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# Effects of Magnesium-Aluminum Hydroxide Antacid on Absorption of Rufloxacin

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**The present study was designed to determine the effects of an antacid suspension containing magnesium hydroxide and aluminum hydroxide (30 ml of Maalox) on the oral bioavailability of rufloxacin (400 mg). Rufloxacin was administered orally to 12 healthy volunteers according to a randomized, balanced, crossover design. Three treatments were administered to each subject, with a 10-day washout period between treatments; the treatments included rufloxacin alone, rufloxacin taken 5 min after antacid, and rufloxacin taken 4 h before antacid. Administration of antacid within 5 min before the administration of rufloxacin resulted in a substantial decrease in rufloxacin absorption, with a mean percent relative bioavailability compared with control values of 64% (range, 42 to 77%). Administration of antacid 4 h after the administration of rufloxacin slightly affected the absorption of the quinolone (mean relative bioavailability, 87%; range, 51 to 110%). Antacids that contain magnesium and aluminum salts reduce the absorption of rufloxacin. The extent of this interaction depends on the time that elapses between administration of the two drugs.**

Rufloxacin is a new oral fluoroquinolone characterized by a broad spectrum of activity against gram-negative and gram-positive aerobic bacteria (3). The antibacterial activity of rufloxacin is roughly comparable to those of norfloxacin in vitro (14, 26) and ciprofloxacin in vivo (2, 20). Pharmacokinetic studies with both healthy subjects (10, 12, 13, 27) and patients with lower respiratory tract infections (4, 21) showed that rufloxacin is eliminated slowly, with a half-life ($t_{1/2}$) in plasma of about 35 h. The absolute bioavailability of rufloxacin in humans is not known. In urine, 30 to 50% of the dose is found as unchanged drug (10, 12, 13, 27), while only 2% is found as *N*-desmethyl rufloxacin (12). The drug penetrates well into most tissues (1, 25, 27), and because of its long $t_{1/2}$ it can be used for once-a-day treatment of urinary (15) and respiratory (5) tract infections. Clinically significant changes in the disposition of rufloxacin occur only in patients with severe renal (18) or hepatic (24) insufficiency.

Antacids are widely used in clinical practice. Coadministration of magnesium- and aluminum-containing antacids has resulted in diminished absorption of several of the antibacterial carboxyquinolones (6–8, 9, 16, 22). The present study was designed to investigate the effects of the antacid Maalox on the pharmacokinetics of rufloxacin in healthy volunteers receiving a single 400-mg oral dose of rufloxacin. The objective was also to determine whether the antacid could be administered to patients who were receiving rufloxacin if administration times were appropriately spaced.

## MATERIALS AND METHODS

**Drugs.** Rufloxacin was supplied as opaque white capsules containing 200 mg of rufloxacin (lot no. 192) by Mediolanum Farmaceutici, Milan, Italy. Each 400-mg dose was individually packaged in a bottle containing two capsules. Antacid (Maalox) was used in its liquid formulation (Rhone-Poulenc Rorer, Origgio, Italy) and was purchased commercially. Each milliliter of antacid contained 36.5 mg of magnesium hydroxide and 32.5 mg of aluminum hydroxide. Excipients were methyl *p*-hydroxybenzoate (1 mg), propyl *p*-hydroxybenzoate (0.5 mg), citric acid (0.6 mg), sorbitol solution (11 mg), mannitol (2.5 mg), peppermint oil (0.6 mg), hydrochloric acid (1.5 mg), saccharin sodium (0.28 mg), and distilled water (913.02 mg).

**Subjects.** Twelve healthy volunteers (11 men, 1 woman) were selected for the study and signed written informed consent forms prior to entering the study. The subjects had a mean age of 28 years (range, 20 to 38 years) and a mean body weight of 72 kg (range, 57 to 82 kg). All subjects had normal histories, physical examinations, and laboratory tests (hematology, serum chemistry profile, and urinalysis). Subjects did not have a history of drug hypersensitivity or intolerance.

**Study design.** The study described here was an open, randomized, balanced, crossover study designed to evaluate the bioavailability of rufloxacin when it is administered with and without antacid. Each subject was assigned to one of three randomization sequences. The three treatments included rufloxacin alone, rufloxacin taken 5 min after the administration of antacid, and rufloxacin taken 4 h before the administration of antacid. After a 10-day washout period, each subject received the appropriate alternate treatment. All subjects fasted overnight prior to rufloxacin dosing and continued fasting until 5 h postdosing. Subjects were not allowed to ingest alcohol or any medication within 24 h prior to the administration of each dose and until 96 h later. Caffeine-containing beverages were allowed.

