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Effect of Sucralfate on Absorption of Norfloxacin and Ofloxacin

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The effect of sucralfate on the pharmacokinetics of norfloxacin and ofloxacin was assessed in two separate crossover studies with healthy volunteers. In both studies, eight subjects were randomized to one of the following three regimens: a 400-mg dose of norfloxacin or ofloxacin alone, norfloxacin or ofloxacin given simultaneously with sucralfate (1 g), or norfloxacin or ofloxacin given 2 h before sucralfate. Coadministration of sucralfate reduced the bioavailability of norfloxacin and ofloxacin by 91% ($P < 0.001$) and 61% ($P < 0.001$), respectively. However, when norfloxacin and ofloxacin were given 2 h before sucralfate, there were no significant alterations in the pharmacokinetics of either fluoroquinolone. Similar results were obtained when the cumulative amount of each fluoroquinolone recovered in the urine was used to calculate bioavailability. To avoid these interactions and potential therapeutic failures, norfloxacin and ofloxacin should not be used concurrently with sucralfate. The interaction can be minimized by maximizing the time between the fluoroquinolone dose and the previous sucralfate dose and giving the fluoroquinolone at least 2 h before another sucralfate dose.

Antacids and sucralfate are known to impair the absorption of fluoroquinolone antimicrobial agents from the gastrointestinal tract by formation of nonabsorbable chelate complexes (1–4, 10, 11, 15–17). Sucralfate has been shown to decrease the absorption of, e.g., ciprofloxacin (3, 15), norfloxacin (17), and fleroxacin (11). The bioavailability of ciprofloxacin and norfloxacin was reduced by about 90% when they were administered with sucralfate. However, coadministration of fleroxacin with sucralfate only slightly decreased the absorption of the former. To our knowledge, there is no published study on the effect of sucralfate on the absorption of ofloxacin.

It has been demonstrated that the interaction with sucralfate can be decreased by staggering the administration times of sucralfate and a fluoroquinolone (15, 17). However, in these studies, sucralfate was given before the fluoroquinolone dose, which may not be the best approach. In addition to the length of the interval separating the intake of a fluoroquinolone and a drug containing cations, the sequence in which the drugs are ingested is important.

The purposes of this investigation were to study the effect of sucralfate on the absorption of ofloxacin and norfloxacin and to determine whether probable interactions could be prevented by giving the fluoroquinolone dose 2 h before sucralfate.

MATERIALS AND METHODS

Subjects and study design. Two separate randomized three-period crossover studies were performed. Treatments were separated by a 7-day washout period. A total of 16 volunteers were recruited to participate in this investigation. The subjects were determined to be healthy on the basis of medical history, physical examination, and laboratory tests. They were thoroughly informed in writing, and verbal consent was obtained. The study protocol was approved by the ethics committee of the Turku University Medical School.

In the first study, eight volunteers (six males and two females, with a mean [± standard deviation] age of 25 ± 4 years and weight of 72.4 ± 12.1 kg) were randomly assigned to take, after an overnight fast, 400 mg of norfloxacin (two 200-mg Lexinor tablets [Astra Pharmaceuticals, Södertälje, Sweden]) alone, norfloxacin with 1 g of sucralfate (one 1-g Antepsin tablet [Medipolar, Oulu, Finland]), or norfloxacin alone followed by 1 g of sucralfate 2 h later. In the second study, the interaction of sucralfate (1 g) with ofloxacin (400 mg, two 200-mg Tarivid tablets [Hoechst AG, Frankfurt am Main, Germany]) was examined in eight volunteers (six males and two females; age, 22 ± 1 years; weight, 66.1 ± 5.9 kg), by using the same design as in the norfloxacin study. All drugs were administered with 200 ml of water, and tablets were swallowed whole. Fasting was continued for 3 h after drug intake. The volunteers could move as desired.

Blood samples (7 ml each) were obtained by direct venipuncture just prior to fluoroquinolone administration and 0.5, 1, 1.5, 2, 3, 5, 9, and 24 h postdose. Samples were collected into sterile vacuum tubes and centrifuged within 30 min of collection. Plasma was stored at −20°C until analyzed. Urine was collected at intervals of 0 to 9 and 9 to 24 h postdose. The total urine volume within each interval was recorded, and a 5-ml portion of each sample was frozen at −20°C until assayed.

