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Inhibition of Enoxacin Absorption by Antacids or Ranitidine

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Ten normal volunteers participated in a randomized, five-way crossover study to determine the effect of concurrent enoxacin and antacid or ranitidine administration on enoxacin absorption. The bioavailability of a single oral 400-mg enoxacin dose was significantly decreased, by 73 and 49%, when Maalox TC was administered 0.5 and 2 h before enoxacin, respectively. Enoxacin bioavailability was not significantly altered when the antacid was given 8 h before or 2 h after enoxacin administration. Ranitidine, administered intravenously 2 h before enoxacin, also significantly decreased enoxacin bioavailability, by 40%. The correlation between the proximity of antacid administration and the magnitude of the decrease in enoxacin bioavailability supports complexation as the mechanism of the antacid-enoxacin interaction. However, reduction of enoxacin bioavailability by ranitidine suggests that elevated gastric pH may also play a role in the antacid-enoxacin drug-drug interaction.

Coadministration of aluminum- or aluminum-and-magnesium-containing antacids with the quinolone antibiotics ciprofloxacin, ofloxacin, and pefloxacin decreases the concentrations in plasma and bioavailabilities of the antibiotics (2; L. W. Fleming, T. A. Moreland, W. K. Stewart, and A. C. Scott, Letter, Lancet ii:294, 1986; G. Hoffken, H. Lode, R. Wiley, P. D. Glatzel, D. Sievers, T. Oschewski, K. Borner, and P. Koeppe, Int. Symp. New Quinolones, p. 141, 1986; U. Jaehde, F. Soergel, H. U. Koch, U. Stephan, B. Gottschalk, and W. Schunack, Clin. Pharmacol. Ther. 41:166, 1987; L. C. Preheim, T. A. Cuevas, J. S. Roccaforte, M. A. Mellencamp, and M. J. Bittner, Letter, Lancet ii:48, 1986). In patients, concomitant antacid administration lowered ciprofloxacin levels in serum by at least 50% (2; Fleming et al., letter; Hoffken et al., Int. Symp. New Quinolones; Preheim et al., letter), and in normal volunteers, the bioavailability of ciprofloxacin was reduced by 90% when Maalox was coadministered (Hoffken et al., Int. Symp. New Quinolones).

The present study was designed to determine the effect of concurrent antacid administration on the pharmacokinetics of the quinolone antibiotic enoxacin. The influence of the time of antacid administration relative to enoxacin administration on enoxacin bioavailability was investigated to determine whether enoxacin could be given to patients receiving intensive antacid therapy. In addition, the effect of ranitidine-induced gastric-acid suppression on enoxacin absorption was also studied.

MATERIALS AND METHODS

Study design. Two males and eight females aged 20 to 40 years and weighing 54 to 78 kg participated in this nonblind, randomized, five-way crossover study. All subjects were in good health as determined by medical history, physical examination, electrocardiogram, and clinical laboratory tests. The protocol was approved by the Human Research Committee, and written informed consent was obtained from each subject.

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To facilitate sample collection, all enoxacin doses (400 mg) were administered in the morning. The five treatments, given at 1-week intervals, were (i) enoxacin alone, 30 min before breakfast; (ii) enoxacin administered 8 h after a bedtime antacid dose, 30 min before breakfast; (iii) enoxacin 30 min after antacid administration, 2 h before dinner; (iv) enoxacin administered 2 h after antacid administration, 0.5 h before dinner; and (v) enoxacin administered 2 h after a 50-mg intravenous ranitidine dose, 30 min before breakfast.

As per clinical use, antacid doses were administered 1 and 3 h after meals and at bedtime during treatments 2, 3, and 4. Enoxacin is typically given twice daily, in the morning before breakfast and in the evening around dinner time. Therefore, enoxacin was administered 30 min before breakfast (treatment 2) and 0.5 and 2 h before dinner (treatments 3 and 4, respectively). Each enoxacin dose was administered with 8 oz (240 ml) of water following an overnight fast (except for medications). Each antacid dose (30 ml of Maalox TC [Rorer] [liquid therapeutic concentrate suspension]) contained 1.8 g of magnesium hydroxide and 3.6 g of aluminum hydroxide.