**Drug administration.** Each subject swallowed two 200-mg capsules of rufloxacin with 100 ml of tap water without chewing or crushing the dosage form. When subjects received rufloxacin with the antacid, they drank 30 ml of antacid 5 min prior to or 4 h after receiving rufloxacin. The 30-ml volume of antacid was accurately measured and was dispensed in a medicine dosing cup. The dose of antacid

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represents a standard single therapeutic dose with a neutralizing capacity of about 69 mEq of $H^+$.

**Sample collection.** Venous blood samples (7 ml) were drawn from a forearm through an indwelling butterfly needle into heparinized tubes immediately before and at 1, 2, 3, 4, 6, 8, 10, 24, 34, 48, 72, and 96 h after receipt of the drug dose. After centrifugation, plasma was separated, frozen, and stored at −20°C until drug analysis. Urine samples were collected from each subject predosing (−2 to 0 h) and over the intervals of 0 to 4, 4 to 10, 10 to 24, 24 to 48, 48 to 72, and 72 to 96 h after rufloxacin dosing. Urine specimens were kept refrigerated during the collection period. The volume of each sample was measured. About 10 ml of urine was transferred to a screw-cap polypropylene tube and was stored at −20°C pending drug analysis.

**Assay.** A modified version of the isocratic high-pressure liquid chromatographic (HPLC) technique described by Kisicki et al. (12) was adopted. The plasma samples (100 μl) were deproteinated with 1 ml of a mixture of acetonitrile and water (95/5) containing 0.1 μg of the internal standard (ofloxacin) per ml. The recovery was 96% for both rufloxacin and the internal standard. After centrifugation, the clear supernatant was transferred to a tube and evaporated under a stream of nitrogen. The residue was dissolved with 0.5 ml of the eluent mixture, and 50 μl was injected onto a Suplex pKb 100, 5-μm, 150-by-4.6-mm column (Supelco). The mobile phase was a mixture of acetonitrile and 0.01 M (pH 3) phosphate buffer (8/92). The column effluent was monitored by a fluorescence detector operating at an emission wavelength of 521 nm and an excitation wavelength of 294 nm. The linear range was 0.05 to 10 μg/ml, and the limit of quantitation was 0.05 μg/ml. The interday coefficient of variation ranged from 3.9% (0.30 μg/ml) to 8.7% (0.15 μg/ml), and the intraday coefficient of variation varied from 0.5% (0.75 μg/ml) to 5.5% (0.15 μg/ml).

**Pharmacokinetic analysis.** The pharmacokinetic parameters of rufloxacin were estimated for each subject by noncompartmental methods. The peak concentration of rufloxacin in plasma ($C_{max}$) and the time to $C_{max}$ ($T_{max}$) were derived directly from the plasma concentration-versus-time curve. The rate constant of the terminal elimination phase (β) was obtained by linear regression of ln of the postabsorption plasma concentrations against time. The $t_{1/2}$ associated with the terminal elimination phase ($t_{1/2\beta}$) was computed as ln(2)/β. The area under the plasma concentration-time curve from time zero to 96 h ($AUC_{0-96}$) was calculated by the linear trapezoidal rule. The area under the plasma concentration-versus-time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-96} + C_{96}/\beta$, in which $C_{96}$ is the concentration of rufloxacin in plasma measured at the last sampling time (96 h). Renal clearance ($CL_R$) was calculated by dividing the amount of drug excreted in urine in the 96 h by $AUC_{0-96}$. The percent drug excreted in urine was calculated by dividing the total amount excreted in urine up to 96 h by the dose. The percent bioavailability of rufloxacin taken with antacid treatments was calculated as $AUC_{0-\infty\ antacid} \cdot 100/AUC_{0-\infty\ alone}$, in which $AUC_{0-\infty\ antacid}$ and $AUC_{0-\infty\ alone}$ are the $AUC_{0-\infty}$ of rufloxacin given with or without antacid, respectively.

**Statistical analysis.** The significance of differences between the pharmacokinetic parameters of rufloxacin after the three different treatments was examined by analysis of variance for normally distributed data and by the Friedman test for not-normally distributed data. Multiple comparisons were made by the Student-Newman-Keuls method. The significance level was $P < 0.05$ (two-sided test). Data are presented as means ± standard deviations (SDs).