Drug assay. Norfloxacin and ofloxacin concentrations in plasma and urine were determined by reversed-phase high-performance liquid chromatography, with a fluorescence detector, as described by Griggs and Wise (5). Briefly, 0.3 ml of 7% perchloric acid was added to 0.5 ml of plasma, and the mixture was vortexed for 15 s. After centrifugation, 20 μl of supernatant was injected onto the column. Urine samples (100 μl) were diluted 1:10 or 1:50 with deionized water and injected onto the column. The drugs were isolated on a C_{18} reversed-phase column (NOVA-PAK, 3.9 mm by 15 cm [Waters Associates, Harrow, United Kingdom]), using as mobile phase a mixture of 18 mM potassium dihydrogen phosphate with 0.13 mM heptane sulfonic acid, methanol, and concentrated phos-

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phoric acid (700:300:1) at a flow rate of 1.1 ml/min. No internal standard was used. The minimal quantifiable concentration of norfloxacin and ofloxacin was 0.1 μg/ml. The between-days coefficients of variation in plasma were 2.6% (mean, 1.6 μg/ml, $n = 9$) and 2.7% (mean, 1.1 μg/ml, $n = 7$) for norfloxacin and ofloxacin, respectively. The within-day coefficients of variation for a low-concentration control plasma sample were 5.2% (mean, 0.18 μg/ml, $n = 9$) for norfloxacin and 5.5% (mean, 0.17 μg/ml, $n = 9$) for ofloxacin. Norfloxacin and ofloxacin urine samples were analyzed in three and two runs, respectively, the concentrations in the individual control samples being 58, 59, and 58 μg/ml for norfloxacin and 95 and 92 μg/ml for ofloxacin.

Pharmacokinetics and statistical analysis. Peak norfloxacin and ofloxacin concentrations in plasma (C_{max}) and the times of the peak concentrations (T_{max}) were obtained directly from the plasma drug-time profile for each subject. The area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) was calculated by using the linear trapezoidal rule method. From the urine data, the total amount of unchanged fluoroquinolone excreted over 24 h following each treatment was calculated.

Statistical analyses were made with the SYSTAT software package (SYSTAT Inc., Evanston, Ill.). Within each study, the parameters of the treatment periods (except for T_{max}) were compared with the control values by the Student t test (two tailed) for paired values. The Wilcoxon paired-sample test was used for analysis of T_{max}. P values of <0.01 were considered to be statistically significant. Results are expressed as means ± standard deviations.

RESULTS

As shown in Fig. 1, norfloxacin concentrations in plasma were profoundly decreased when norfloxacin was administered with sucralfate. The mean AUC_{0-24} of norfloxacin was reduced by 91% ($P < 0.001$) and the mean C_{max} was reduced by 92% ($P < 0.001$) by sucralfate (Table 1). The mean total amount of norfloxacin recovered in the urine was decreased by 91% ($P < 0.001$) when norfloxacin was administered with sucralfate (Table 1 and see Fig. 3). The T_{max} showed no statistically significant difference between the treatments. In contrast, when norfloxacin was taken 2 h before sucralfate, no significant differences were observed in AUC_{0-24}, C_{max}, T_{max}, or urine recovery of norfloxacin. However, considerable interindividual variability was observed in the relative bioavailability of norfloxacin when it was administered 2 h before sucralfate (Table 1 and see Fig. 4).

The bioavailability of ofloxacin was also significantly reduced by simultaneous administration of sucralfate (Fig. 2). The mean AUC_{0-24} of ofloxacin was lowered by 61% ($P < 0.001$) and the mean C_{max} was lowered by 70% ($P < 0.001$) by sucralfate (Table 1). Similarly, coadministration of sucralfate resulted in a reduction of 54% ($P < 0.001$) in the mean amount of ofloxacin excreted in the urine over 24 h (Fig. 3 and Table 1). The T_{max} was not significantly affected by coadministration of sucralfate. As in the case of norfloxacin, there were no significant differences in any of the pharmacokinetic parameters or in the urinary recovery of ofloxacin when it was given 2 h before sucralfate. The relative bioavailabilities of ofloxacin for the sucralfate treatments showed little interindividual variability (Fig. 4).

