Effect of an Antacid Containing Magnesium and Aluminum on Absorption, Metabolism, and Mechanism of Renal Elimination of Pefloxacin in Humans†

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The effects of an antacid containing magnesium and aluminum hydroxide on the pharmacokinetics of pefloxacin in 10 healthy volunteers were investigated. In a randomized crossover design, each subject received an oral dose of 400 mg of pefloxacin either with or without multiple doses of the antacid. The concentrations of pefloxacin and its metabolites in plasma and urine were determined by high-performance liquid chromatography assays. We found that coadministration of magnesium and aluminum hydroxide caused a decrease of levels of pefloxacin in plasma and urine. The area under the plasma concentration-time curve decreased significantly (P < 0.001), suggesting impaired absorption of pefloxacin from the gastrointestinal tract. The relative bioavailability of pefloxacin after the antacid treatment was 44.4% ± 23.8%, compared with that after a single administration. The underlying mechanism of this drug interaction is the formation of chelate complexes and probably also physical adsorption to the aluminum hydroxide gel. The metabolism of pefloxacin was not altered by the antacid treatment. Renal clearance was found to depend on urinary pH. Terminal half-life was significantly shorter after the antacid treatment, probably because of an increase in nonrenal clearance. In conclusion, pefloxacin should be given at least 2 h before the antacid to ensure sufficient therapeutic efficacy of the quinolone.

Under clinical conditions, antacids may be administered together with the new quinolone antibacterial agents. Antacids are known to alter both absorption of drugs from the gastrointestinal tract and renal elimination (12). A decrease in the rate and extent of absorption of orally administered drugs by a concomitant antacid treatment may reduce drug activity considerably. Alteration of urinary pH may lead to changes in renal excretion of acidic and basic drugs.

In this investigation, the influence of an antacid containing magnesium and aluminum hydroxide on the pharmacokinetics and bioavailability of pefloxacin was evaluated. Pefloxacin is a newer quinolone carboxylic acid derivative with a broad spectrum of activity (3). A decrease in the bioavailability of several quinolones after concomitant intake of magnesium-aluminum hydroxide has recently been described elsewhere (5, 9, 13, 18, 19) and reviewed (4, 24). However, the extent of this interaction among individual quinolones, was quite different, which makes a prediction of the extent of the effect of the antacid on new derivatives difficult. Therefore, antacid-quinolone interaction studies are required for each newly developed quinolone. Pefloxacin differs from other quinolones in its extensive metabolism and in its considerable reabsorption in the kidney tubules (14). For that reason, an interaction with antacids at the hepatic and renal sites was also assessed in this study.

MATERIALS AND METHODS

Volunteers. Five female and five male subjects aged from 19 to 30 years (mean age, 24.9 years), with a mean weight of 71.4 ± 9.0 kg, participated in this study after informed consent had been obtained. All subjects were determined to be in good health prior to the study on the basis of physical examinations, medical histories, and laboratory tests. Hematological and biochemical tests were repeated after the study. No other medication and no ingestion of alcohol were permitted.

Study design. After an overnight fasting period of 9 h, the subjects received an oral dose of 400 mg of pefloxacin once with and once without coadministration with a suspension of magnesium and aluminum hydroxide (Maalox 70; Arznei Müller-Rorer GmbH, Bielefeld, Germany). The study was performed in a randomized crossover fashion separated by a washout period of at least 1 week. Each dose of the antacid contained 600 mg of magnesium hydroxide and 900 mg of aluminum hydroxide gel. The antacid treatment started the day before pefloxacin administration. One bag of antacid suspension was given every 2 h, starting at 8 a.m. The last dose was given at 10 p.m. On the day of pefloxacin administration, subjects received five additional bags 2.5 h and 1 h before and 1, 3, and 5 h following oral administration of the quinolone. The subjects remained in the fasting state for 6 h after drug intake.

Sample collection. Blood was taken from an indwelling intravenous cannula immediately before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 30, 36, and 48 h after drug administration. The samples were heparinized, centrifuged, and frozen immediately at −30°C. Urine was collected before dosing and from 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 30, 30 to 36, and 36 to 48 h after intake of pefloxacin. Urine samples were frozen at −30°C as soon as each volume and pH value had been determined.

Drug analysis. Plasma samples were analyzed for unchanged pefloxacin and urine samples were analyzed for pefloxacin and
its main metabolites, pefloxacin N-oxide and norfloxacin, by reversed-phase high-performance liquid chromatography (HPLC) assays (15).

