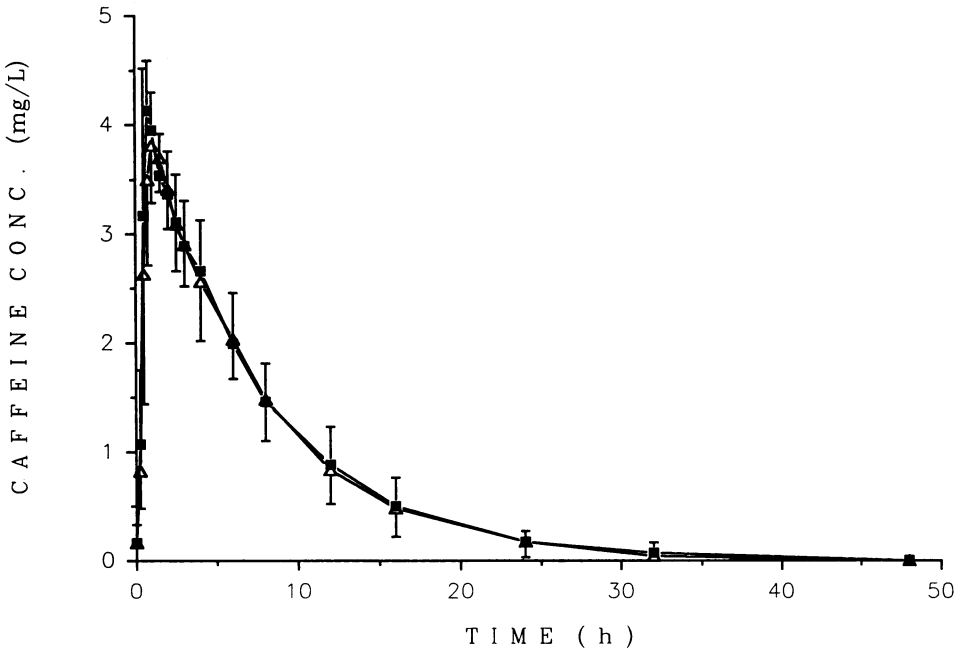


FIG. 1. Steady-state concentrations (± standard deviation of the mean) of caffeine in plasma following the last doses of the caffeine-placebo (■) and caffeine-lomefloxacin (△) regimens.

was calculated by dividing the dose administered (i.e., 200 mg) by the AUC_{0-24}. The absolute bioavailability of oral caffeine was assumed to be 100% (2).

Statistical analysis. Based on our previously published data (10), a prestudy power analysis indicated that a sample size of 16 would yield 90% power (probability) of detecting a ≥10% increase in the AUC (or decrease in the CL) of caffeine, as a result of lomefloxacin coadministration, at the 5% level of significance (4). Differences in the mean pharmacokinetic parameters of caffeine between treatments were evaluated by Student's *t* test for paired comparisons. The chi-square test was used to evaluate differences in the frequency of CNS-related adverse effects between treatments. Statistical significance was defined as $P < 0.05$. Results are expressed as means ± standard deviations.

RESULTS

Trough concentrations of caffeine following the last two doses within each regimen were not significantly different (0.16 ± 0.17 versus 0.17 ± 0.10 μg/ml for caffeine-placebo and 0.16 ± 0.17 versus 0.17 ± 0.14 μg/ml for caffeine-lomefloxacin). In addition, trough concentrations of lomefloxacin were not significantly different (0.37 ± 0.10 μg/ml before the fourth dose compared with 0.37 ± 0.09 μg/ml before the fifth dose), indicating that steady-state conditions were achieved for both caffeine and lomefloxacin.

Multiple oral doses of lomefloxacin did not significantly alter the steady-state pharmacokinetic parameters of caffeine or paraxanthine (Table 1 and Fig. 1 and 2). For the caffeine-placebo and caffeine-lomefloxacin regimens, the C_{max} (4.35 ± 0.63 versus 4.07 ± 0.56 μg/ml), AUC_{0-24} (30.3 ± 6.9 versus 29.7 ± 6.6 μg · h/ml), and $t_{1/2}$ (4.8 ± 1.1 versus 4.8 ± 1.2 h) values of caffeine were not significantly different. Corresponding values for paraxanthine were 1.32 ± 0.23 versus 1.34 ± 0.27 μg/ml, 21.3 ± 4.9 versus 20.8 ± 4.6 μg · h/ml, and 9.2 ± 2.9 versus 9.2 ± 4.0 h. Differences in these parameters were not statistically significant.

All subjects completed the investigation. Although no severe adverse effects were reported, mild CNS-related complaints were documented in 8 of 16 subjects (caffeine-placebo arm of the study) and 10 of 16 subjects (caffeine-lomefloxacin arm of the study) ($P > 0.05$). Headache (seven versus five subjects), lightheadedness (three versus three subjects), and jitteriness (two versus five subjects) occurred in subjects in the placebo and lomefloxacin-containing regimens, respectively.

DISCUSSION

Since the first published reports of CNS toxicity associated with concomitant theophylline and enoxacin administration (13, 32), numerous investigations have been performed to assess the potential for individual quinolones to interfere with the biotransformation of methylxanthines. In vitro and clinical studies have consistently shown that enoxacin is the most potent inhibitor of xanthine metabolism, with marked reductions in theophylline and caffeine clearance of 41 to 74% and 78 to 79%, respectively (1, 9, 14, 17, 19, 26, 29, 32, 33). Ciprofloxacin and pefloxacin are intermediate in their ability to reduce xanthine clearance (about 30% reduction for both theophylline and caffeine), while nalidixic acid, norfloxacin, ofloxacin, and fleroxacin have little or no influence on theophylline or caffeine disposition (3, 5, 6, 9–11, 16, 21, 25, 34).

