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Sucralfate Reduces the Gastrointestinal Absorption of Norfloxacin

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The effect of sucralfate on the bioavailability of norfloxacin after single 400-mg doses of norfloxacin was evaluated in eight healthy males. Subjects received each of the following treatments in random sequence: (i), norfloxacin, 400 mg alone; (ii) sucralfate, 1 g, concurrently with norfloxacin, 400 mg; and (iii) sucralfate, 1 g, followed by norfloxacin, 400 mg, 2 h later. One day before administration of treatments 2 and 3, 1 g of sucralfate was given at 7 a.m., 11 a.m., 5 p.m., and 10 p.m. Blood samples were collected immediately before the norfloxacin dose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postdose. Urine was collected in divided intervals: from 0 to 12, from 12 to 24, and from 24 to 48 h. Norfloxacin concentrations in plasma and urine were determined by high-performance liquid chromatography. Mean area under the plasma concentration-versus-time curve extrapolated to infinity decreased significantly ($P < 0.001$) after norfloxacin was given with and 2 h after sucralfate. The relative bioavailabilities were 1.8% when norfloxacin was taken with sucralfate and 56.6% when it was taken 2 h after sucralfate. After norfloxacin was given alone, the mean norfloxacin concentrations in urine collected during intervals of 0 to 12, 12 to 24, and 24 to 28 h were 118.9 ± 72.3, 18.8 ± 12.5, and 2.4 ± 2.2 μg/ml, respectively. After norfloxacin was given with sucralfate, however, the mean norfloxacin concentrations in urine collected during the same time intervals were 6.8 ± 4.7, 1.8 ± 1.4, and 0 ± 0 μg/ml, respectively. Because of low pH and relatively high magnesium concentration in urine, susceptibilities of bacteria in urine are 8- to 32-fold lower than in broth. This fact, in combination with the reduced bioavailability of norfloxacin in the presence of sucralfate or antacids, is likely to result in treatment failure. The effect of sucralfate given after norfloxacin was not examined, nor was the effect of sucralfate given more than 2 h before norfloxacin. Administration of norfloxacin with sucralfate should therefore be avoided.

Norfloxacin, a fluoroquinolone, possesses antibacterial activity against a wide spectrum of gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae* (10). It is principally used for the treatment of urinary tract infections caused by organisms resistant to other oral antimicrobial agents. Absorption of orally administered drug is not sufficient to provide concentrations in tissue and serum that exceed MICs for many pathogens. However, concentrations in urine are high, exceeding 40 μg/ml 12 h after a 400-mg dose (13).

Concurrent administration with aluminum- and magnesium-containing antacids decreases the absorption of oral fluoroquinolones (G. Hoffken et al., Letter, Eur. J. Clin. Microbiol. **4**:345, 1985; U. Jaehde, F. Sorgel, H. Koch, U. Stephan, B. Gottschalk, and W. Schunack, Clin. Pharmacol. Ther. **41**:66, 1987; L. C. Preheim et al., Letter, Lancet **ii**:294, 1986). In one study, the total urinary recovery of ciprofloxacin decreased from 24 to 2.1% and mean peak concentrations in serum decreased from 1.7 to 0.1 μg/ml after administration with these antacids (Hoffken et al., Eur. J. Clin. Microbiol., 1985). This interaction appears to be caused by chelation complex formation involving the aluminum cations of sucralfate and the carboxylic acid and ketone groups at positions 3 and 4 on the quinolone nucleus. The resulting complex is not absorbed through the intestinal mucosa. Although this interaction has not been studied with all quinolone antimicrobial agents, one would expect it to occur with all members of this class.

Sucralfate is a poorly absorbed complex of aluminum hydroxide and sulfated sucrose that is useful for treating peptic ulcers (4, 7). Once solubilized in the stomach, aluminum ions are released from the sucralfate molecule while the negatively charged sulfated sucrose skeleton binds to damaged mucosa, providing a protective barrier. It is possible that the free aluminum ions (16 per sucralfate molecule) bind with norfloxacin and other quinolones, thereby reducing absorption. In this study, the effect of sucralfate on the absorption of oral norfloxacin was evaluated.