For determination of the level of pefloxacin in plasma, the mobile phase consisted of 50% methanol and 50% 0.1 M phosphate buffer adjusted to pH 4.9. A Nucleosil C18 5-μm reversed-phase column heated to 40°C (Bischoff GmbH, Lel-enberg, Germany) was used as the stationary phase. Plasma samples were deproteinized by the addition of acetonitrile (1:2), and the supernatant was injected into the mobile phase at a flow rate of 1.2 ml/min.

For determination of the levels of pefloxacin and its metabolites in urine, the mobile phase consisted of 24.1% methanol, 2.6% acetonitrile, and 73.3% 0.1 M phosphate buffer adjusted to pH 5.75. A C18 µBondapak reversed-phase column (Waters Association, Eschborn, Germany) was used for this assay. Urine samples were diluted with bidistilled water and were injected into the mobile phase at a flow rate of 1.0 ml/min.

The fluorescence of the mobile phase was monitored by a Perkin Elmer 650-10 LC Fluorescence Spectrometer (Perkin-Elmer, Überlingen, Germany) to detect pefloxacin, pefloxacin N-oxide, and norfloxacin. The excitation wavelength was 275 nm, and the emission wavelength was 415 nm.

The calibration graphs were linear between 0.078 and 10 μg/ml for pefloxacin in plasma, 0.78 and 100 μg/ml for pefloxacin in urine and between 3.13 and 200 μg/ml for the metabolites in urine, with coefficients of correlation greater than 0.999. The lower limit of quantitation in plasma or urine was the lowest level of the calibration curve.

The within-day precision (coefficient of variation) was found to be 3.2% for 2.5 μg of pefloxacin per ml in plasma, 6.9% for 0.63 μg of pefloxacin per ml in plasma, 3.1% for 100 μg of pefloxacin per ml in urine, and 5.1% for 12.5 μg of pefloxacin per ml in urine. The between-day precision was 2.7% for 3.8 μg of pefloxacin per ml in plasma, 3.4% for 1.5 μg of pefloxacin per ml in plasma, 3.8% for 40.2 μg of pefloxacin per ml in urine, and 7.3% for 8 μg of pefloxacin per ml in urine.

Pharmacokinetic calculations. The area under the plasma concentration-time curve (AUC) was estimated by the trapezoidal rule and extrapolated to infinity. The extrapolation was performed by dividing the last measurable plasma concentration by the terminal elimination rate constant (β). β was estimated by modeling the plasma concentration to an exponential function with a negative exponent by an extended least-squares optimization procedure (23a). Terminal half-life (t1/2) was calculated according to the formula t1/2 = In 2/β. The maximum concentration in plasma (Cmax) and the time to peak concentration in plasma (Tmax) were taken directly from the plasma level curve. The relative bioavailability of pefloxacin after coadministration with Maalox 70 was calculated by dividing the AUC after combined administration by the AUC after single administration.

Recovery from urine was calculated as a percentage of the dose. Renal clearance (CLR) was determined by dividing the cumulative renal excretion of pefloxacin until the last measurable concentration in plasma by the corresponding plasma AUC. In addition, CLR from individual urine collections were also calculated by dividing the amounts of pefloxacin in the urine samples by the respective AUCs during the collection interval. Only the 4- and 6-h collection periods were used, since for longer collection periods in vitro changes of the pH of urine which would have lead to a bias of the results were to be expected. The metabolic ratio (MR) of pefloxacin was calculated by dividing the amount excreted in urine as metabolite by the amount excreted as unchanged pefloxacin.

Statistical analysis. Student’s paired t test was performed to describe significant differences in pharmacokinetic parameters and urinary pH after single and combined administrations with Maalox 70. The significance level was set to P < 0.05.

The relationship between urine pH and CLR of pefloxacin (calculated for each urine collection interval for each volunteer) was investigated by linear regression (procedure GLM [22a]). To increase the power of the statistical analysis, the data were grouped according to the ranges of urine pHs: 5.0 to 5.6, 5.61 to 5.8, 5.81 to 6.0, 6.01 to 6.4, 6.41 to 6.8, 6.81 to 7.2, and 7.21 to 7.8. Each group contained between 13 and 17 observations. An analysis of covariance (procedure GLM [22a]) was performed with the group as the class variable and the urine pH as the continuous variable. Finally, the different pH groups were compared by Duncan’s multiple range test (procedure GLM [22a]).

RESULTS

Mean concentrations of pefloxacin in plasma after single and combined administrations with the antacid are plotted in Fig. 1. Coadministration with magnesium and aluminum hydroxide reduced the levels of pefloxacin in plasma considerably at any time of the observation period. The mean pharmacokinetic parameters as well as the results of the statistical analysis are summarized in Table 1. Cmax were significantly decreased and T max were prolonged following the antacid treatment, but the differences in T max were not significant and were considerably affected by an extremely high T max value of 6 h for one subject. t1/2 were significantly shorter when pefloxacin was given together with the antacid.