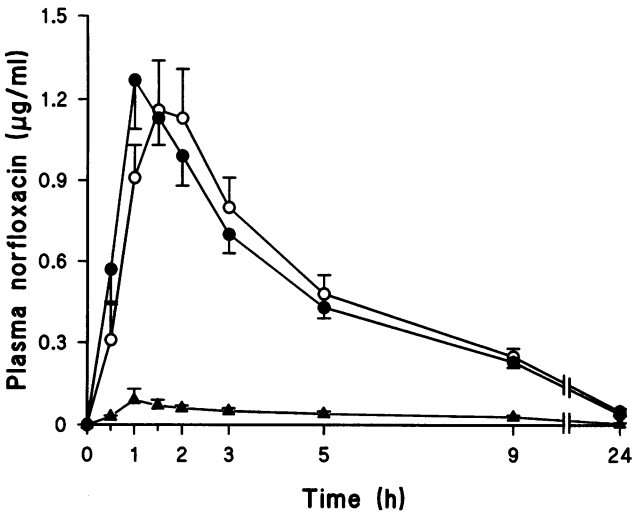

FIG. 1. Plasma norfloxacin concentration-versus-time profiles for 400 mg of norfloxacin alone (○), 400 mg of norfloxacin 2 h before 1 g of sucralfate (●), and 400 mg of norfloxacin with 1 g of sucralfate (▲). Values are means ± standard errors.

DISCUSSION

The present study demonstrated that the bioavailability of norfloxacin and ofloxacin is markedly reduced by concomitant ingestion of sucralfate. However, there was an obvious difference in the extent of the interaction between the two fluoroquinolones, ofloxacin being much less affected than norfloxacin. In contrast, when sucralfate was given 2 h after norfloxacin and ofloxacin, it had no significant effect on the bioavailability of either fluoroquinolone.

A drug interaction between sucralfate and ciprofloxacin, enoxacin, fleroxacin, and norfloxacin has been reported previously (3, 6, 11, 17). Some investigators have also evaluated the effect of staggered dosing of fluoroquinolones and sucralfate on the extent of the interaction. Sucralfate reduced the bioavailability of ciprofloxacin by 88% (with 1 g of sucralfate administered four times on the day before the study and the fifth dose given with ciprofloxacin) (3). However, when a 1-g dose of sucralfate was given 6 and 2 h before ciprofloxacin, only a 30% decrease in the bioavailability of ciprofloxacin was observed (15). Sucralfate had an even more dramatic effect on the absorption of norfloxacin. The relative bioavailability was only 2% when norfloxacin was given with sucralfate (1 g) and 57% when it was given 2 h after sucralfate (1 g). (Both treatments included a 1-day pretreatment with sucralfate [17].) When sucralfate (1 g) was given with enoxacin, the extent of enoxacin absorption was reduced by 88%, but if enoxacin was administered 2 h before sucralfate, the reduction was less than 10% (6). By contrast, giving enoxacin 2 h after sucralfate resulted in a greater than 50% reduction in enoxacin absorption (6). Lubowski et al. (11) have recently shown that fleroxacin is not as susceptible to interaction with sucralfate as are the fluoroquinolones mentioned above. The absorption of fleroxacin was reduced by 24% when it was given concomitantly with sucralfate (1 g). (Sucralfate was given every 6 h, starting 24 h before and continuing for 48 h after the fleroxacin dose.)