MATERIALS AND METHODS

Eight healthy male volunteers between the ages of 18 and 40 were recruited to participate in this study. The study was approved by the Millard Fillmore Hospital Human Research Committee, and informed consent was obtained from all subjects. Subjects were required to be nonsmokers and weigh within 10% of ideal body weight as described in the Metropolitan Insurance Height and Weight Table. They were determined to be healthy by medical history, physical examination, and laboratory profiles. None of the subjects was taking medications within 1 week before or during the study.

The subjects received each of three treatments in a randomized crossover fashion separated by a 7-day washout period. For treatment A (control), subjects were given a single oral 400-mg dose of norfloxacin (Noroxin; Merck Sharp & Dohme; lot N9956). For treatment B, subjects ingested 1 g of sucralfate (Carafate; Marion Laboratories, Inc.; lot N7145) with a 400-mg norfloxacin dose. Norfloxacin (400 mg) was given 2 h after a 1-g sucralfate dose for treatment C. One day before receiving treatments B and C, subjects took 1 g of sucralfate four times a day at 7 a.m., 11 a.m., 5 p.m., and 10 p.m.

Subjects abstained from alcoholic beverages for 48 h

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TABLE 1. Pharmacokinetic parameters for three norfloxacin treatments[a]

Treatment	C_{max} (μg/ml)[b]	T_{max} (h)	AUC_{0-24} (μg · h/ml)[b]	$AUC_{0-\infty}$ (μg · h/ml)[b]	Half-life (h)	Urinary recovery (%)[b]
A	1.35 ± 0.69	1.28 ± 0.56	6.08 ± 2.68	7.09 ± 3.11	4.82 ± 1.31	29.3 ± 12.4
B	0.13 ± 0.07	1.50 ± 0.41	0.13 ± 0.16	0.13 ± 0.16	—[c]	1.8 ± 0.6
C	0.97 ± 0.60	1.21 ± 0.39	3.54 ± 2.18	4.01 ± 2.62	4.10 ± 1.43	22.0 ± 13.0

[a] Treatments: A, 400 mg of norfloxacin alone; B, 400 mg of norfloxacin concurrently with 1 g of sucralfate; C, 400 mg of norfloxacin 2 h after 1 g of sucralfate. C_{max}, peak norfloxacin concentration; T_{max}, time of peak norfloxacin concentration. Values are means ± standard deviations.
[b] $P < 0.001$; significant only for treatments A versus B and C versus B.
[c] None of the subjects had a sufficient number of concentrations in plasma above the minimal quantifiable concentration to determine a half-life.

before norfloxacin administration and fasted from at least 8 h before until 4 h after the norfloxacin dose. All tablets were swallowed whole, and compliance was assessed by tablet counts on each study day.

Blood samples (5 ml each) were obtained from an indwelling venous catheter or by direct venipuncture immediately before norfloxacin administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postdose. The blood was collected in heparinized vacuum tubes (Vacutainer) and centrifuged within 1 h to separate the plasma. Plasma was stored frozen at −20°C until analyzed. Subjects voided before norfloxacin administration to obtain a baseline urine sample. After the norfloxacin dose, urine was collected during the intervals 0 to 12, 12 to 24, and 24 to 48 h postdose. The total urine volume within each collection interval was determined, and a 10-ml portion of each sample was frozen at −20°C until assayed.

Norfloxacin assay. Norfloxacin concentrations in plasma and urine were determined by high-performance liquid chromatography. Samples were thawed and vortexed before analysis.

Plasma samples. To 0.5 ml of plasma were added 0.1 ml of 0.2 M (pH 7.4) phosphate buffer, 0.2 ml of internal standard (Abbott 56619, 40 μg/ml), and 0.2 ml of a 67% perchloric acid and acetonitrile (1:4) mixture. The mixture was immediately vortexed for 5 s and allowed to stand for 15 min. The supernatant was clarified by centrifuging for 5 min. A 20-μl portion of the sample was injected onto the column.

