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Effect of Sucralfate on Pharmacokinetics of Fleroxacin in Healthy Volunteers

TERESA J. LUBOWSKI,[1,2] CHARLES H. NIGHTINGALE,[3,4]* KEVIN SWEENEY,[1,4] AND RICHARD QUINTILIANI[5,6]

Departments of Pharmacy[1] and Research[3] and Division of Infectious Disease/Allergy Immunology,[6] Hartford Hospital, Hartford, Connecticut 06115; Department of Pharmacy, Strong Memorial Hospital, Rochester, New York 14642[2]; University of Connecticut School of Pharmacy, Storrs, Connecticut 06269[4]; and University of Connecticut School of Medicine, Farmington, Connecticut 06032[5]

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The effect of sucralfate on the pharmacokinetics of fleroxacin was assessed in 20 healthy male volunteers. The study was of a two-way crossover design in which subjects were randomized to one of the following two regimens at the time of entry: (i) a single 400-mg dose of fleroxacin alone or (ii) a 400-mg dose of fleroxacin given once and 1 g of sucralfate given every 6 h starting 24 h before fleroxacin treatment and continuing for 48 h after fleroxacin treatment. Blood samples were collected immediately before fleroxacin administration and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 h postdosing. Fleroxacin concentrations in plasma and urine were determined by high-performance liquid chromatography. While concurrent administration of fleroxacin and sucralfate resulted in a decrease in the area under the plasma concentration-time curve, a decrease in the maximum concentration, and an increase in the time to the maximum concentration ($P < 0.05$), these changes were modest compared with the interaction of other quinolones with sucralfate. The relative bioavailability of fleroxacin given with sucralfate, calculated from the area under the concentration-time curve, was 76% compared with that of fleroxacin alone. This is significantly better than the bioavailabilities of other quinolones (1.8 to 12.3%) when they are administered with sucralfate.

Fleroxacin is a trifluorinated quinolone with in vitro activity against a broad array of gram-positive and gram-negative aerobic pathogens. Compared with the other fluoroquinolones, fleroxacin exhibits a long half-life and attains high concentrations in plasma, allowing once-daily administration (9).

Sucralfate is a complex salt of sucrose sulfate and aluminum hydroxide used in the treatment and prophylaxis of peptic ulcer disease. The primary structure of sucralfate contains 16 aluminum ions. As sucralfate reacts with acids and is solubilized in the stomach, the eight aluminum salts are dissociated. This results in the release of aluminum ions, and the remaining negatively charged viscous substance binds to damaged mucosa to provide a protective barrier (2).

A drug interaction between sucralfate and ciprofloxacin, enoxacin, and norfloxacin has been reported. Parpia et al. (4) reported a relative bioavailability of 1.8% when norfloxacin was taken with a 1-g dose of sucralfate (4). Garrelts et al. (1) reported a relative bioavailability of 12.5% for ciprofloxacin when it was administered with a 1-g dose of sucralfate (1). Ryerson et al. (5) reported a relative bioavailability of 12.3% for enoxacin when it was administered with a 1-g dose of sucralfate (5). The postulated mechanism of this interaction is a complexation between the aluminum ions of sucralfate and the quinolone. Since norfloxacin, enoxacin, and ciprofloxacin display variable decreases in their relative bioavailabilities, the interaction may be dependent on the chemical structure of the quinolone. The purpose of the study described here was to determine the effect of concurrent administration of sucralfate on the pharmacokinetics of fleroxacin.

* Corresponding author.

MATERIALS AND METHODS

Subjects and study design. Twenty healthy male subjects participated in the study. The subjects' ages ranged from 19 to 35 years. The study was approved by the Hartford Hospital Institutional Review Board, and informed consent was obtained from all subjects. All subjects were within ±15% of their ideal body weights according to the Metropolitan Life Insurance tables. They were all determined to be healthy by medical history, physical examination, and laboratory parameters. None of the subjects were taking any medications, including antacids, within 1 week before and during the study period. None of the subjects were smokers.