Blood samples for the enoxacin and oxometabolite assay were collected before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after each enoxacin dose. Volunteers voided immediately prior to each enoxacin dose, and a sample of urine was saved for base-line determinations. Urine was collected for 48 h after each dose for determination of enoxacin and oxometabolite concentrations (0- to 24- and 24- to 48-h collections).

Assay. Plasma and urine samples were frozen at −70°C until assayed for enoxacin and oxometabolite concentrations. Plasma proteins were precipitated with a 4:1 solution of acetonitrile–60% perchloric acid. Plasma samples (0.5 ml) were mixed with 0.05 ml of internal standard (difloxacin [A-56619]; 0.02 mg/ml) and 0.2 ml of the acetonitrile-perchloric acid solution. After vortexing, samples were centrifuged for 5 min, and a 0.075-ml volume of the supernatant was analyzed. Urine samples (0.2 ml) were mixed with 0.5 ml of water, 0.2 ml of internal standard (0.2 mg/ml), and 0.2 ml of phosphate buffer (pH 7.4). Eluates (0.01 ml) from C18

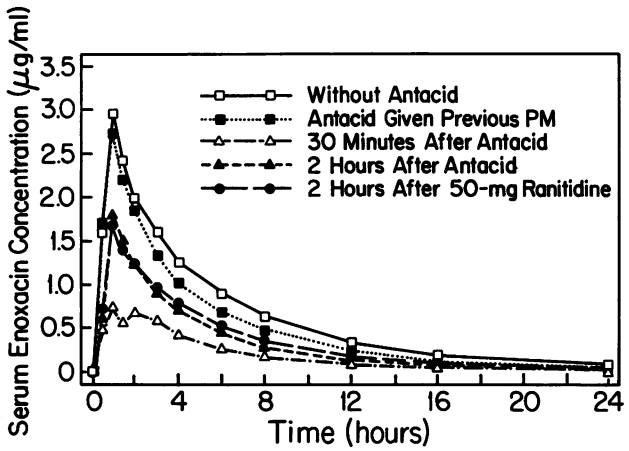

FIG. 1. Mean concentrations of enoxacin in plasma following a single 400-mg enoxacin dose.

solid-phase extraction cartridges (Analytichem) were analyzed.

Samples were injected onto a Whatman RAC II Partisil ODS 3 column (5 μm [particle size], 4.6 by 100 mm). High-pressure liquid chromatography was performed with a Waters 6000 pump, a Waters 712B autosampler, a Kratos UV detector at 340 nm, and a Spectra-Physics SP4270 integrator, with acetonitrile– 0.1 M citrate (15:85) as the mobile phase at a flow rate of 1 ml/min. Each liter of the citrate buffer contained 0.65 ml of 20% (wt/wt) tetrabutylammonium hydroxide and 450 mg of ammonium perchlorate.

For plasma, standard curves were linear from 0.025 to 5 μg/ml for enoxacin and from 0.0125 to 2.5 μg/ml for the oxometabolite. Overall recoveries were 109, 92, and 87% for enoxacin, the oxometabolite, and the internal standard, respectively. The overall intra- and interday variabilities of seeded plasma controls were 2.53 and 3.14%, respectively, for enoxacin and 5.23 and 3.79%, respectively, for the oxometabolite.

For urine, standard curves were linear from 0.833 to 250 μg/ml for enoxacin and the oxometabolite. Overall recoveries were 108, 100, and 106% for enoxacin, the oxometabolite, and the internal standard, respectively. The overall intra- and interday variabilities of seeded urine controls were 6.32 and 2.45%, respectively for enoxacin and 10.8 and 3.74%, respectively, for the oxometabolite.

Pharmacokinetic analysis. The peak concentration in plasma (C_{max}) and time to peak (T_{max}) were obtained by inspection of the plasma concentration-time curves. The area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) for enoxacin and the oxometabolite was calculated by using the linear trapezoidal rule. The elimination rate constant (k_{el}) was calculated by using linear regression of the terminal linear portion of the log concentration-time curve. The elimination half-life ($t_{1/2\beta}$) was calculated as $0.693/k_{el}$. Oxometabolite concentrations in urine and plasma were converted to enoxacin equivalents by multiplying them by the molecular weight of enoxacin divided by the molecular weight of the oxometabolite: 320/334 = 0.958.