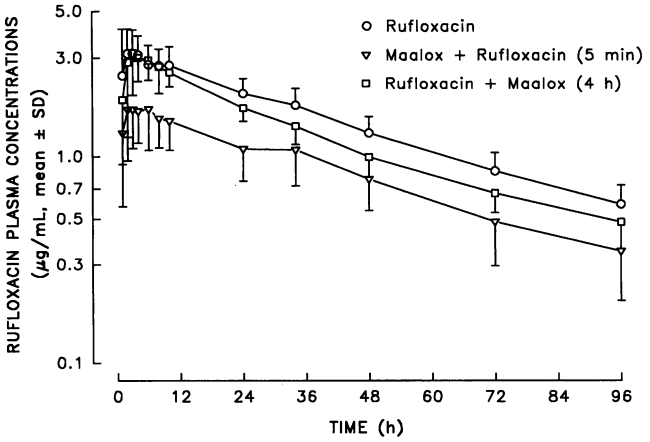


FIG. 1. Mean ± SD plasma rufloxacin concentration-versus-time curves for rufloxacin administered alone (circles), rufloxacin administered 5 min after the administration of antacid (triangles), and rufloxacin administered 4 h prior to administration of antacid (squares).

Multiple linear regression analyses were conducted to determine the relative importance of treatment, plasma rufloxacin concentration, and urinary flow rate to rufloxacin $CL_R$.

## RESULTS

**Pharmacokinetics.** The mean plasma rufloxacin concentration-versus-time profiles after oral administration of a 400-mg dose of rufloxacin with and without coadministration of antacid are depicted in Fig. 1. The mean pharmacokinetic parameters for rufloxacin after the three treatments are listed in Table 1. Corresponding mean urinary concentrations and cumulative urinary excretion of rufloxacin are presented in Table 2 and in Fig. 2, respectively.

Administration of antacid 5 min before the administration of a 400-mg rufloxacin dose resulted in a mean 36% decrease in relative bioavailability (range, 24 to 66%, $P < 0.05$). A modest, but still statistically significant ($P < 0.05$), decrease in bioavailability (−13%) was noted when the antacid was given 4 h after the administration of a rufloxacin dose (Fig. 3). When antacid was given 5 min before the administration of rufloxacin, the mean $C_{max}$ decreased by 43%. Conversely, when antacid was administered 4 h after administration of the antibacterial agent, $C_{max}$ did not decrease in comparison with that after the administration of rufloxacin alone. The median $T_{max}$ was delayed from 2.5 h to 4.5 h when antacid was given simultaneously with rufloxacin and to 3.5 h when antacid was given 4 h after administration of rufloxacin, but the differences did not reach statistical significance. The mean $t_{1/2\beta}$ of rufloxacin administered with antacid was slightly but not significantly longer than that of rufloxacin administered alone. Multiple linear regression analysis revealed that $CL_R$ was not directly affected by antacid but was inversely correlated with concentrations in plasma ($P = 0.05$) and was linearly proportional with urinary flow ($P < 0.01$). Thus, $CL_R$ rose with decreasing rufloxacin concentrations in plasma and with higher urine flow rates. This explains the slight rise in $CL_R$, although not significant, observed with the coadministration of antacid (19 and 9%

TABLE 1. Pharmacokinetic parameters of 400 mg of rufloxacin administered orally for the three treatments[a]

| Treatment | $T_{max}$ (h)[b] | $C_{max}$ (μg/ml) | $t_{1/2\beta}$ (h) | $AUC_{0-96}$ (μg · h/ml) | $AUC_{0-\infty}$ (μg · h/ml) | $CL_R$ (ml/min) | $f_e$ (%) | $R$ (%) |
|---|---|---|---|---|---|---|---|---|
| Rufloxacin | 2.5 (1–6) | 3.74 ± 1.03 | 39.0 ± 5.5 | 144 ± 28 | 178 ± 36 | 12.9 ± 6.3 | 27.7 ± 13.6 | |
| Antacid + rufloxacin (5 min) | 4.5 (1–10) | 2.12 ± 0.58[c] | 45.2 ± 9.7 | 86 ± 15[c] | 111 ± 21[c] | 15.3 ± 7.7 | 19.4 ± 10.2[c] | 64.1 ± 12.4 |
| Rufloxacin + antacid (4 h) | 3.5 (2–8) | 3.97 ± 1.28 | 40.8 ± 9.0 | 122 ± 17[c] | 151 ± 22[c] | 14.1 ± 5.4 | 25.3 ± 8.6 | 87.3 ± 15.5 |

[a] Values are means ± SDs unless indicated otherwise. $f_e$, drug excreted in urine; $R$, bioavailability of rufloxacin taken with antacid; the other abbreviations are defined in the text.
[b] Values are medians (ranges).
[c] $P < 0.05$ versus rufloxacin treatment alone.

with 5 min and 4 h of time between administration of antacid and drug, respectively). When rufloxacin was given 5 min after antacid was given, concentrations in urine were 30 to 40% lower than those after the administration of rufloxacin alone. On the contrary, the levels of drug measured in urine following the administration of rufloxacin 4 h before the administration of antacid were similar to those after the administration of rufloxacin alone (Table 2). The urinary recovery of rufloxacin after ingestion of antacid reflected (Fig. 2) its negative effect on absorption (−30 and −9%, with simultaneous and delayed antacid administrations, respectively). However, a significant decrease in the percent recovered in urine was noted only after the 5-min antacid pretreatment.