Subjects received each of two regimens in a randomized crossover fashion; administration of the two regimens was separated by a 7-day washout period. The sequence was balanced so that 10 subjects received regimen A first and 10 subjects received regimen B first. For regimen A, subjects were given a single 400-mg dose of fleroxacin with 240 ml of water following an overnight fast. For regimen B, subjects were given a 400-mg dose of fleroxacin and a 1-g dose of sucralfate with 240 ml of water following an overnight fast. One day before receiving regimen B, subjects took 1 g of sucralfate at 6 a.m., 12 p.m., 6 p.m., and 12 a.m. This sucralfate dose continued to be given every 6 h for 48 h. The fifth dose of sucralfate was given immediately before the 400-mg dose of fleroxacin. All tablets were swallowed whole, and compliance was assessed by tablet count.

Blood samples (5 ml each) were obtained by direct venipuncture immediately before fleroxacin administration and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 h postdosing. Blood samples were collected into sterile vacuum tubes (Vacutainer) and were centrifuged within 15 min of collection, and plasma was stored frozen at −20°C until analysis. After the fleroxacin dose, urine was collected during the intervals of 0 to 24 and

24 to 48 h postdose. The total urine volume within each sampling period was determined and recorded. Samples of urine (10 ml) at each collection interval were stored at −20°C until analysis. During the processing of the blood and urine samples, all Vacutainer tubes and collection vials were protected from light with aluminum foil to eliminate the possibility of light-catalyzed degradation.

Assay methodology. Serum and urine samples were analyzed for fleroxacin by high-performance liquid chromatography. After extraction, the drug was isolated on a C_{18} reverse-phase column by using a mobile phase of 13% acetonitrile–2% methanol–81% 0.01 M phosphate buffer with 0.005 M tetrabutylammonium hydrogen sulfate at a flow rate of 1 ml/min. Fleroxacin was detected on a fluorescence detector at an excitation wavelength of 274 nm and a 418-nm emission cutoff. The internal standard was pipemidic acid. The injection volume was 20 μl, and the run time was 10 min.

The samples were extracted as follows. (i) A total of 250 μl of sample, 20 μl of 30 μg of internal standard per ml, and 250 μl of 25% Na_2SO_4 (plasma) or 0.5 μl of phosphate buffer (pH 7.5) (urine) were mixed together. (ii) Methylene chloride (3.5 μl) was added, and the mixture was shaken for 10 min and centrifuged at 2,500 rpm for 10 min using a Sorvall GLC-1 centrifuge. (iii) The aqueous layer was removed by aspiration. (iv) A total of 200 μl of NaOH (plasma) or 1/15 M Na_3PO_4 (pH 12.5) (urine) was added to 3.0 ml of the organic layer, and the mixture was shaken and centrifuged at 2,500 rpm for 10 min using a Sorvall GLC-1 centrifuge. (v) The aqueous layer was injected into the column.

Interday variabilities of 0.2- and 3.0-μl/ml control plasma samples were excellent, with coefficients of variation of 4.12 and 2.95%, respectively. Intraday variabilities for these samples were 6.01 and 3.33%, respectively. The inter- and intraday variabilities for the urine control samples were 5.44 and 4.41% and 6.08 and 3.94%, respectively. The assay limit of sensitivity was 0.05 μg/ml. The linear range of the assay was 0.05 to 5.0 μg/ml.

Pharmacokinetics and statistical analysis. Peak fleroxacin concentrations in plasma (C_{max}) and the time to peak concentrations in plasma (T_{max}) were determined from the observed concentrations. The total area under the plasma concentration-time curve (AUC) from time zero to the last measured concentration was determined by using the trapezoidal rule. Mean renal clearance was calculated by dividing the total amount of fleroxacin excreted from 0 to 48 h by the AUC from 0 to 48 h.