Statistical analysis. Pharmacokinetic parameters were compared by analysis of variance (crossover), by using the method of least squares as applied in the general linear model of SAS (3). The model evaluated subject within sequence, period, and treatment effects. The Scheffe procedure was used for multiple comparisons when treatment effects achieved statistical significance ($P < 0.05$).

TABLE 1. Enoxacin pharmacokinetic parameters[a]

Treatment	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24} (mg · h/liter)	$t_{1/2\beta}$ (h)
1 (control)	3.17 ± 1.08	1.00 ± 0.33	14.5 ± 6.83	3.78 ± 1.17
2 (8 h)	2.88 ± 0.50	1.05 ± 0.28	12.0 ± 3.95	3.23 ± 0.81[b]
3 (0.5 h)	0.95 ± 0.73[b]	1.50 ± 0.53	3.89 ± 2.73[b]	2.86 ± 0.80[b]
4 (2 h)	1.95 ± 1.50	1.25 ± 0.36	7.59 ± 5.03[b]	3.01 ± 0.75[b]
5 (ranitidine)	1.75 ± 0.53[b]	1.15 ± 0.34	8.57 ± 2.74[b]	3.93 ± 1.16

[a] Mean ± standard deviation is shown for each parameter.
[b] Significantly different ($P < 0.05$) from control (treatment 1).

RESULTS

Levels of enoxacin in plasma were markedly decreased by the concomitant administration of Maalox TC (Fig. 1), and the extent of the interaction was related to the timing of the enoxacin dose relative to that of the antacid. The maximum antacid effect was observed when Maalox was administered 30 min before the dose of enoxacin (treatment 3). Statistically significant decreases in mean AUC_{0-24}, C_{max}, and $t_{1/2\beta}$ of 73, 70, and 24%, respectively, were observed (Table 1). Maalox given 2 h before enoxacin (treatment 4) also significantly decreased the mean AUC_{0-24}, C_{max}, and $t_{1/2\beta}$ by 49, 42, and 20%, respectively. Maalox administered 8 h before enoxacin or seven additional times beginning 2 h after enoxacin ingestion (treatment 2) did not produce significant changes in mean AUC_{0-24} or C_{max}. The enoxacin $t_{1/2\beta}$ was significantly decreased, by 15%. Treatment 5, intravenous ranitidine administered 2 h before enoxacin, produced a statistically significant 40% decrease in mean AUC_{0-24} and a 44% decrease in C_{max}. Mean $t_{1/2\beta}$ was not significantly affected.

The disposition of the oxometabolite was also affected by the administration of antacid (Table 2). Administration of Maalox 30 min before enoxacin significantly decreased the mean AUC_{0-24} of the oxometabolite by 68% and decreased its C_{max} by 55%. Maalox administered 2 h before enoxacin decreased the mean AUC_{0-24} of the oxometabolite by 43%.

Decreased urinary recoveries of enoxacin and the oxometabolite (Table 3) also indicate that coadministration of Maalox TC reduced the absorption of enoxacin. Administration of antacid 30 min before enoxacin resulted in a statistically significant 67% decrease in the amount of enoxacin recovered in the urine. Urinary oxometabolite recovery (expressed as enoxacin equivalents) was also significantly decreased, by 58%. Total recovery of drug (enoxacin plus the oxometabolite) in the urine was decreased by 67%. As expected, administration of antacid 2 h before enoxacin also significantly reduced the urinary recovery of enoxacin and the oxometabolite, but to a lesser extent. Recoveries of enoxacin, oxoenoxacin, and total drug were reduced by 39, 32, and 38%, respectively.

