Influence of an Antacid Containing Aluminum and Magnesium on the Pharmacokinetics of Cefixime

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Interaction studies in dogs have indicated that antacids significantly decrease the oral bioavailability of cefixime. Twelve healthy adult male volunteers participated in a randomized, four-way crossover trial to evaluate the influence of an aluminum-magnesium antacid (Maalox; 20 ml) on the pharmacokinetics of cefixime (400 mg). Regimens were (i) cefixime alone; (ii) cefixime simultaneous with antacid; (iii) cefixime 2 h before antacid; and (iv) cefixime 2 h after antacid. Serial blood and urine samples were collected over a 24-h period following each dose of cefixime. There was a 1-week washout interval between regimens. Cefixime concentrations in serum and urine were analyzed by high-performance liquid chromatography. Maximum cefixime concentrations in serum for regimens i through iv were (mean ± standard deviation) 4.9 ± 1.4, 5.7 ± 1.3, 5.1 ± 1.0, and 5.5 ± 1.5 μg/ml, respectively. Corresponding values for area under the serum concentration-time curve extrapolated to infinity were 38.3 ± 14.5, 42.8 ± 13.9, 38.5 ± 9.8, and 41.6 ± 16.7 μg · h/ml. There was a trend toward increased concentrations in serum and area under the curve of cefixime when it was administered concomitantly with antacid; however, these differences were not statistically significant (P > 0.05; analysis of variance). We conclude that single-dose administration of an aluminum-magnesium antacid does not significantly decrease the oral bioavailability of cefixime.

Nonsystemic antacids containing aluminum and magnesium are widely used in the treatment of gastrointestinal disorders. Coadministration of antacids has been found to interfere with the absorption of many drugs, including tetracyclines, cefuroxime axetil, and fluoroquinolone antibiotics (1, 6, 10, 12).

Cefixime is an investigational oral cephalosporin that has good in vitro activity against a broad range of respiratory and urinary tract pathogens and is very stable against various β-lactamases (9). It has an absolute bioavailability of 40 to 52%, and food does not interfere with the overall extent of drug absorption (3–5).

Interaction studies in beagle dogs have shown that pretreatment with an aluminum-magnesium antacid (Maalox; 30 ml) significantly reduces the maximum concentration in serum and area under the serum concentration-time curve (AUC) of cefixime (12.5 mg/kg given as an oral solution) by 54 and 58%, respectively (data on file at Lederle Laboratories, Pearl River, N.Y.). Another study in dogs revealed a slight (20%) but statistically significant (P < 0.05) reduction in the AUC of cefixime when antacid (30 ml) was administered 2 h before cefixime; however, there was no reduction in the AUC when antacid was given 2 h after cefixime (data on file at Lederle Laboratories). This interaction has not been previously studied in humans; therefore, the purpose of this study was to determine the influence of an aluminum-magnesium antacid on the pharmacokinetics of cefixime administered concomitantly with, 2 h before, and 2 h after cefixime in healthy volunteers.

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MATERIALS AND METHODS

Volunteers. Twelve healthy, nonsmoking adult male volunteers participated in this investigation. The study was approved by the Medical College of Virginia Committee on the Conduct of Human Research, and written informed consent was obtained from all subjects. Subjects were required to have a normal medical history, physical examination, and laboratory profile. Exclusion criteria included hypersensitivity to beta-lactam antibiotics, the use of medications for chronic conditions, and weight deviating more than 10% from ideal body weight. The mean ± standard deviation age and weight were 27 ± 3.4 years and 71.0 ± 4.3 kg, respectively.