Sucralfate is a complex salt of sucrose sulfate and aluminum hydroxide that contains roughly 200 mg of aluminum per g (12). Once dissolution has occurred in the gastric juice, trivalent aluminum ions are released. It is generally accepted that

TABLE 1. Pharmacokinetic parameters for norfloxacin and ofloxacin after single oral doses of 400 mg given alone, 2 h before sucralfate, and with sucralfate[a]

Treatment	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24}		Urine recovery	
			μg · h/ml	% of control	mg	% of control
Norfloxacin alone (control)	1.29 ± 0.54	1.6 ± 0.4	7.39 ± 2.65	100	136 ± 49	100
Norfloxacin 2 h before 1 g of sucralfate	1.41 ± 0.38	1.3 ± 0.5	7.02 ± 1.68	95[b]	121 ± 33[c]	90[b]
Norfloxacin with 1 g of sucralfate	0.10 ± 0.10[d]	1.8 ± 1.4	0.64 ± 0.41[d]	8.7[b]	12.0 ± 7.2[d]	8.8[b]
Ofloxacin alone (control)	3.05 ± 0.75	1.6 ± 0.7	29.5 ± 7.37	100	355 ± 22	100
Ofloxacin 2 h before 1 g of sucralfate	3.26 ± 0.60	1.3 ± 0.4	27.9 ± 6.30	95	351 ± 31[e]	96
Ofloxacin with 1 g of sucralfate	0.93 ± 0.25[d]	2.9 ± 1.5	11.5 ± 2.66[d]	39	165 ± 23[d]	46

[a] Data are mean values (± standard deviations as appropriate) for eight subjects.
[b] Excluding one subject on the basis of AUC data (control, 2.04 μg · h/ml; norfloxacin 2 h before sucralfate, 8.23 μg · h/ml; norfloxacin with sucralfate, 0.58 μg · h/ml) gave the following values: norfloxacin 2 h before sucralfate, 84% ($P = 0.14$); norfloxacin with sucralfate, 8.0% ($P < 0.001$). (The urine data of this subject were in good agreement with the AUC data.) The corresponding values after reanalysis of the urine data were 80% ($P = 0.06$) and 8.3% ($P < 0.001$).
[c] The urine data of one subject were excluded from the calculations because of accidental loss of urine during collection.
[d] Significantly different ($P < 0.01$) from control.
[e] The urine data of two subjects were excluded from the calculations because of accidental loss of urine during collection.

the mechanism of the interaction between drugs containing metal ions and fluoroquinolones is chelate formation, resulting in impaired absorption of fluoroquinolones. Chelation probably occurs between the cation and the 4-keto and 3-carboxyl groups of fluoroquinolones (2, 7). Sucralfate has been shown not to affect substantially the bioavailability of, e.g., aspirin, cimetidine, diazepam, erythromycin, ibuprofen, ketoprofen, naproxen, prednisone, propranolol, or warfarin (12). This supports the hypothesis that the mechanism of inhibition of fluoroquinolone absorption by sucralfate is related to chelation and not to the presence of a physical barrier against absorption through the gastrointestinal mucosa. The larger effect of sucralfate on the absorption of norfloxacin compared with that of ofloxacin observed in this study comes as no surprise since fluoroquinolones clearly differ in their potential to interact with metallic cations (8, 9, 13, 14).

The interaction with sucralfate could be completely or almost completely avoided in all subjects in the ofloxacin study and in most subjects in the norfloxacin study by giving the fluoroquinolone dose 2 h before the sucralfate dose. Since the maximum concentration of both norfloxacin and ofloxacin in plasma was reached, on average, in less than 2 h (control treatment), it is reasonable to assume that the absorption process was in most cases completed before the fluoroquinolones came into contact with released aluminum ions. In the study by Parpia et al. (17), the mean relative bioavailability of norfloxacin was less than 60% when it was given 2 h after sucralfate. Clearly, not only the time interval between administrations of these interacting drugs, but also the sequence in which they are given, is important when trying to prevent this harmful interaction. Sucralfate is usually administered four times a day; with this dosing schedule, the interaction with fluoroquinolones probably cannot be avoided because of the constant presence of aluminum ions in the gastrointestinal tract.