A univariate analysis of variance was used to test for differences between AUC, C_{max} and T_{max} for each of the treatment regimens. A two-one-sided t test was used to determine the 90% confidence intervals of the C_{max}, T_{max}, and the AUC of the sucralfate and control regimens (6). Analyses were conducted with SAS (Cary, N.C.) version 5 software. A P value of <0.05 was considered statistically significant.

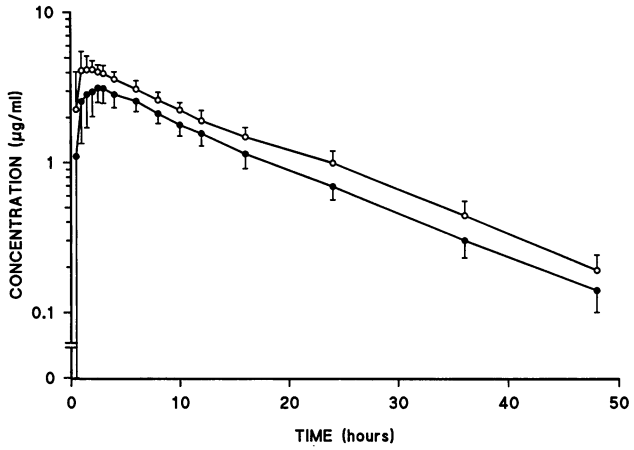

FIG. 1. Mean concentrations in serum of fleroxacin (400 mg) (○) and fleroxacin (400 mg) with sucralfate (1,000 mg) (●).

RESULTS

The profiles of the mean plasma fleroxacin concentration-time data are shown in Fig. 1 for both regimens. The observed mean C_{max}s were 5.3 ± 0.9 and 3.9 ± 0.6 μg/ml/70 kg for the fleroxacin and fleroxacin-sucralfate regimens, respectively. The observed minimum concentrations were 0.21 ± 0.06 and 0.15 ± 0.05 μg/ml/70 kg for the fleroxacin and fleroxacin-sucralfate regimens, respectively. In 18 of 20 subjects, the C_{max} was lower when fleroxacin was administered with sucralfate. For two of the subjects, the C_{max} was higher with the fleroxacin-sucralfate regimen. The mean AUCs from 0 to 48 h were 70.3 ± 8.7 and 53.4 ± 6.9 μg · h/ml/70 kg for the fleroxacin and fleroxacin-sucralfate regimens, respectively, resulting in a relative bioavailability of 76%. In all subjects there was a decrease in the AUC in the fleroxacin-sucralfate regimens. The observed mean T_{max}s for the fleroxacin and fleroxacin-sucralfate regimens were 1.7 ± 0.9 and 2.5 ± 1.2 h, respectively. In 14 subjects, the T_{max} was greater with the fleroxacin-sucralfate regimen, 3 subjects had the same T_{max}s, and in 3 subjects the T_{max} was greater with the fleroxacin regimen. By using analysis of variance, there was no significant difference between the fleroxacin and fleroxacin-sucralfate regimens in subject, period, or sequence effect. There was a significant treatment effect detected in the AUC, C_{max}, and T_{max} values between the two regimens. The P values are listed in Table 1. The mean renal clearances for the fleroxacin and fleroxacin-sucralfate regimens were 64.5 ± 14.6 and 66.2 ± 19.3 ml/min/70 kg, respectively. The fractions of the dose of fleroxacin excreted in 48 h were 67 and 50% for the fleroxacin and fleroxacin-sucralfate regimens, respectively. The 90% confidence intervals for the AUC, C_{max}, and T_{max} of the

TABLE 1. Fleroxacin Pharmacokinetic Parameters[a]

