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Effects of Aluminum Hydroxide and Calcium Carbonate Antacids on the Bioavailability of Ciprofloxacin

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This study was designed to determine the effects of an aluminum hydroxide antacid and a calcium carbonate antacid on the bioavailability of ciprofloxacin (Cipro). Cipro (750 mg) was administered orally to 12 healthy volunteers in a three-way randomized crossover design. The three treatments included Cipro alone, four 850-mg calcium carbonate tablets taken 5 min before Cipro, and three 600-mg aluminum hydroxide tablets taken 5 min before Cipro. The relative bioavailability of Cipro when given with calcium carbonate was approximately 60% of the control value. When Cipro was given with aluminum hydroxide, the relative bioavailability was approximately 15%. Urinary recovery of Cipro in the aluminum hydroxide treatment group was approximately one-fourth of that in the calcium carbonate group. Although calcium carbonate decreased absorption to a lesser extent than aluminum hydroxide, these data suggest that antacids containing either aluminum or calcium should not be given concomitantly with Cipro.

Ciprofloxacin is a widely used antimicrobial agent belonging to the quinolone class. As has been previously demonstrated both in healthy volunteers (5) and in elderly patients (8), absorption of ciprofloxacin is decreased by concomitant administration of antacids which contain both aluminum and magnesium. Recently it was shown that the extent of this interaction with the antacid Maalox decreases as the time interval between antacid administration and ciprofloxacin dosing increases (7). Fleming and coworkers observed that Titralac, an antacid that contains only calcium, did not inhibit ciprofloxacin absorption in chronic ambulatory peritoneal dialysis patients (2). Golper et al. (4) observed that in three patients taking aluminum hydroxide, the peak concentration of ciprofloxacin was decreased. Thus, we decided to confirm the observations of Fleming and Golper in a well-controlled crossover design study. Therefore, the two objectives of this study were to investigate the effect of concomitant administration of aluminum hydroxide (Amphojel) or calcium carbonate (Alka-Mints) on ciprofloxacin absorption.

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MATERIALS AND METHODS

Twelve healthy male volunteers participated in a single-dose three-way randomized crossover study. The volunteers ranged in age from 21 to 45 (mean ± standard deviation, 34.7 ± 7.5) years and weighed between 62 and 87 (mean ± standard deviation, 75.8 ± 9.0) kg. The volunteers fasted from midnight on the night preceding dosing until 4 h postdosing. They received each of the following three treatments in a randomized fashion: 750 mg of ciprofloxacin, 750 mg of ciprofloxacin administered 5 min after four Alka-Mints tablets (850 mg of calcium carbonate per tablet), and 750 mg of ciprofloxacin taken 5 min after three Amphojel tablets (600 mg of aluminum hydroxide per tablet). These antacid doses were chosen to approximate the acid-neutralizing capacity of a 30-ml dose of Maalox so that this study could be compared to prior research. In each treatment, the volunteers also consumed 180 ml of water. The subjects consumed a standardized meal 4 h after ciprofloxacin dosing. Blood samples were collected into nonheparinized tubes by direct venipuncture immediately before each dose and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 h after dosing. The serum was separated and frozen at −20°C until it could be analyzed. In addition, urine was collected at the following intervals: 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h after ciprofloxacin dosing. The total volume was recorded, and an aliquot was frozen for future analysis. The serum and urine samples were assayed for ciprofloxacin by using a high-performance liquid chromatographic method developed by Krol and coworkers (6). The isopropyl analog of ciprofloxacin was used as an internal standard. The urine samples were chromatographed on a polystyrene divinyl benzene column, which was monitored by UV absorbance. Serum ciprofloxacin concentrations were measured spectrofluorometrically, since this antimicrobial agent has native fluorescence. In serum, analytical recovery was 90 to 100% when measured against a pure unextracted standard. The intraday and interday coefficients of variation ranged from 4 to 9%. The limit of quantitation was 0.1 μg/ml. Recovery of ciprofloxacin from urine was 100%. Coefficients of variation ranged from 6 to 8%. The limit of quantitation in urine was 0.1 μg/ml.

