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Sucralfate Significantly Reduces Ciprofloxacin Concentrations in Serum

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The effect of sucralfate on the bioavailability of ciprofloxacin was evaluated in eight healthy subjects utilizing a randomized, crossover design. The area under the concentration-time curve from 0 to 12 h was reduced from 8.8 to 1.1 μg · h/ml by sucralfate ($P < 0.005$). Similarly, the maximum concentration of ciprofloxacin in serum was reduced from 2.0 to 0.2 μg/ml ($P < 0.005$). We conclude that concurrent ingestion of sucralfate significantly reduces the concentrations in serum produced by a 500-mg dose of ciprofloxacin. On the basis of these findings, ciprofloxacin and sucralfate should not be administered concurrently.

Several initial reports indicated that aluminum-containing antacids significantly impair the absorption of ciprofloxacin from the gastrointestinal tract (G. Hoffken et al., Letter, Eur. J. Clin. Microbiol. 4:345, 1985; L. C. Preheim et al., Letter, Lancet ii:48, 1986; L. W. Fleming et al., Letter, Lancet ii:294, 1986; J. J. Schentag et al., Clin. Pharmacol. Ther. 43:135, 1988). It has been postulated that the 3-carboxyl and 4-oxo functional groups on the ciprofloxacin molecule bind with the aluminum cations present in the antacid, thus resulting in the formation of a nonabsorbable complex (J. J. Schentag et al., Clin. Pharmacol. Ther. 43:135, 1988).

Sucralfate, which contains 16 aluminum ions per molecule, is widely used in the treatment of peptic ulcer disease and other gastrointestinal disorders (3). Once dissolution occurs in the stomach, aluminum is released from the molecule, as was evidenced by an increase in aluminum concentrations in serum and urinary excretion (5, 7, 9). Sucralfate has recently been reported to significantly impair the absorption of norfloxacin, another fluoroquinolone (8). Relative bioavailability when the two agents were taken concomitantly was reduced to 1.8%. Even when norfloxacin was administered 2 h after sucralfate, relative bioavailability was only 56.6%.

The objective of this study was to determine whether concurrent administration of sucralfate and ciprofloxacin reduced the bioavailability of ciprofloxacin, as measured by the area under the concentration-versus-time curve (AUC).

Eight healthy subjects (six males) were recruited to participate in the study. The protocol was approved by the local Institutional Review Board, and all subjects provided written informed consent. The participants were 24 to 36 years of age and weighed 77 ± 14 kg (mean ± standard deviation), and prestudy laboratory values were within 10% of normal limits. The weights of the patients were within 30% of ideal body weight. They were asked to abstain from alcohol for 72 h and all medications for 2 weeks before each study day. The subjects received each treatment in a randomized, crossover manner, separated by a 14-day washout period. Subjects assigned to treatment A (control) received a single 500-mg oral dose of ciprofloxacin (Cipro; Miles Pharmaceuticals, Inc.; lot BEA 9) with 240 ml of water, following an overnight fast, at 7 a.m. Subjects assigned to treatment B took 1 g of sucralfate (Carafate; Marion Laboratories; lot R8395) four times a day, 30 min before meals and at bedtime, on the day prior to the study. They then received ciprofloxacin (500 mg) and sucralfate (1 g), along with 240 ml of water, at 7 a.m. on the day of the study. Breakfast was provided to all subjects on the day of the study at 9 a.m.

Blood samples (7 ml each) were obtained from an indwelling venous catheter or by direct venipuncture immediately before ciprofloxacin administration and at 0.5, 1.0, 1.5, 2, 4, 6, 8, and 12 h postdose. Blood samples were collected into sterile vacuum tubes (Vacutainer), allowed to clot for approximately 30 min, and then centrifuged within 1 h. Serum was stored frozen at −80°C until analysis, which occurred within 2 weeks.