**Safety.** Rufloxacin was very well tolerated. No adverse events were reported by any subject after any treatment. No significant changes in biochemical or hematological variables were observed after rufloxacin treatment.

## DISCUSSION

The results of the present study indicate that the average bioavailability of rufloxacin is reduced from the control value by approximately 36% with 5-min spaced antacid administration and by only 13% when antacid is administered 4 h later.

The mechanism of the interaction between quinolones and antacids seems to be the formation of chelate complexes between the 3-carboxyl and the 4-oxo substituents of quinolones and metal ions (11, 23). Aluminum, in particular, forms a very stable complex with quinolones (23). Gastrointestinal absorption of the resulting complexes is limited. Studies with nalidixic acid have indicated that aluminum chelates with quinolones in a 1:1 to 3:1 molar ratio (11). The dose of antacid administered (30 ml) contains 12.5 mmol of aluminum ion and 18.8 mmol of magnesium ion. A 400-mg rufloxacin dose is equivalent to about 1 mmol of rufloxacin. Therefore, aluminum and magnesium were present in great excess in the present study.

Clinical failures caused by the quinolone-antacid interaction are poorly documented in the literature. Preheim et al. (19) suggested that antacids may interfere with the efficacy of ciprofloxacin, particularly in patients infected with *Pseudomonas aeruginosa*. Noyes and Polk (17) reported a case of clinical failure in a patient with concomitant administration of norfloxacin and a magnesium- and aluminum-containing antacid. It is difficult to anticipate the clinical impact of the antacid interaction with rufloxacin. The amount of magnesium-aluminum hydroxide administered in the present study is a standard therapeutic dose, but the single-dose design that we adopted does not apply to real clinical situations with multiple doses of antacid. A substantial reduction in rufloxacin absorption may be expected if magnesium-aluminum hydroxide antacid is administered simultaneously with rufloxacin. When antacid was administered 4 h after the administration of rufloxacin, we found that concentrations in urine were similar to those measured after the administration of rufloxacin alone. This indicates that, despite a minor reduction of the absorption of rufloxacin (−13%), levels in urine should still sufficiently exceed the MIC for rufloxacin-susceptible uropathogens (14, 26).

The pharmacokinetic profile of rufloxacin found in the present study is similar to that described previously in healthy volunteers. In particular, it is confirmed that the drug is eliminated slowly from the body. The mean $t_{1/2\beta}$ after the administration of rufloxacin alone was 39 h. This value compares well with those obtained in other single-dose studies, in which $t_{1/2\beta}$ ranged from 28 to 44 h (10, 12, 13, 27).

The rate of absorption of rufloxacin seemed to be delayed by antacid coadministration. The time to the peak was prolonged from 2.5 to 4.5 h when antacid was given simultaneously with rufloxacin, but the difference did not reach statistical significance. This was likely because relatively few samples were taken during the absorption phase, which led to a poor estimate of $T_{max}$. The extent of absorption was also reduced by antacid coadministration and depends on the time that elapses between administration of the two drugs. When antacid is given 5 min before the administration of rufloxacin, antacid seems to interfere with the gastrointestinal absorption of the quinolone that takes places in the first part of the gastrointestinal tract. This is suggested by the

TABLE 2. Urine rufloxacin concentrations for the three treatments

| Treatment | Rufloxacin concn (μg/ml) at the following intervals (h)[a]: | | | | | |
|---|---|---|---|---|---|---|
| | 0–4 | 4–10 | 10–24 | 24–48 | 48–72 | 72–96 |
| Rufloxacin | 34.2 ± 22.6 | 49.2 ± 34.8 | 40.2 ± 16.5 | 32.7 ± 17.1 | 22.2 ± 11.5 | 15.6 ± 9.1 |
| Antacid + rufloxacin (5 min) | 23.8 ± 11.6 | 28.6 ± 13.0 | 25.7 ± 13.6 | 19.5 ± 11.1 | 13.0 ± 8.1 | 9.8 ± 4.8 |
| Rufloxacin + antacid (4 h) | 36.8 ± 20.1 | 47.8 ± 16.7 | 42.5 ± 16.1 | 32.8 ± 11.8 | 17.7 ± 6.6 | 11.6 ± 4.0 |

[a] Values are means ± SDs.

