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Effects of Magnesium-Aluminum Hydroxide and Calcium Carbonate Antacids on Bioavailability of Ofloxacin

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The effects of 15- and 5-ml doses of magnesium-aluminum hydroxide (MAH) and calcium carbonate (CC) antacids, respectively, on the bioavailability of ofloxacin after single oral 400-mg doses of ofloxacin were investigated in a 32-subject, randomized, crossover, open-label study. On four separate occasions, subjects received ofloxacin alone or antacid 24 h before, 2 h before, or 2 h after ofloxacin administration (n = 16 for each antacid). CC administration had no significant effect on the rate and extent of ofloxacin absorption regardless of the timing of antacid administration. A small but significant negative effect of MAH administration 2 h before ofloxacin administration was noted as evidenced by area under the curve and peak concentration in plasma data. Simultaneous administration of ofloxacin with either antacid was not investigated in this study. It appears that MAH and CC antacids in the doses used in this study generally do not interfere in a clinically significant manner with the bioavailability of ofloxacin, provided that an interval of at least 2 h separates the administration of these products.

Ofloxacin is a synthetic carboxyquinolone antimicrobial agent which exhibits broad-spectrum in vitro bactericidal activities against gram-positive and gram-negative aerobes (8). The clinical efficacy of ofloxacin has been documented in patients with respiratory tract, upper and lower urinary tract, gonococcal and nongonococcal urethritis, and skin and soft tissue infections (8, 14).

Coadministration of some antacids and sucralfate has resulted in diminished absorption of several of the carboxyquinolones. This phenomenon has been reported to be due to the formation of insoluble chelates in the gastrointestinal tract (5–7, 9–12). Although the majority of these interaction studies have investigated the quinolone ciprofloxacin, four reports have suggested the existence of a similar interaction between antacids and ofloxacin (7, 12; G. Höffken, P. Olschewski, B. Sievers, H. Lode, K. Borner, and P. Koeppe, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 485, 1986; F. P. V. Maesen, B. I. Davies, W. H. Geraedts, and C. A. Sumajow, Letter, J. Antimicrob. Chemother. **19**:848–850, 1987).

This study was designed to rigorously characterize the interaction potential between ofloxacin and two commonly used antacid preparations: (i) magnesium-aluminum hydroxide (Maalox; Rorer Pharmaceutical Corp., Fort Washington, Pa.) and (ii) calcium carbonate (Titralac; 3M Riker, St. Paul, Minn.).

The study was approved by the Human Subjects Research Committee, Hennepin County Medical Center. Thirty-two normal, healthy male volunteers who participated in the study were between the ages of 18 and 40 years, and all subjects gave written, informed consent prior to participation. The patients were healthy, as determined by comprehensive medical history, physical examination, electrocardiography, and laboratory profiles. None of the subjects was taking medications within 1 week before or during the study. None of the subjects had a history or current evidence of significant renal, hepatic, cardiovascular, hematologic, neurologic, psychiatric, respiratory, or metabolic disease.

A parallel study design was followed wherein 16 subjects were randomly assigned to receive single doses of ofloxacin (2 × 200 mg, lot 4007; Ortho Pharmaceutical Corporation, Raritan, N.J.) and calcium carbonate (5 ml) and 16 were to receive single doses of ofloxacin (2 × 200 mg) and magnesium-aluminum hydroxide (15 ml). The assignment of study phase ordering was achieved by using a Latin square design. In both study arms, all patients received 400 mg of ofloxacin alone (regimen 1), ofloxacin preceded 2 h by antacid administration (regimen 2), ofloxacin followed 2 h later by antacid administration (regimen 3), and ofloxacin preceded 24 h by antacid administration (regimen 4). All subjects were fasted for at least 8 h prior to and for 1 h following administration of the second component of each regimen. Use of antacids, bismuth subsalicylate, or other gastrointestinal preparations at any time during the study period was prohibited. Study phases were separated by washout periods of at least 4 days.

Blood samples of 5 ml were obtained just prior to ofloxacin administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h following ofloxacin administration. Plasma was separated via centrifugation and stored frozen at −20°C until analysis.

The concentration of ofloxacin in plasma was determined by a high-pressure liquid chromatography method. After extraction at pH 7 with dichloromethane, the extract was injected onto a C_{18} μBondapak column (25 cm by 4.6 mm [inner diameter]; Waters Associates Inc., Milford, Mass.). The mobile phase consisted of 1.74 g of potassium dihydrogen phosphate and 20 mg of 1-hexanesulfonic sodium salt (Eastman Kodak Co., Rochester, N.Y.) dissolved in 650 ml of distilled water, combined with 350 ml of methanol, and adjusted to pH 3 with phosphoric acid. The imidazolic derivative of ofloxacin (Daiichi Seiyaku) was used as the internal standard. Detection was done with a UV detector at 313 nm. The limit of quantitation was 0.01 mg/liter, and the extraction efficiency was greater than 95%. The assay was linear over the concentration range of 0.025 to 9 mg/liter. The intra- and interday coefficients of variation ranged from