Equipment consisted of a high-performance liquid chromatography pump (Waters Associates, Inc.; model 6000A), an autosampler (Spectra-Physics; model SP8770-110), a UV detector (Kratos Spectroflow; model 757) set at 280 nm, and an integrator (Hewlett Packard Co.; model 3390A). Separation was achieved with a 5-μm octadecylsilane (Whatman Partisil Rac II) column (4.6 mm by 10 cm). The mobile phase consisted of a mixture of 130 ml of acetonitrile and 870 ml of 0.1 M citric acid, to which 0.54 g of ammonium perchlorate and 0.5 ml of 0.5 M tetrabutylammonium hydroxide were added. This was filtered and degassed before use. The flow rate was 1.5 ml/min.

Plasma standard curves were linear over a concentration range of 0.1 to 4 μg/ml. The minimal quantifiable norfloxacin concentration in plasma was 0.1 μg/ml. The overall relative standard deviations of seeded quality controls ranged from 3.4 to 5.6%.

Urine samples. Urine samples were prepared for extraction by adding 0.1 ml of 0.2 M (pH 7.4) phosphate buffer, 0.1 ml of a 50-μg/ml internal standard (Abbott 56619), and 0.8 ml of distilled deionized water to 0.1 ml of urine. The mixture was vortexed for 10 s. To a Bondalute C-18 extraction cartridge (Analytichem International) were added sequentially 2 ml of methanol, 2 ml of distilled deionized water, 1 ml of the prepared urine sample, 2 ml of distilled deionized water, 1 ml of 0.1 M (pH 6.5) phosphate buffer, 2 ml of distilled deionized water, and 1 ml of 10% acetonitrile in 0.1 M citric acid. Norfloxacin and the internal standard were then eluted with two 0.5-ml samples of 50% acetonitrile in 0.1 M (pH 2.5) phosphate buffer and two 0.5-ml samples of 0.1 M citric acid. The eluant was collected and vortexed for 5 s, and 10 μl was injected onto the column. Equipment consisted of a high-performance liquid chromatography pump (Waters; model 6000A), an autosampler (Waters WISP, model 712), a fluorescence detector (Schoeffel L. C.; model FS-970) set at 280 nm excitation with a 440-nm emission filter, and an integrator (Spectra-Physics; model SP4270). Separation was achieved with a 5-μm octadecylsilane column (Whatman Partisil Rac II; 4.6 mm by 10 cm). The mobile phase used was the same as for the plasma samples, except that 150 ml of acetonitrile was mixed with 850 ml of 0.1 M citric acid mixture. The flow rate was 1.0 ml/min.

Standards were prepared with norfloxacin concentrations ranging from 1.0 to 100.0 μg/ml. Peak area ratios were linearly related to concentrations over this range. The minimal quantifiable norfloxacin concentration in urine was 1.0 μg/ml. The overall relative standard deviations of seeded quality controls ranged from 2.3 to 9.9%.

Pharmacokinetics. Peak norfloxacin concentrations (C_{max}) and the time of the peak concentration (T_{max}) were determined from observed concentrations. The terminal elimination rate constant (k_{el}) was determined by linear regression of the ln plasma concentration-versus-time plot. Half-life was calculated as $\ln 2/k_{el}$. The total area under the plasma concentration-versus-time curve (AUC) from time zero to the last measured concentration (lmc) (AUC_{0-lmc}) was determined by using the trapezoidal rule. AUC from time zero to infinity ($AUC_{0-\infty}$) was calculated as AUC_{0-lmc} added to lmc/k_{el}. Mean renal clearance was calculated by dividing the total amount of norfloxacin excreted in 48 h by the AUC extrapolated to infinity.