Treatment	AUC (μg · h/ml/70 kg)	C_{max} (μg/ml)	T_{max} (h)	CL_R (ml/min/70 kg)[b]	% Urinary excretion
Fleroxacin	70.3 ± 8.7	5.3 ± 0.9	1.7 ± 0.9	64.5 ± 14.6	67.0 ± 13.5
Fleroxacin-sucralfate	53.4 ± 6.9	3.9 ± 0.6	2.5 ± 1.2	66.2 ± 19.3	50.0 ± 13.2
Treatment P value	0.0001	0.0001	0.0186	0.7179	0.0006

[a] Values are means ± standard deviations.
[b] CL_R, renal clearance.

fleroxacin and fleroxacin-sucralfate regimens were 70.1 to 81.8%, 65.5 to 81.8%, and 117 to 184%, respectively.

DISCUSSION

Although there was a significant drug interaction between fleroxacin and sucralfate resulting in a 76% relative bioavailability, the magnitude of the effect was less than those reported with norfloxacin (1.8%), enoxacin (12.3%), and ciprofloxacin (12.5%). Shimada et al. (7) investigated the effect of dried aluminum hydroxide gel on the pharmacokinetics of fleroxacin. The peak concentration was significantly reduced, but no significant difference in the AUC was found. The investigators reported (7) that the interaction between fleroxacin and dried aluminum hydroxide gel is not as great as those between ofloxacin, enoxacin, and norfloxacin and dried aluminum hydroxide. The mechanism of this interaction is believed to be complexation of the free aluminum ions of sucralfate with the quinolone. The lack of a difference in the renal clearance of fleroxacin calculated in the present study further supports this mechanism. All of the quinolone molecules have a carboxyl group at position 3, a keto group at position 4, a piperazine ring at position 7, and a fluorine atom at position 6. Fleroxacin is structurally different, possessing additional fluorine atoms at positions 8 and 1, reducing the potential for a complexation interaction with sucralfate.

Several investigators have reported a decrease in the extent of the interaction between sucralfate and quinolones by administering the sucralfate either 2 h before or 2 h after the quinolone is administered. Parpia et al. (4) improved the relative bioavailability of norfloxacin from 1.8 to 56.6% by administering norfloxacin 2 h after they administered a 1-g dose of sucralfate. Ryerson et al. (5) reported an increase in the relative bioavailability of enoxacin from 12.3 to 46% if enoxacin was given 2 h after sucralfate and from 12.3 to 92% if enoxacin was given 2 h before sucralfate. Nix et al. (3) reported a relative bioavailability of 70% when 1-g doses of sucralfate were given 6 and 2 h before ciprofloxacin. VanSlooten et al. (8) investigated the interaction of ciprofloxacin with sucralfate given as 2 g every 12 h. In that study, five doses of sucralfate were given, and the relative bioavailability of ciprofloxacin improved from 4.29% with concurrent administration to 82.9 and 96.5% when ciprofloxacin was given 2 h and 6 h before the fifth dose of sucralfate, respectively (8). Interactions with sucralfate seems to be minimized if the quinolone is administered 2 h before the sucralfate dose. This is reasonable, since the quinolones reach their maximum concentration 1 to 2 h after dosing. The enoxacin study used only single-dose sucralfate. Sucralfate is reported to be present in the stomach for at least 6 h after dosing (2). Therefore, these data cannot be compared with the multiple-dose data or extrapolated to patients taking multiple doses of sucralfate.

Although coadministration of sucralfate reduced the AUC and C_{max} of fleroxacin, the reduction was modest, and for most organisms, it may not be clinically significant. Therefore, there is a possibility that sucralfate-fleroxacin dosing schedules do not have to be altered in order to avoid the interaction. The once-daily dosing of fleroxacin, however, facilitates the ease of dose manipulation around a sucralfate schedule. Since fleroxacin has an absolute bioavailability of 100% and a relative bioavailability of 76% with concurrent administration of sucralfate, any manipulation of the timing of the sucralfate dose would improve the relative bioavailability of fleroxacin (9).

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