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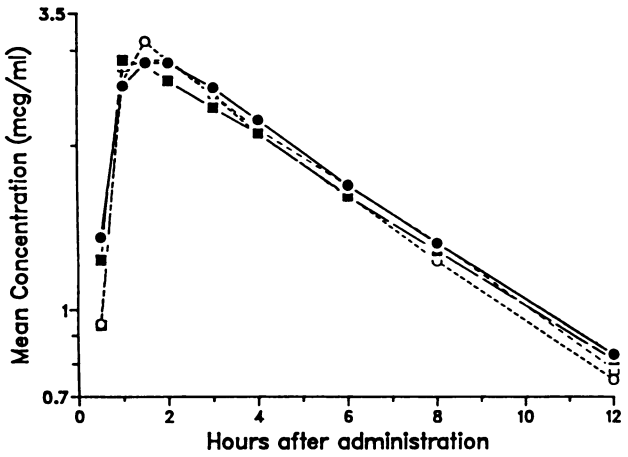

FIG. 1. Mean plasma ofloxacin concentration-versus-time curves for ofloxacin alone (●), calcium carbonate antacid administered 2 h prior to ofloxacin (■), calcium carbonate antacid administered 24 h prior to ofloxacin (○), and calcium carbonate antacid administered 2 h following ofloxacin (□).

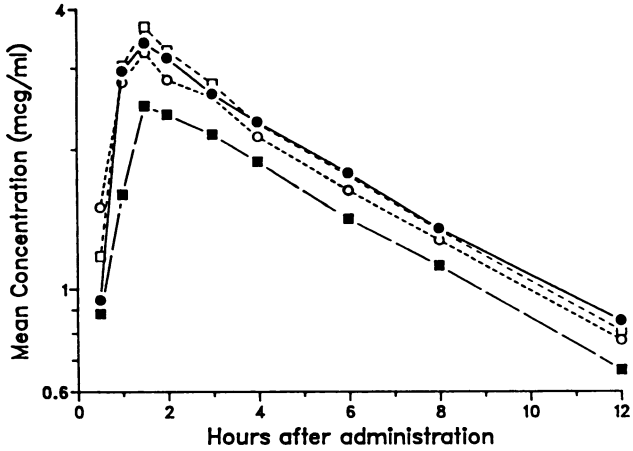

FIG. 2. Mean plasma ofloxacin concentration-versus-time curves for ofloxacin alone (●), magnesium-aluminum hydroxide antacid administered 2 h prior to ofloxacin (■), magnesium-aluminum hydroxide antacid administered 24 h prior to ofloxacin (○), and magnesium-aluminum hydroxide antacid administered 2 h following ofloxacin (□).

3 to 6% over the standard curve concentration range of 0.025 to 9 mg/liter (3).

Peak concentration in plasma (C_{max}) and time to achieve C_{max} (T_{max}) were determined by visual inspection of the plasma concentration-versus-time curves. The area under the plasma concentration-versus-time curve from time zero to 12 h following administration (AUC_{0-12}) was calculated by using the linear trapezoidal rule (4). Percent relative bioavailability was determined as the ratio of the AUC_{0-12} for the ofloxacin-antacid regimens to the AUC_{0-12} for the ofloxacin alone regimen times 100.

Bartlett's test was used to assess the homogeneity of variance between treatment regimens. Separate analysis of variance with Tukey's range test was performed for each antacid to determine between-regimen differences for AUC_{0-12}, C_{max}, and T_{max} values. Power calculations were performed by the method of Wagner (13) and Cohen (2). All statistical evaluations were performed by using the Statistical Analysis System (SAS Institute, Raleigh, N.C.) (1). Statistical significance was assessed at the 5% level.

Fifteen of 16 and 14 of 16 subjects in the calcium carbonate and magnesium-aluminum hydroxide treatment groups, respectively, completed the entire study. The dropouts occurred for personal or administrative reasons unrelated to the study. The mean plasma concentration-versus-time profiles for the calcium carbonate and magnesium-aluminum hydroxide treatment groups are depicted in Fig. 1 and 2, respectively.

In the calcium carbonate treatment group, there were no significant differences among regimens 1, 2, 3, and 4 with respect to AUC_{0-12} or C_{max} (Table 1). In addition, no significant differences among regimens 1, 2, 3, and 4 were noted with respect to T_{max}. The minimum detectable differences with 80% power for AUC_{0-12}, C_{max}, and T_{max} were 7.7, 18.0, and 40.0%, respectively.

In the magnesium-aluminum hydroxide treatment groups, significant differences were seen between regimen 2 (antacid 2 h prior to ofloxacin) and regimens 1, 3, and 4 with respect to AUC_{0-12} (16.69 ± 3.89, 21.24 ± 3.01, 21.61 ± 3.48, and 20.23 ± 3.18 mg · h/liter, respectively; $P < 0.05$) and C_{max} (2.6 ± 1.0, 3.7 ± 0.9, 3.8 ± 0.9 and 3.5 ± 0.9 mg/liter, respectively; $P < 0.05$) (Table 2). In addition, the T_{max} was significantly longer in regimen 2 than in regimens 3 and 4 (2.0 ± 0.7, 1.5 ± 0.5, 1.5 ± 0.5 h, respectively; $P < 0.05$). The minimum detectable differences with 80% power for AUC_{0-12}, C_{max}, and T_{max} were 12.0, 25.0, and 36.0%, respectively. The observed mean decreases in AUC_{0-12} and C_{max} and mean increase in T_{max} compared with the control phase were 21.8, 29.7, and 25.0%, respectively.