Pharmacokinetic and statistical analyses. The maximum concentration in serum and the time required to reach this concentration were obtained from the observed data for each patient. The area under the serum concentration-versus-time curve was calculated by using a linear trapezoidal estimation. However, the terminal elimination rate constant was calculated by using the RSTRIP program, which utilizes both a curve-stripping algorithm and a nonlinear least-squares minimization procedure based on a modification of the Levenburg-Marquadt technique. The weighting scheme that we used for these data was $1/y^2$. The average renal clearance was determined by dividing the total amount excreted in the urine by the corresponding area under the

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TABLE 1. Ciprofloxacin pharmacokinetic parameters following three treatments

Treatment[a]	Mean ± SD[b]							
	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-t} (μg/h/ml)	CL_R (liters/h)	A_e (mg)[c]	A_e (% of dose)[c]	λ (h^{-1})	$t_{1/2}$ (h)
A	3.18 ± 1.29	1.24 ± 0.39	13.50 ± 4.61	18.4 ± 4.8	239.9 ± 61.0	31.3 ± 8.1	0.177 ± 0.061	3.9 ± 1.35
B	1.69 ± 0.48	1.29 ± 0.68	7.82 ± 3.09	20.8 ± 6.4	151.4 ± 51.6	20.2 ± 6.9	0.114 ± 0.046	6.1 ± 2.4
C	0.60 ± 0.58	1.61 ± 1.44	2.08 ± 1.20	16.9 ± 5.6	35.4 ± 25.2	4.7 ± 3.4	0.106 ± 0.062	6.5 ± 3.8

[a] Ciprofloxacin alone (A), with $CaCO_3$ (B), or with $Al(OH)_3$ (C).
[b] C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; AUC_{0-t}, area under the serum concentration-time curve from time zero to time t; CL_R, renal clearance; A_e, total amount excreted in urine; λ, terminal elimination rate constant; $t_{1/2}$, half-life.
[c] Collection interral, 0 to 24 h.

serum concentration-time curve from time zero to time t. Statistical comparisons between groups were made by using analysis of variance for crossover designs specifically for the parameters maximum concentration of the drug in serum, time to maximum concentration of the drug in serum, area under the serum concentration-time curve, renal clearance, and total amount excreted in urine. A Duncan's multiple-range test was used to evaluate differences in treatment means at $\alpha = 0.05$ if the analysis of variance detected a statistical difference.

RESULTS

The mean pharmacokinetic parameters following each of the three treatments are listed in Table 1. From these data, it appears that average bioavailability was reduced from the control value by approximately 85% with concomitant aluminum hydroxide administration and by 40% with calcium carbonate. Table 1 also shows that no significant changes in renal clearance resulted from administration of the antacids. Although the average area under the serum concentration-time curve was reduced after concomitant calcium carbonate administration, the effect in individual subjects varied. This variability is exemplified in Fig. 1 and 2. As shown in Fig. 1, the volunteer's serum concentrations were not significantly affected by calcium carbonate administration. In contrast, Fig. 2 shows a dramatic reduction in another volunteer's serum concentrations after coadministration of calcium carbonate. Therefore, this interaction may not be seen clinically in all patients because of this variability. However, one must realize that the maximum concentration of the drug in the patient's serum in Fig. 2 is 50% higher than that in Fig. 1, thus accentuating this difference. In contrast, however, it is interesting that the effects of aluminum hydroxide were identical in these patients.

DISCUSSION

The mean concentrations of ciprofloxacin in serum in a prior study (7) in which Maalox was administered concurrently were compared with those for the aluminum hydroxide treatment alone in this study and found to be almost superimposable, thus suggesting that the effect of Maalox could be totally attributable to the effect of aluminum hydroxide alone. However, further study of magnesium hydroxide alone is needed to test this hypothesis. If an interaction were not found, this information would be useful to nursing home practitioners who prescribe large quantities of Milk of Magnesia.

Sahai et al. (9) corroborated our findings with respect to the calcium carbonate interaction. In their study, a calcium supplement (Os-Cal) containing 500 mg of elemental calcium was given three times a day for 5 days and the ciprofloxacin dose was given at the same time as Os-Cal. Their study, like the present one, demonstrated an approximately 40% decrease in the bioavailability of ciprofloxacin. In contrast, when ciprofloxacin was given with a high-fat/high-calcium meal consisting of 729 mg of dietary calcium, no significant decrease in bioavailability was shown (3). The precise conditions required for ciprofloxacin to form chelate complexes with other cations have not been fully elucidated, but the carboxyl group seems to be the most likely site for chelation. Thus, the gastric pH would need to be elevated sufficiently to ionize the carboxyl group in the presence of cations. Therefore, the lack of interaction with dairy products might be attributable to a gastric pH that was not elevated suffi-