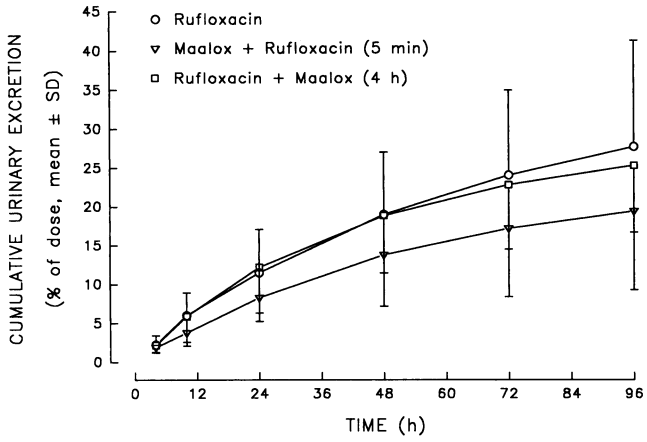


FIG. 2. Mean ± SD cumulative urinary excretion for rufloxacin administered alone (circles), rufloxacin administered 5 min after the administration of antacid (triangles), and rufloxacin administered 4 h prior to administration of antacid (squares).

43% reduction in the $C_{max}$. The inhibitory effect on the primary absorption of rufloxacin affects the entire profile of the level in plasma, with a 40% decrease in $AUC_{0-96}$. When antacid was administered 4 h after the administration of rufloxacin, $C_{max}$ was not influenced at all. This suggests that the primary absorption of rufloxacin is minimally or not influenced by administration of antacid over a sufficiently spaced period of time. However, since rufloxacin undergoes transintestinal secretion (22a), antacid administered 4 h after rufloxacin administration can inhibit intestinal reabsorption of the quinolone. This seems to be confirmed by the observation that the only differences in the curves of the mean level in plasma of rufloxacin alone versus that of rufloxacin plus antacid given 4 h later occurred at between 6 and 12 h. After that, the curves became parallel. The consequent impact on total $AUC_{0-96}$ was minor (−15%).

The effect of antacids on elimination of rufloxacin is more complex. There is one report (8) that shows that multiple doses of antacid (Maalox) enhance the $CL_R$ of temafloxacin by 20%. In the present study, we found that the $CL_R$ of rufloxacin is increased, although not significantly, by 19% with the simultaneous administration of antacid. The mechanism of this interesting phenomenon is unclear. Quinolones undergo both renal tubular secretion and reabsorption. Nonpolar quinolones like rufloxacin are extensively reabsorbed. Thus, one possible explanation (8) is that the increase in the $CL_R$ of rufloxacin with antacid is due to a reduction in renal tubular reabsorption. The decrease in tubular reabsorption may be caused by reduced concentrations of drug in plasma and a reduced filtration rate. Indeed, in the present study we found that the $CL_R$ of rufloxacin is inversely correlated to rufloxacin concentrations in plasma. Even though $CL_R$ was enhanced after antacid coadministration, $t_{1/2}$ tended to increase. The cause of this apparently paradoxical observation is unknown, but it may be related to a sustained release of unabsorbed rufloxacin from the antacid-rufloxacin complex as it moves down the gastrointestinal tract.

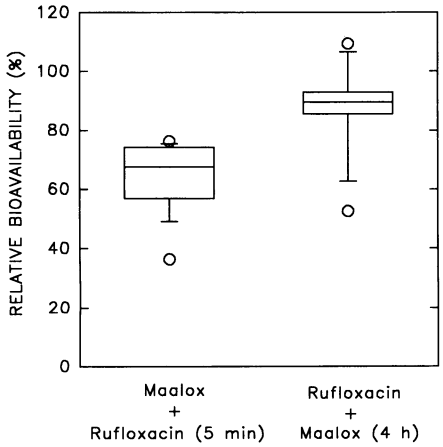


FIG. 3. Box plots (median, 27th to 75th percentiles, 10th to 90th percentiles, and extremes) of relative bioavailability of rufloxacin administered 5 min after the administration of antacid and rufloxacin administered 4 h prior to the administration of antacid.

In conclusion, the results of the present study indicate that to avoid substantial interaction between antacid and rufloxacin, the administration of the two agents should be spaced by at least 4 h. Studies with multiple doses of antacid are needed to confirm the lack of a clinically significant interaction with rufloxacin under real therapeutic conditions.

## ACKNOWLEDGMENT

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