Statistical analysis. Differences in the mean $AUC_{0-\infty}$, the percentage of the norfloxacin dose excreted, and the peak norfloxacin concentrations among the three treatment groups were examined for significance by analysis of variance appropriate for a three-way crossover design. An alpha value of 0.05 was used. Tukey's test was used when differences were noted.

RESULTS

Eight subjects completed the study. Ages ranged from 20 to 28 years (mean, 23 years), and weights ranged from 67.7 to 89.1 kg (mean, 75.7 kg). All subjects tolerated the protocol well, with only a few minor complaints of headaches, which required no treatment. Headaches were not correlated with norfloxacin concentrations in plasma.

Norfloxacin pharmacokinetic parameters for each treatment group are provided in Table 1. The mean plasma

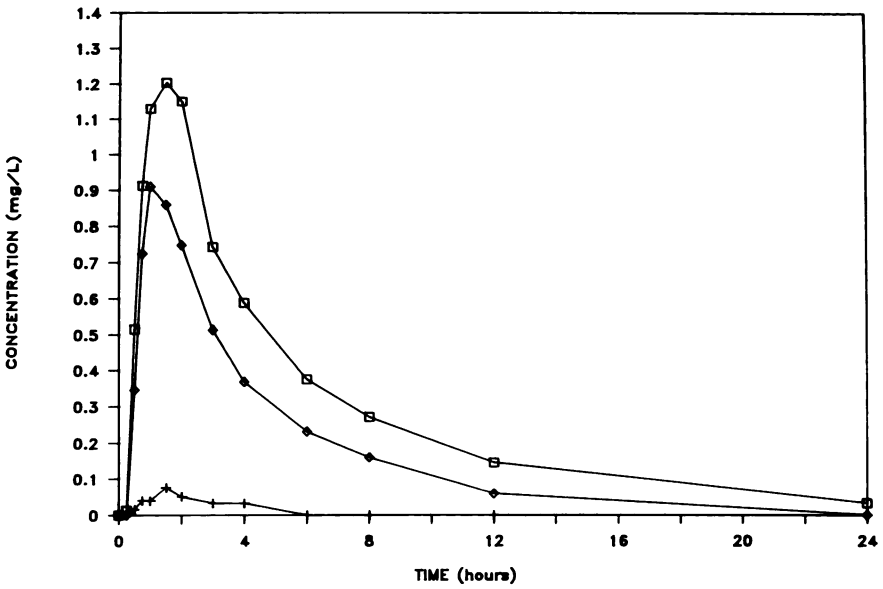

FIG. 1. Mean plasma norfloxacin concentration-versus-time curves for 400 mg of norfloxacin alone (□), 400 mg of norfloxacin with 1 g of sucralfate (+), and 400 mg of norfloxacin 2 h after 1 g of sucralfate (◇).

norfloxacin concentration-versus-time plots for the three treatment groups are shown in Fig. 1. All subjects had lower norfloxacin concentrations in plasma after taking norfloxacin with sucralfate than after taking norfloxacin alone. All subjects given norfloxacin with sucralfate had concentrations in plasma that were frequently below the minimal quantifiable concentration, and therefore k_{el} could not be determined. Mean AUC_{0-24} and $AUC_{0-\infty}$ decreased significantly ($P < 0.001$) when norfloxacin was administered with or 2 h after sucralfate compared with values obtained with norfloxacin alone. The relative bioavailability of norfloxacin when the drug was administered with sucralfate was 1.8%, whereas when the drug was administered 2 h after sucralfate, the relative bioavailability of norfloxacin was 56.6%. The mean percentage of the norfloxacin dose recovered in urine was significantly ($P < 0.001$) lower after norfloxacin was administered with sucralfate than after norfloxacin was administered alone or 2 h after sucralfate.

Mean norfloxacin concentrations in urine during collection intervals were lower when norfloxacin was given with sucralfate and 2 h after sucralfate than when norfloxacin was given alone (Table 2). Mean renal clearances were 318.4 ± 134.8 and 382.6 ± 80.8 ml/min for norfloxacin alone and for norfloxacin taken 2 h after sucralfate treatments, respectively. It was not possible to calculate renal clearances for the norfloxacin-with-sucralfate treatment, since many plasma samples had undetectable norfloxacin concentrations.