Maximum postdose ciprofloxacin concentrations in serum (C_{max}) and the time associated with C_{max} (T_{max}) were determined from the measured concentrations. AUC from 0 to 12 h (AUC_{0-12}) was estimated by using the trapezoidal rule. The significances of differences between the two means for AUC_{0-12}, C_{max}, and T_{max} were calculated by the Wilcoxon matched pairs signed ranks test.

Concentrations of ciprofloxacin in serum were determined in duplicate by a specific high-pressure liquid chromatographic assay modified slightly from that developed by Weber et al. (10).

Concentrations of ciprofloxacin in serum were quantitated by pipetting 250 μl of serum into 13- by 100-mm culture tubes containing 250 μl of acetonitrile and vortexing thoroughly. Each tube was then centrifuged for 10 min at 2,000 × *g*, and the supernatant was decanted. Twenty-five microliters of the supernatant was then injected onto a C-18 μBondapak reversed-phase column (3.9 mm by 30 cm; Waters Associates, Inc.). Protection of the column was achieved through the use of a Guard-PAK module containing a μBondapak C-18 insert (Waters Associates, Inc.).

The mobile phase consisted of acetonitrile in a phosphate buffer, adjusted to pH 3.3 with phosphoric acid, and filtered with a 0.45-μm-pore-size nylon membrane. A high-pressure solvent pump (M6000A; Waters Associates, Inc.) was used to maintain a constant flow rate through the column of 2 ml/min. A_{270} of the effluent from the column was monitored

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TABLE 1. Individual AUC_{0-12} comparisons for ciprofloxacin with and without the coadministration of sucralfate

Subject	AUC_{0-12} (μg · h/ml)	
	Ciprofloxacin alone	Ciprofloxacin plus sucralfate
1	8.6	0.2
2	11.7	1.0
3	9.5	0.0
4	7.5	0.8
5	6.6	0.7
6	8.0	0.8
7	10.2	3.3
8	8.1	2.1

by using a variable-wavelength UV-visible spectrum detector (SF770 Spectraflow; Applied Biosystems, Ramsey Analytical Division). A dual-pen recorder (Omniscribe B-5000; Houston Instruments) received the signal from the detector at 1 cm/min. Peak heights were used for quantitation of ciprofloxacin present in the sample.

Standard concentrations of 0.1, 1, 2, 3, 4, 5, and 10 μg/ml were prepared by diluting a 1,000-μg/ml ciprofloxacin stock solution with pooled blood bank serum. A calibration curve was constructed by a least-squares linear regression analysis of peak height versus concentration. The intra- and interassay coefficients of variation were 2.5 and 5.0%, respectively. The interday coefficients of variation were 1.7% at 10 μg/ml and 6.4% at 0.1 μg/ml. The assay was able to accurately detect concentrations of ciprofloxacin in serum as low as 0.1 μg/ml.

Table 1 shows the individual values for AUC_{0-12} for subjects receiving treatments A and B. The AUCs were lower in all subjects when they took sucralfate plus ciprofloxacin as compared with when they took ciprofloxacin alone. The AUCs were decreased to such a great extent when the subjects took sucralfate that concentrations in serum were frequently beneath the reliable sensitivity of the assay. The mean $AUCs_{0-12}$ were significantly different ($P < 0.005$) between treatments A and B (Table 2). The large magnitude of this difference could also be seen when the C_{max} values of the two treatments were compared ($P < 0.005$), while the T_{max} showed no significant difference. Actual plots of the mean concentration-time data of each treatment are shown in Fig. 1, which illustrates the marked reduction in AUC_{0-12} between the two groups.

Sucralfate produces a profound reduction in the concentrations of ciprofloxacin in serum and the bioavailability of ciprofloxacin when the two are ingested concurrently. There is a 10-fold reduction in C_{max} achieved. AUC_{0-12} for ciprofloxacin is only 12.5% of that when ciprofloxacin is administered alone. Ciprofloxacin and sucralfate should not be administered concurrently. The likelihood of therapeutic failure seems high, especially for moderately susceptible bacteria.