To avoid potential treatment failures, the concurrent use of norfloxacin or ofloxacin and sucralfate should be avoided altogether. If it is not possible to avoid concomitant use of norfloxacin or ofloxacin and sucralfate, the interaction can be minimized by maximizing the time between the fluoroquin-

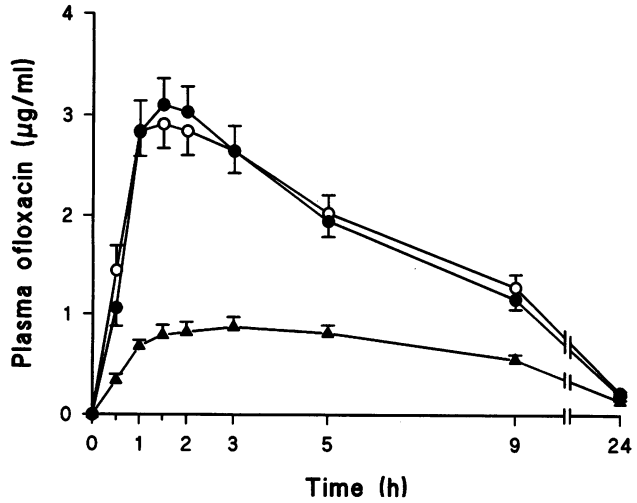

FIG. 2. Plasma ofloxacin concentration-versus-time profiles for 400 mg of ofloxacin alone (○), 400 mg of ofloxacin 2 h before 1 g of sucralfate (●), and 400 mg of ofloxacin with 1 g of sucralfate (▲). Values are means ± standard errors.

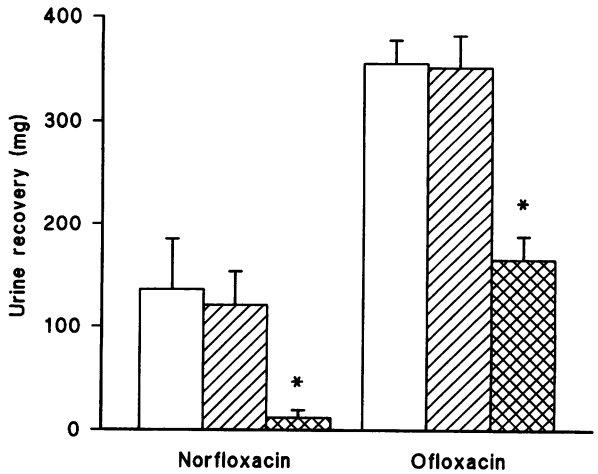

FIG. 3. Urinary recoveries (mean ± standard deviations) of norfloxacin (400 mg) and ofloxacin (400 mg) over 24 h in eight subjects after intake of each fluoroquinolone alone (open bars), 2 h before 1 g of sucralfate (hatched bars), and with 1 g of sucralfate (cross-hatched bars). *, significantly different from control ($P < 0.01$).

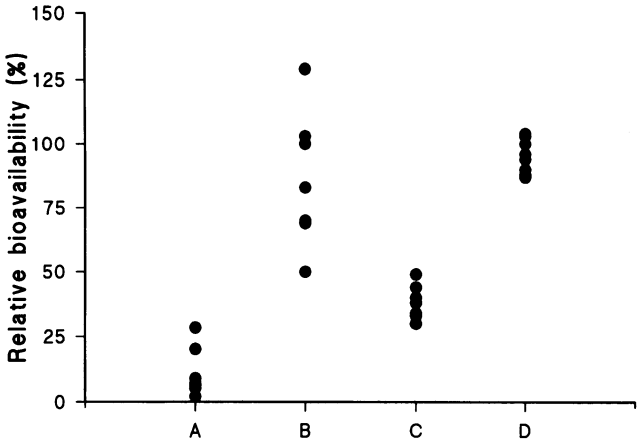

FIG. 4. Individual relative bioavailabilities of norfloxacin and ofloxacin after the sucralfate treatments (i.e., AUC_{0-24} values for the sucralfate treatments are given as percentages of the respective control values). A, norfloxacin with sucralfate; B, norfloxacin 2 h before sucralfate (one subject not included; see footnotes to Table 1); C, ofloxacin with sucralfate; D, ofloxacin 2 h before sucralfate.

olone dose and the previous sucralfate dose and by giving the fluoroquinolone dose at least 2 h before another sucralfate dose.

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