Five studies with a total of more than 70 healthy volunteers have demonstrated that lomefloxacin does not interfere with theophylline metabolism (12, 15, 18, 27, 31a).

Figure 3 depicts the slight structural variations between enoxacin and lomefloxacin that apparently yield differences in their abilities to inhibit xanthine N-demethylation reactions. A recent study involving human liver microsomes was

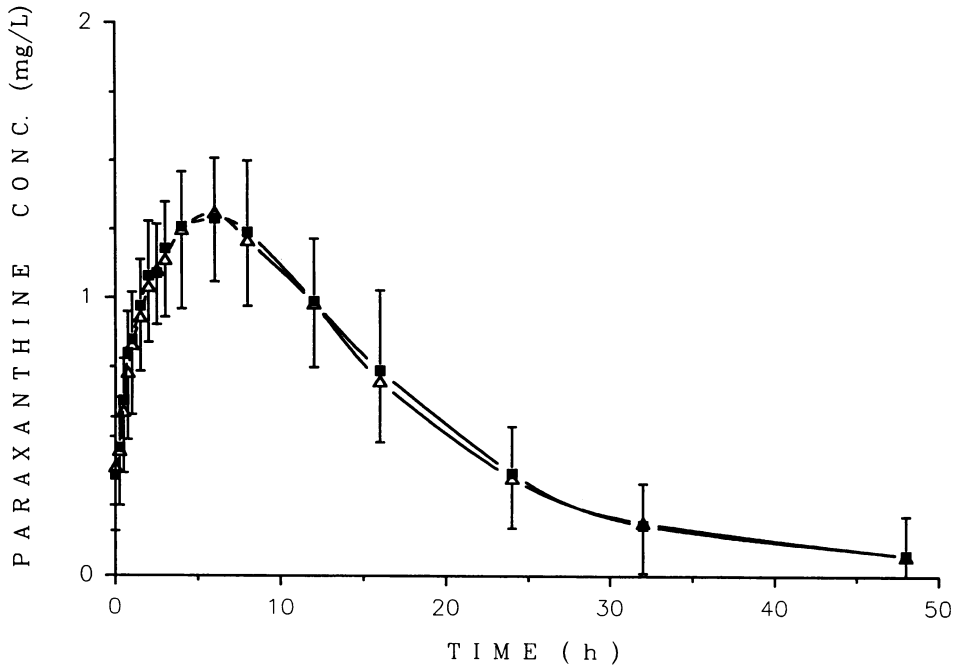
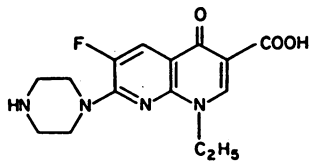
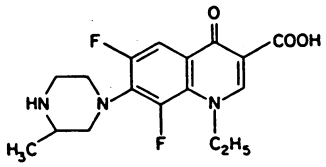


FIG. 2. Steady-state concentrations (± standard deviation of the mean) of paraxanthine in plasma following the last dose of the caffeine-placebo (■) and caffeine-lomefloxacin (△) regimens.

performed to provide initial data on the structural requirements necessary for caffeine inhibition (5a). They concluded that a second N atom in the quinolone nucleus leads to the most profound inhibitory effects. The resultant configuration of alternating N and C atoms structurally resembles that of theophylline and caffeine, and may therefore explain the competitive inhibition reported with enoxacin (22). Lomefloxacin, ofloxacin, and fleroxacin lack a second N atom and are associated with minimal or no inhibition of xanthine metabolism. However, ciprofloxacin and pefloxacin also lack a second N atom in their core structures, but they demonstrate intermediate inhibitory abilities. The structural explanation(s) is multifactorial, and no single theory offered to date can fully explain (or predict) this interaction.



ENOXACIN



LOMEFLOXACIN

FIG. 3. Chemical structures of enoxacin and lomefloxacin.

Data from the present study indicate that multiple-dose lomefloxacin does not alter the disposition of caffeine or its primary metabolite, paraxanthine, at steady-state conditions. Mild CNS effects were common in both the caffeine-placebo group (8 of 16 subjects) and the caffeine-lomefloxacin group (10 of 16 subjects). Although headache was the most common adverse effect, the majority of subjects (five of seven in the placebo group and four of five in the lomefloxacin-containing group) registered those complaints on caffeine-free study days, suggesting that caffeine withdrawal may have been responsible (24). In addition, the frequency of lightheadedness and jitteriness was similar between the two treatments, and all reports occurred on days when caffeine was administered.

Most studies, including the present one, have assessed potential quinolone-caffeine interactions in young healthy volunteers and have used single daily doses of caffeine of 100 to 230 mg (equivalent to 1 to 3 "cups" [180 to 540 ml] of American coffee). Since as many as 20 to 40% of coffee drinkers in the United States consume from 600 to over 1,000 mg of caffeine daily (7), further study in this population is warranted. In addition, since elderly individuals are generally thought to be more susceptible to the development of drug-induced CNS-related adverse effects (31), they should also be studied to rule out a potentially significant pharmacodynamic interaction between quinolones and caffeine.

We conclude that lomefloxacin has no significant effect on the disposition of caffeine or on the frequency of CNS-related adverse effects in young volunteers. Restriction of caffeine intake in this population is not necessary.

ACKNOWLEDGMENTS

The assistance of Mark Oliveira, Beth Ratliff Healy, and Donna West in conducting this study is greatly appreciated.

This work was supported by a grant from G. D. Searle & Co.

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