TABLE 2. Oxometabolite pharmacokinetic parameters[a]

Treatment	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24} (mg · h/liter)
1 (control)	0.52 ± 0.18	1.5 ± 0.37	2.74 ± 1.33
2 (8 h)	0.48 ± 0.18	1.35 ± 0.41	2.16 ± 0.81
3 (0.5 h)	0.23 ± 0.11[b]	1.5 ± 0.40	0.88 ± 0.50[b]
4 (2 h)	0.38 ± 0.27[b]	1.55 ± 0.60	1.57 ± 0.95[b]
5 (ranitidine)	0.41 ± 0.20	1.45 ± 0.37	1.93 ± 0.68

[a] Mean ± standard deviation is shown for each parameter.
[b] Significantly different ($P < 0.05$) from control.

TABLE 3. Recovery of enoxacin and the oxometabolite after 48 h

Treatment	Amt (mg) of following drug recovered[a]:		
	Enoxacin	Oxometabolite[b]	Enoxacin plus oxometabolite[b]
1 (control)	182.2 ± 54.5	42.3 ± 12.5	234 ± 51.7
2 (8 h)	138.4 ± 64.1[c]	33.0 ± 13.4	171 ± 71.9
3 (0.5 h)	62.5 ± 51.9[c]	17.3 ± 13.1[c]	80.4 ± 54.8[c]
4 (2 h)	115.8 ± 57.1[c]	28.9 ± 11.4	146 ± 84.7
5 (ranitidine)	128.2 ± 42.6[c]	33.5 ± 11.7	152 ± 45.5

[a] Mean ± standard deviation is shown for each value.
[b] Expressed as enoxacin equivalents.
[c] Significantly different ($P < 0.05$) from control (treatment 1).

DISCUSSION

Current speculation about the mechanism of the interaction between antacids and quinolone antibiotics has focused on drug-cation chelation. In vitro studies of Timmons and Sternglanz (5) demonstrated the formation of complexes of nalidixic and oxolinic acids with divalent cations.

The correlation between the proximity of Maalox administration and the magnitude of the decrease in enoxacin bioavailability is consistent with complexation as a potential mechanism of antacid-enoxacin interaction. Differences in meals, to simulate the clinical situation, should not have influenced study results, because the bioavailability of enoxacin is unchanged when the drug is coadministered with food (4).

The $t_{1/2\beta}$ of enoxacin was also decreased by concomitant antacid administration. If enoxacin was subject to enterohepatic recirculation, complexation and interruption of this pathway could explain the decrease in half-life. In addition, enoxacin could passively diffuse back into the intestine and be bound to the antacid.

Reduction of enoxacin bioavailability by ranitidine suggests that additional mechanisms may contribute to enoxacin-antacid drug-drug interaction. In vitro data indicate that the solubility of enoxacin is dependent on solvent pH (data on file, Parke-Davis). As the buffer pH increased from 1 to 4.4, the solubility of enoxacin decreased approximately 16-fold. Since intravenous administration of 50 mg of ranitidine has been reported to increase the gastric pH to at least 5 (1), decreased enoxacin bioavailability observed following ranitidine administration probably is the result of reduced gastric enoxacin dissolution and subsequent gastrointestinal absorption. Similar effects have not been reported in previous studies of other quinolones. Ranitidine did not affect the bioavailability of ciprofloxacin or ofloxacin following oral administration (Hoffken et al., Int. Symp. New Quinolones), and coadministration of a calcium-containing antacid did not, in patients, alter ciprofloxacin concentrations in plasma (Fleming et al., letter).

As has been reported for other quinolone antibiotics, enoxacin C_{max} and AUC_{0-24} were markedly decreased by coadministration of a magnesium- and aluminum-containing antacid. This effect was prominent when enoxacin was given 0.5 to 2 h after antacid ingestion. Maalox TC given both 8 h before and 2 h after enoxacin administration did not decrease enoxacin bioavailability. Hence, it should be possible to minimize antacid-induced decreases in enoxacin absorption by widely separating antacid and enoxacin dosing or by giving antacid after much of the enoxacin dose is absorbed (2 h postdose). However, it appears that in patients receiving intensive antacid regimens, 1 and 3 h after meals and at bedtime, reduced enoxacin availability in the evening cannot be avoided.

Until further data become available, it is recommended that concomitant administration of quinolone antibiotics and magnesium- or aluminum-containing antacids be avoided. Further investigation of the effects of H_2 antagonists and other types of antacids on the bioavailability of oral quinolones is also required.

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