The AUC of pefloxacin decreased significantly after combined administration. Calculation of the relative bioavailability of pefloxacin following concomitant antacid treatment yielded a mean value of 44.4% ± 23.8% compared with that of pefloxacin alone. The individual relative bioavailability values ranged from 21.3 to 99.3% (Table 2). In one subject (no. 10), we did not observe a decrease in AUC following combined treatment of pefloxacin and the antacid. The extent of the interaction was also apparent from urine data. Renal excretion values of pefloxacin and its metabolites as percentages of the administered dose are presented in Table 3. The antacid diminished the cumulative renal excretion (0 to 48 h) of pefloxacin, pefloxacin N-oxide, and norfloxacin to 46.8% ± 18.5%, 46.4% ± 18.6%, and 45.5% ± 17.2%, respectively.
TABLE 1. Mean pharmacokinetic parameters of pefloxacin with and without coadministration of magnesium-aluminum hydroxide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pefloxacin without antacid*</th>
<th>Pefloxacin with antacid*</th>
<th>Result of statistical analysis (paired t test P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (µg/ml)</td>
<td>5.1 ± 1.0</td>
<td>2.0 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>1.05 ± 0.67</td>
<td>1.95 ± 1.64</td>
<td>NS</td>
</tr>
<tr>
<td>AUC (µg·h/ml)</td>
<td>56.5 ± 13.9</td>
<td>25.8 ± 17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>10.6 ± 3.0</td>
<td>9.6 ± 3.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CL_{R} (ml/min)</td>
<td>11.9 ± 2.4</td>
<td>13.4 ± 3.6</td>
<td>NS*</td>
</tr>
<tr>
<td>MR of pefloxacin N-oxide</td>
<td>2.10 ± 0.64</td>
<td>2.13 ± 0.78</td>
<td>NS</td>
</tr>
<tr>
<td>MR of norfloxacin</td>
<td>1.69 ± 0.50</td>
<td>1.62 ± 0.53</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations.
* NS, not significant.

The metabolism of pefloxacin was evaluated by calculation of the MR. We found no effect of magnesium and aluminum on MRs, suggesting no alteration in the conversion of pefloxacin to pefloxacin N-oxide and norfloxacin. The CL_{R} calculated from cumulative renal excretion divided by the corresponding AUC of pefloxacin was slightly increased after the antacid treatment, but the difference was not statistically significant. During the first 12 h after pefloxacin administration, the urinary pH in all subjects was elevated. Mean urinary pH values were 6.11 ± 0.54 without and 7.18 ± 0.32 with the antacid. The difference was statistically significant (P < 0.001). To evaluate whether the tendency for a higher CL_{R} after coadministration of the antacid is caused by an elevation of urinary pH, we calculated CL_{R}s for the individual urine samples and compared the mean CL_{R}s for seven different pH ranges. In Fig. 2, mean CL_{R}s are plotted versus mean urinary pHs for each group. CL_{R} exhibits a minimum at neutral pH and increases with acidification and alkalization of the urine.

The findings presented intuitively in Fig. 2 were confirmed by statistical analysis. A linear regression analysis pooling all observations of all urine collection intervals in all patients demonstrated that there is no simple linear relationship (r² = 0.005314 [P = 0.4429]). An analysis of covariance which correlated urine pH with C_{1/2} of pefloxacin within the defined groups of pH ranges reached only borderline significance (P = 0.0578). However, when the groups of pH ranges were compared with Duncan's multiple range test at a significance level (P) of 0.05, it was clearly shown that the group with the lowest pH range (5.0 to 5.6) was different from the group with the highest pH range (7.21 to 7.8); however, both groups were significantly (P < 0.05) different from the two groups which form the trough in Fig. 2, i.e., which range from 6.41 to 6.8 and from 6.81 to 7.2. Thus, the inverse bell shape of the curve in Fig. 2 was confirmed statistically.