TABLE 2. Mean concentrations of norfloxacin in urine at various time intervals after three treatments

Treatment[a]	Concn (μg/ml)[b] in urine at:		
	0 to 12 h	12 to 24 h	24 to 48 h
A	118.9 ± 72.3	18.8 ± 12.5	2.4 ± 2.2
B	6.8 ± 4.7	1.8 ± 1.4	0.0 ± 0.0
C	62.6 ± 63.4	11.2 ± 9.5	3.1 ± 1.6

[a] Treatments: A, 400 mg of norfloxacin alone; B, 400 mg of norfloxacin taken concurrently with 1 g of sucralfate; C, 400 mg of norfloxacin taken 2 h after 1 g of sucralfate.

[b] Values are means ± standard deviations.

DISCUSSION

The study presented here demonstrates that norfloxacin bioavailability is reduced in the presence of sucralfate. There were pronounced decreases in AUC_{0-24}, $AUC_{0-\infty}$, and C_{max} when subjects were given norfloxacin with or 2 h after sucralfate. Urinary norfloxacin concentrations decreased by more than 90% when norfloxacin was given with sucralfate. After subjects were given a single 400-mg norfloxacin dose alone, however, the AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, T_{max}, half-life, mean renal clearance, and percentage of the norfloxacin dose recovered in the urine (urinary recovery) were similar to those previously reported (13).

The most plausible explanation for this interaction is the formation of norfloxacin-aluminum chelates. Each sucralfate molecule has 16 aluminum ions (7) which are available to form chelation complexes with norfloxacin. A similar reaction occurs with quinolones and aluminum-magnesium-containing antacids. Currently, there are no published reports on the interaction of norfloxacin with sucralfate or with antacids. However, antacids containing magnesium and aluminum hydroxides and those containing calcium carbonate decrease the relative bioavailability of norfloxacin 98.5 and 65.3%, respectively, when norfloxacin is given 5 min after the antacid (D. E. Nix et. al., submitted for publication). Hoffken et al. (Eur. J. Clin. Microbiol., 1985) reported that total urinary recovery of ciprofloxacin decreased from 24 to 2.1% and that mean peak concentrations in serum decreased from 1.7 to 0.1 μg/ml after administration with aluminum and magnesium hydroxide antacids. Preheim and co-workers (Lancet, 1986) reported that mean peak ciprofloxacin concentrations in serum samples from patients treated with frequent antacid therapy were more than 60% lower than concentrations in samples from those not taking antacids.

Sucralfate preferentially binds to proteins in ulcerated tissue, forming a physical barrier against the diffusion of acid across the gastrointestinal mucosa (8, 9). This has led to the

speculation by several investigators (1, 2, 11) that sucralfate may form a barrier against drug absorption. Studies have shown that sucralfate does not affect the bioavailability of prednisone (2), cimetidine (1), aspirin (5), ibuprofen (11), or chlorpropamide (6). This supports the hypothesis that the mechanism of drug absorption inhibition by sucralfate is related more to chelation formation than to the presence of a physical barrier against absorption through the gastrointestinal mucosa. The quinolone interaction with antacids that contain aluminum and magnesium salts may result from complexation with aluminum or from altered quinolone dissolution in the stomach because of the higher pH. Since sucralfate causes a similar decrease in norfloxacin absorption, it appears that aluminum is responsible for the interaction.

Because of low pH (3, 14) and relatively high magnesium concentrations (12), norfloxacin MICs for many bacteria are 8- to 32-fold higher in urine than in broth. This fact, in combination with the reduction in norfloxacin bioavailability and reduced urinary concentrations when norfloxacin is given with sucralfate or antacids, is likely to result in failure of treatment for urinary tract infections. The administration of norfloxacin with sucralfate should be avoided.

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