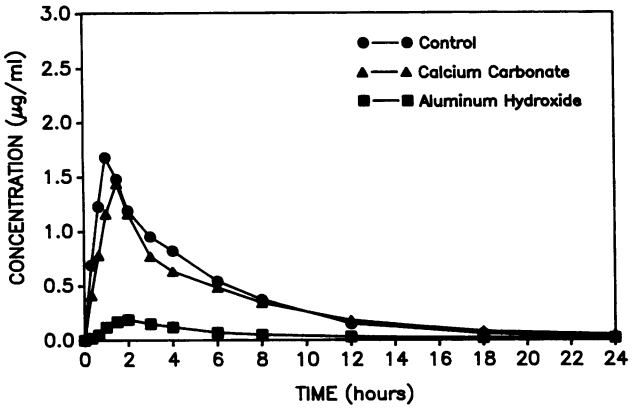

FIG. 1. Concentrations of ciprofloxacin in serum for subject 1.

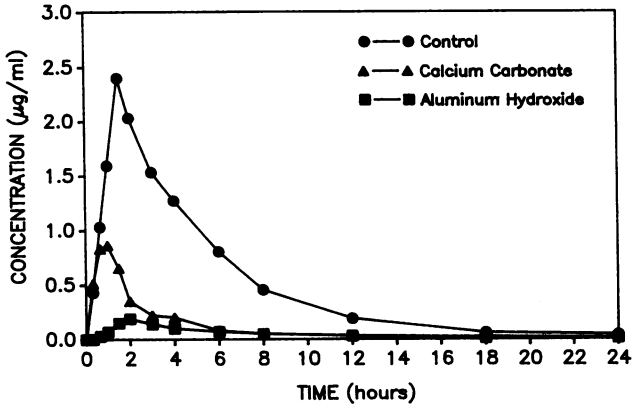

FIG. 2. Concentrations of ciprofloxacin in serum for subject 2.

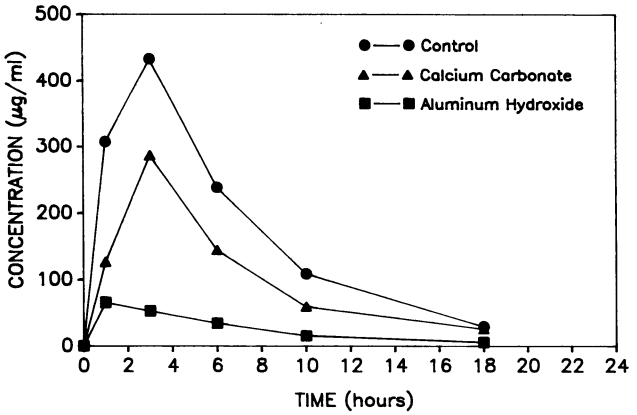

FIG. 3. Concentrations of ciprofloxacin in urine plotted at the midpoint of the collection interval.

ciently to ionize the carboxyl group. Alternatively, it could be due to a decrease in the availability of calcium to chelate ciprofloxacin because of a lipid barrier.

It is important not only to quantitate the extent of a drug interaction but, when possible, also to assess its clinical impact. The amount of calcium carbonate administered in the present study might only be given clinically to a dialysis patient requiring high doses for phosphate binding. Therefore, these results may be most useful to health professionals caring for dialysis patients. However, as one can see from the plot of the urinary concentrations in Fig. 3, despite the 40% decrease in ciprofloxacin absorption with calcium carbonate administration, the urinary concentrations would still sufficiently exceed the MIC for ciprofloxacin-susceptible uropathogens. Furthermore, calcium supplementation of bacterial growth medium used for in vitro testing, unlike magnesium, did not reduce the antibacterial activity of ciprofloxacin (1). Therefore, the presence of calcium in the urine should not adversely increase the MIC for susceptible bacteria.

The results from a study of the Maalox interaction (7) suggest that the interaction with a single antacid dose can be circumvented by administering the antacid 2 h after the ciprofloxacin dose. It is important to realize that in patients requiring aggressive antacid therapy for peptic ulcer disease, antacids cannot be given concomitantly with ciprofloxacin. However, it has been suggested that an H_2 antagonist may be a useful alternative to antacids for these patients (7).

We conclude from this study that aluminum hydroxide or high-dose calcium carbonate should not be given concomitantly with ciprofloxacin.

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