Estimated pharmacokinetic parameters (Table 2) in our subjects who took ciprofloxacin alone were very similar to parameters reported by other investigators (1, 2, 4). The effect of sucralfate on ciprofloxacin absorption was very consistent and produced marked changes in pharmacokinetic parameters when compared with the effects of ciprofloxacin alone. No subject achieved a C_{max} greater than 0.4 μg/ml; in five of the eight subjects, the C_{max} was 0.2 μg/ml. One of the subjects, during the interaction phase, did not have detectable concentrations of ciprofloxacin at any time. In contrast, there was a great deal of variability in T_{max} with

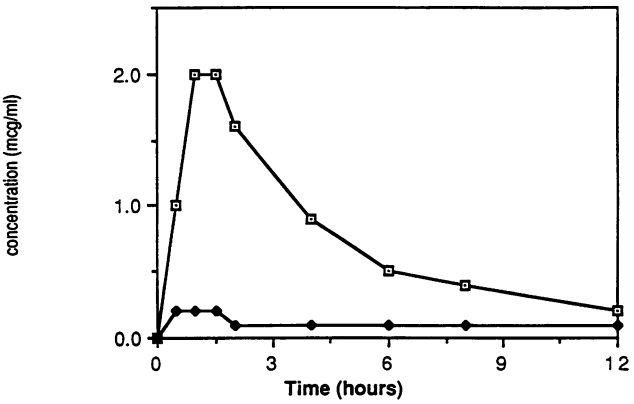

FIG. 1. Plot of mean concentrations of ciprofloxacin in serum versus time for subjects receiving ciprofloxacin alone (⊡) and with sucralfate (◆).

treatment B, with a standard deviation as large as the mean value. This differed from treatment A, where there was very little variability in the T_{max}. On the basis of the low, but nearly constant, concentrations of ciprofloxacin in serum achieved throughout the 12-h sampling period, it appears that coadministration of sucralfate also slows the rate of absorption of ciprofloxacin. It is unknown whether the binding between ciprofloxacin and sucralfate is reversible, although this would not be expected if complexation between the two molecules occurs. We cannot rule out continued absorption of ciprofloxacin past 12 h. However, this seems unlikely, as six of the eight subjects receiving treatment B had undetectable concentrations of ciprofloxacin in serum at 12 h. Because of the close approximation of these concentrations of ciprofloxacin in serum to the limit of detectability of the assay, it would be very difficult to determine whether continued absorption was occurring.

It has recently been reported that administration of sucralfate 6 and 2 h prior to administration of ciprofloxacin results in a 30% reduction in bioavailability (6). A decrease of more than 50% was noted in one-third of the subjects in that study. The question still remains as to what would happen if ciprofloxacin was given 2 h before sucralfate, instead of vice versa. Since T_{max} occurs early in most patients (1.4 ± 0.3 h in our study), perhaps this would allow extensive absorption to occur before sucralfate is administered. Since this would result in administration of ciprofloxacin 4 h after the previous dose of sucralfate (when it is being given every 6 h), this time interval should also be studied.

In summary, ciprofloxacin and sucralfate should not be administered concurrently. A significant reduction in bioavailability occurs with this combination, with the likelihood of therapeutic failure, especially for moderately susceptible bacteria. Additional work is necessary to evaluate alternative dosing strategies to minimize or avoid this interaction.

TABLE 2. Comparison of mean pharmacokinetic parameters for ciprofloxacin between the control and sucralfate interaction groups

Group	AUC_{0-12} (μg · h/ml)	C_{max} (μg/ml)	T_{max} (h)
Treatment A	8.8 (1.7)[a]	2.0 (0.5)	1.4 (0.3)
Treatment B	1.1 (1.1)	0.2 (0.1)	1.3 (1.2)

[a] Values in parentheses indicate one standard deviation.

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