Drug administration and sample collection. Subjects were admitted into the Antibiotic Research Unit of the Biopharmaceutics-Pharmacokinetics Center, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, on the morning of each study day after an overnight fast. They abstained from caffeine and alcoholic beverages beginning 48 h prior to each of the 4 study days. The two study drugs were cefixime (400-mg tablets; lot P88-018; Lederle Laboratories) and aluminum hydroxide (225 mg/5 ml)-magnesium hydroxide (200 mg/5 ml) oral antacid suspension (Maalox; lot 76751; Rorer Pharmaceutical Corp., Ft. Washington, Pa.). Regimens were (i) cefixime alone, (ii) cefixime simultaneous with antacid, (iii) cefixime 2 h before antacid, and (iv) cefixime 2 h after antacid. All doses of cefixime were administered as one 400-mg tablet followed by 240 ml of water, and each dose of antacid was administered as a 20-ml of suspension. The dose of antacid administered was chosen based on the labeled directions for consumer use. Subjects were not permitted to eat until 4 h after receiving their dose of cefixime. Subjects received each of the four treatment regimens in a randomized, crossover manner separated by a 7-day washout period.

Blood samples were obtained from an indwelling venous catheter immediately before cefixime administration and at
TABLE 1. Pharmacokinetic parameters for four cefixime regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cmax (μg/ml)</th>
<th>Tmax (h)</th>
<th>t1/2 (h)</th>
<th>AUCo-∞ (μg·h/ml)</th>
<th>Ae0-24 (mg)</th>
<th>CL0 (ml/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>4.9 ± 1.4</td>
<td>4.0 ± 1.1</td>
<td>2.6 ± 0.6</td>
<td>38.3 ± 14.5</td>
<td>63.9 ± 20.4</td>
<td>26.7 ± 4.5</td>
</tr>
<tr>
<td>ii</td>
<td>5.7 ± 1.3</td>
<td>3.7 ± 1.0</td>
<td>2.6 ± 0.5</td>
<td>42.8 ± 13.9</td>
<td>75.9 ± 16.0</td>
<td>28.6 ± 5.7</td>
</tr>
<tr>
<td>iii</td>
<td>5.1 ± 1.0</td>
<td>3.8 ± 0.7</td>
<td>2.7 ± 0.5</td>
<td>38.5 ± 9.8</td>
<td>63.8 ± 15.4</td>
<td>24.3 ± 5.1</td>
</tr>
<tr>
<td>iv</td>
<td>5.5 ± 1.5</td>
<td>4.0 ± 0.9</td>
<td>2.9 ± 0.6</td>
<td>41.6 ± 16.7</td>
<td>60.8 ± 21.1</td>
<td>23.8 ± 7.8</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. Differences in parameters among the four regimens were not statistically significant (P > 0.05).

RESULTS

Aluminum-magnesium antacid did not significantly alter the pharmacokinetic parameters of cefixime when administered simultaneously with, 2 h before, or 2 h after cefixime (Table 1; P > 0.05; analysis of variance). The mean ± standard deviation Cmax values for regimens i through iv were 4.9 ± 1.4 (cefixime alone), 5.7 ± 1.3 (cefixime with antacid), 5.1 ± 1.0 (cefixime 2 h before antacid), and 5.5 ± 1.5 (cefixime 2 h after antacid) μg/ml. Corresponding values for AUCo-∞ were 38.3 ± 14.5, 42.8 ± 13.9, 38.5 ± 9.8, and 41.6 ± 16.7 μg·h/ml. Visual inspection of the mean cefixime concentration-versus-time curves (Fig. 1) suggested an increase in cefixime concentrations in serum for the three antacid-containing regimens as compared with cefixime alone; however, these differences were not statistically significant (P > 0.05; analysis of variance; F = 0.183 with 3 and 33 df in the numerator and denominator, respectively).

The administration of cefixime and antacid was well tolerated. Three episodes of headache and one complaint of nausea were reported for the 48 doses of cefixime administered.

DISCUSSION

Historically, oral antibiotics have been reserved for the treatment of mild infections in nonhospitalized patients. Currently, greater emphasis is being placed on the outpatient management of moderate to severe infections with orally active antimicrobial agents such as the new fluoroquinolones and expanded-spectrum cephalosporins. In selected situations a patient can receive a short course of parenteral therapy in the hospital setting followed by oral therapy on an outpatient basis for the remainder of the treatment period. The advantages resulting from sequential parenteral-oral antibiotic therapy are many; however, these advantages can only be realized if patient compliance is assured and drug absorption is reliable (7).