Indications of a possible interaction between ofloxacin and aluminum-based antacids have been reported (7, 12; Hoffken et al., 26th ICAAC; Maesen et al., Letter, J. Antimicrob. Chemother.). In patients with chronic renal insufficiency, reductions in ofloxacin efficacy (measured by elimination of bacterial strains) were associated with concomitant therapy with aluminum hydroxide phosphate binder therapy (12). In a study in healthy volunteers, administration of magnesium-aluminum hydroxide antacid within a 24-h period prior to ofloxacin administration was reported to reduce oral absorp-

TABLE 1. Pharmacokinetic parameters[a] for the ofloxacin-calcium carbonate treatment group

Regimen[b] (no. of subjects)	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-12} (mg · h/liter)	Relative bioavailability (%)
1 (14)	3.2 ± 0.7 (2.0–4.3)	1.7 ± 0.6 (1.0–3.0)	20.45 ± 3.10 (14.93–26.17)	100
2 (14)	3.3 ± 0.9 (2.0–5.0)	1.4 ± 0.6 (1.0–3.0)	19.68 ± 2.60 (13.84–22.82)	103.6 ± 10.8 (75.9–109.5)
3 (16)	3.3 ± 0.7 (2.2–4.6)	1.6 ± 0.8 (1.0–4.0)	20.13 ± 2.42 (15.11–24.40)	97.9 ± 9.8[c] (85.5–111.9)
4 (15)	3.5 ± 0.6 (2.5–4.8)	1.6 ± 0.7 (1.0–3.0)	19.58 ± 2.73 (15.28–24.15)	95.9 ± 8.2[c] (82.6–111.9)

[a] Values are means ± standard deviations. Ranges of values are given in parentheses.
[b] Regimens are described in the text.
[c] Data are given for 14 subjects.

TABLE 2. Pharmacokinetic parameters[a] for the ofloxacin–magnesium-aluminum hydroxide treatment group

Regimen[b] (no. of subjects)	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-12} (mg · h/liter)	Relative bioavailability (%)
1 (15)	3.7 ± 0.9 (1.9–5.3)	1.6 ± 0.5 (1.0–3.0)	21.24 ± 3.01 (14.08–25.45)	100
2 (15)	2.6 ± 1.0[c] (1.3–4.7)	2.0 ± 0.7[d] (1.0–3.0)	16.69 ± 3.89[c] (9.47–24.11)	79.2 ± 17.1[c] (48.4–107.3)
3 (15)	3.8 ± 0.9 (2.0–5.5)	1.5 ± 0.5 (1.0–3.0)	21.61 ± 3.48 (15.04–26.76)	101.9 ± 8.4[e] (87.2–118.1)
4 (15)	3.5 ± 0.9 (1.9–5.9)	1.5 ± 0.5 (1.0–3.0)	20.23 ± 3.18 (13.77–25.10)	95.3 ± 6.9 (77.7–104.0)

[a] Values are means ± standard deviations. Ranges of values are given in parentheses.
[b] Regimens are described in the text.
[c] $P < 0.05$ for regimen 2 versus regimens 1, 3, and 4.
[d] $P < 0.05$ for regimen 2 versus regimens 3 and 4.
[e] Data are given for 14 subjects.

tion by as much as 70%. Unfortunately, no details or data are provided to evaluate this study (Hoffken et al., 26th ICAAC). In another study in healthy volunteers, concomitant administration of ofloxacin and dry aluminum hydroxide gel granules with or without water was shown to reduce the rate and extent of ofloxacin absorption. Unfortunately, the short blood collection schedule of 6 h following ofloxacin administration and the lack of detailed data make it difficult to evaluate the extent of the interaction (7). In a study of patients with acute exacerbations of chronic bronchitis, concomitant administration of ofloxacin and magnesium-aluminum hydroxide antacid was shown to slightly reduce the extent of ofloxacin absorption by a mean of 21.8%, although this was not statistically significant (Maesen et al., Letter, J. Antimicrob. Chemother.).

The study reported herein demonstrates that there is no significant interaction between ofloxacin and low doses of calcium carbonate antacid when administration of the two agents is separated by at least 2 h. A modest reduction in ofloxacin absorption may be expected if low-dose magnesium-aluminum hydroxide antacid is administered 2 h prior to ofloxacin.

However, the results of this study should be interpreted with caution, since the effects of more frequently used antacid doses of 20 or 30 ml and simultaneous ofloxacin-antacid administration were not evaluated. Further studies are required to assess these effects. Until these are studied, it seems prudent not to administer antacids within 2 h prior to or following administration of ofloxacin.

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