DISCUSSION

The results of this study show that the bioavailability of pefloxacin is reduced to about 45% after coadministration of magnesium and aluminum hydroxide, suggesting that the absorption process of pefloxacin is impaired by the antacid. For that reason, it is possible that the effective concentration of pefloxacin at the site of action is not reached, particularly in infections with less susceptible bacteria. Even though this interaction exhibits a wide intrapersonal variation, it has a clearly different extent than those previously reported for other quinolones. Ciprofloxacin (9.5%), ofloxacin (30.8%), and temafloxacin (39.8%) were more affected and fleroxacin (69.8%) was less affected by magnesium and aluminum hydroxide than pefloxacin (9, 13, 24, 27). Since our experimental design was almost identical to that used in these studies, this comparison of data may be valid. An intrapersonal comparison of the interaction of quinolones with a single dose of 1 g of aluminum hydroxide also resulted in large differences among individual compounds; the relative bioavailabilities for norfloxacin, enoxacin, and ofloxacin were 2.7, 15.4, and 52.1%, respectively (23).

TABLE 2. Individual relative bioavailability of pefloxacin following a concomitant treatment with magnesium-aluminum hydroxide

<table>
<thead>
<tr>
<th>Subject</th>
<th>AUC (µg·h/ml)</th>
<th>Relative bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pefloxacin without antacid</td>
<td>Pefloxacin with antacid</td>
</tr>
<tr>
<td>1</td>
<td>66.49</td>
<td>14.13</td>
</tr>
<tr>
<td>2</td>
<td>81.61</td>
<td>22.91</td>
</tr>
<tr>
<td>3</td>
<td>44.18</td>
<td>25.09</td>
</tr>
<tr>
<td>4</td>
<td>58.27</td>
<td>31.12</td>
</tr>
<tr>
<td>5</td>
<td>44.21</td>
<td>14.21</td>
</tr>
<tr>
<td>6</td>
<td>43.71</td>
<td>10.61</td>
</tr>
<tr>
<td>7</td>
<td>37.97</td>
<td>10.03</td>
</tr>
<tr>
<td>8</td>
<td>60.91</td>
<td>27.94</td>
</tr>
<tr>
<td>9</td>
<td>57.67</td>
<td>32.65</td>
</tr>
<tr>
<td>10</td>
<td>70.10</td>
<td>69.60</td>
</tr>
</tbody>
</table>

Mean ± SD: 56.51 ± 13.94, 25.83 ± 17.50, 44.41 ± 23.76

FIG. 2. Effect of urinary pH on CL_{R} of pefloxacin (means ± standard errors).

TABLE 3. Mean renal excretion of pefloxacin and its metabolites pefloxacin N-oxide and norfloxacin with and without coadministration of magnesium-aluminum hydroxide (n = 10)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Renal excretion (% of dose)*</th>
<th>Results of statistical analysis (paired t test P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pefloxacin (unchanged)</td>
<td>9.4 ± 2.2</td>
<td>4.4 ± 2.0</td>
</tr>
<tr>
<td>Pefloxin N-oxide</td>
<td>17.9 ± 2.7</td>
<td>8.2 ± 3.1</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>15.9 ± 3.0</td>
<td>7.0 ± 2.5</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations.
One mechanism of this gastrointestinal interaction may be the formation of chelate complexes. The most likely site in the quinolone molecule for chelate formation has been proposed to be between the 3-carboxyl and the 4-oxo group (16, 21). The physicochemical properties of drug complexes may be quite different from those of the drug itself, leading to an alteration and in most cases to a reduction in the rate and extent of absorption (8). There is much evidence that free aluminum ions contribute to the interaction indicated by a comparison of the effects of the same amounts of aluminum hydroxide and aluminum chloride on the absorption of ofloxacin in rats (26). Whereas the relative bioavailability of ofloxacin was 80% following coadministration of aluminum hydroxide, it was reduced to 31.2% when the drug was given with aluminum chloride, which releases more free aluminum ions than aluminum hydroxide. The determination of complex stability constants indicated that aluminum ions form stable chelate complexes with quinolones, whereas the magnesium-quinolone complex is less stable (26). Moreover, the importance of aluminum ions for this interaction has been shown in healthy volunteers by coadministration of sucralfate, which contains 16 aluminum ions per molecule. The bioavailabilities of several quinolones were found to be considerably reduced when sucralfate was given concomitantly (7, 20).

The physicochemical properties of the complex between aluminum ions and nalidixic acid, which has the same structural features in the 3 and 4 position of the nucleus, have been characterized by Nakano et al. (16). The nalidixic acid-to-aluminum ion ratio of the complex was found to be 3 to 1, which means a threefold increase in molecular size. Furthermore, the complex was found to exhibit a higher solubility in water and a lower lipophilicity and reduced permeability through a cellulose membrane than nalidixic acid itself (16).

On the basis of these results, it is suggested that the formation of aluminum-quinolone complexes is responsible for the absorption inhibition. Since the stability constants of those complexes are rather similar among individual quinolones (26), the differences in the extents of interaction remain unexplained.

The second possible mechanism is the physical adsorption of the quinolones to the aluminum hydroxide gel. We are not aware of any study of gel binding of quinolines. It is imaginable that hydrophilic molecules have a higher affinity to the hydrophilic aluminum hydroxide gel than lipophilic compounds. The octanol-water partition coefficients of quinolones indicate considerable differences in their lipophilicity (13a). It is evident that the more-lipophilic gysre inhibitors fleroxacin, ofloxacin, and pefloxacin are less affected by antacids than the hydrophilic derivatives ciprofloxacin, enoxacin, and norfloxacin. For these reasons, it is very likely that physical adsorption as well as complexation contribute to the gastrointestinal interaction between quinolones and antacids.

Physical adsorption may also be responsible for the shorter terminal t₁/₂ of pefloxacin after the antacid treatment. Recently, we reported that coadministration of charcoal significantly increases nonrenal elimination of intravenously administered quinolones (14a, 25). This suggests that quinolones undergo secretion from blood to the gastrointestinal lumen and subsequent reabsorption. In our study, pefloxacin is exposed to a comparable situation. The presence of an adsorptive agent in the gastrointestinal tract impairs reabsorption, increasing nonrenal clearance and decreasing terminal t₁/₂. Similar findings were recently reported by Grasela et al. (10) and Nix et al. (17).

With regard to the physicochemical interaction mechanisms described above, it is surprising that absorption in one subject is not affected by magnesium-aluminum hydroxide. At present, we have no explanation for this nonresponse. It is imaginable that this subject emptied the antacid from the gastrointestinal tract much faster than other subjects.

In other studies, the time interval between the intake of the quinolone and the antacid and the order of intake were shown to be of great significance for the extent of the quinolone-antacid interaction. Whereas when given 5 to 10 min after the magnesium-aluminum hydroxide treatment, the relative bioavailability of ciprofloxacin was 15.2%, it was found to increase when the time interval between the treatments was prolonged, reaching values of 23.2% 2 h and 70% 4 h later (18). However, when the order of intake was changed and ciprofloxacin was given 2 h before the antacid, no absorption impairment was observed (18). Similar results were reported for ofloxacin (5).

Recently, the effect of other divalent cations on the absorption of quinolones has been investigated as well. In an intravenous study with magnesium carbonate, no impairment of magnesium-aluminum hydroxide treatment (9.0%). However, calcium had no effect on the pharmacokinetics of ofloxacin (5) or of ciprofloxacin when given together with a high-fat breakfast (6). Moreover, the absorption has been shown to be impaired by ferrous sulfate, ferrous fumarate, and multivitamins with zinc (2, 22). These findings suggest that quinolones can potentially interact with all di- and trivalent cations.

After an intravenous treatment with aluminum over 3 weeks, specific alterations in the mesosomal function of rats were observed (1). However, with our 2-day treatment of magnesium and aluminum hydroxide, we did not observe any alteration in the metabolic pattern of pefloxacin. The reduced renal excretion of the metabolites can be attributed to the lower bioavailability of the parent compound, since the MRS were not affected.

The Cₐ of pefloxacin was found to depend on the urinary pH, reflecting the betaine structure of the pefloxacin molecule. The relatively low Cₐ of pefloxacin suggests an extensive reabsorption of pefloxacin in the kidney tubules. At neutral pH, the zwitterionic pefloxacin molecule exhibits a maximum of lipophilicity (11, 24), which favors reabsorption and minimizes Cₐ. Under acidic and alkaline pH conditions, pefloxacin is positively or negatively charged, leading to a reduction of reabsorption and an increase of Cₐ. In view of the nonlinear pH dependence of Cₐ of pefloxacin, one may conclude that an elevation of pH can lead either to a decrease or to an increase of Cₐ, depending on the absolute pH value reached after the antacid treatment. In a recent study with temafloxacin, a quinolone with a higher contribution of tubular secretion to Cₐ, we found no effect of urinary pH. However, Cₐ was shown to increase with decreasing plasma concentrations and increasing urinary flow rates (9).

In conclusion, pefloxacin and antacids containing magnesium-aluminum hydroxide should not be administered concomitantly. In severely ill patients who need both treatments, the interaction at the gastrointestinal site can be avoided if the antacid is given at least 2 h after the quinolone, when a considerable part of the administered dose is already absorbed. The urinary pH dependence of the Cₐ of pefloxacin is of no clinical significance with regard to the low contribution of renal excretion to the overall elimination of pefloxacin. However, the pH dependence of the Cₐ of pefloxacin gives an insight into the mechanism of its renal excretion that has not been previously described.
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