The ability of antacids to interfere with the absorption of tetracycline antibiotics has long been recognized (1, 10). More recently, magnesium-aluminum antacids have been found to significantly decrease the bioavailability of oral fluoroquinolones by forming insoluble, nonabsorbable chelates (6). There has already been at least one report of probable clinical failure as a result of this interaction (M. Noyes and R. Polk, Letter, Ann. Intern. Med. 109:168, 1988). In the only published study evaluating the influence of an antacid on the absorption of a cephalosporin, Sommers et al. found that the Cmax and AUC of cefuroxime axetil were dramatically decreased as a result of coadministration with sodium bicarbonate and ranitidine (12). The decrease in

1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 h postdose. After coagulation and centrifugation, the separated serum was stored frozen at −70°C until assayed. Urine was collected during the intervals from 2 to 0 (baseline), 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h postdose. The total volume of urine within each interval was recorded, the pH was measured, and a 10-ml portion of each sample was frozen at −70°C until analyzed. Serum and urine samples were assayed within 6 weeks.

Cefixime assay. Cefixime concentrations in serum and urine were measured by reversed-phase high-performance liquid chromatography with UV detection by a modification of the method of Falkowski et al. (2). The modification consisted of the use of 7-hydroxy-coumarin (Aldrich Chemical Co., Milwaukee, Wis.) as the internal standard. The lowest limits of sensitivity for the assay were 0.05 and 5.0 μg/ml in serum and urine, respectively. Corresponding ranges of linearity were 0.05 to 30.0 and 5.0 to 75.0 g/ml. Urine samples found to contain more than 75 μg/ml were diluted with blank human urine and reanalyzed to bring the assayed samples within the range of linearity. The day-to-day precision (coefficients of variation) ranged from 3.0 to 7.7% for the serum assay and from 1.8 to 4.7% for the urine assay.

Pharmacokinetics. The pharmacokinetic parameters of cefixime were determined with compartmental and model-independent methods. The maximum cefixime concentration (Cmax) and the time of the maximum concentration (Tmax) were determined by inspection of the observed concentrations in serum. Terminal elimination rate constants (keq) were determined by nonlinear least-squares regression analysis with an unweighted one-compartment open model with first-order absorption and elimination (PCNONLIN; 13). Weighting factors of 1/C and 1/C² did not significantly improve the fit of the data, as determined by the Akaike information criteria (17). Half-life (t1/2) was calculated with 0.693/keq. The AUC from 0 h to time t (AUCo-t) was determined by the trapezoidal rule. The area of the residual trapezoids was calculated by dividing the last measured concentration at time t by keq. The extrapolation to infinity (AUCo-∞) was calculated from the sum of (AUCo-t) and residual area. Renal clearance (CLR) was calculated by dividing the total amount of cefixime excreted in the urine over 24 h (Ae0-24) by AUCo-24.

Statistical analysis. Differences in the mean pharmacokinetic parameters between treatments were evaluated by repeated-measures analysis of variance. Statistical significance was defined as P < 0.05.
bioavailability was thought to be due to decreased drug dissolution with raised intragastric pH.

Data from the present study indicate that the oral absorption of cefixime is not adversely affected by the coadministration of aluminum-magnesium antacids. In fact, there is a trend toward increased concentrations of aluminum-magnesium antacids. In fact, there is a trend toward increased concentrations of cefixime in serum when antacid is administered simultaneously as compared with when cefixime is given alone; however, because of a relatively large degree of intersubject variability in cefixime concentrations, any real increase in bioavailability of less than 20% may have been obscured by an insufficient sample size. In addition, since we used a single dose of antacid to simulate the typical "as-needed" administration, it is possible that repeated dosing of antacid could result in a statistically significant increase in cefixime bioavailability. Further studies are necessary to document this possibility.

The most likely explanations for the trend toward enhanced cefixime absorption with the antacid-containing regimen are delayed gastric emptying and gastrointestinal transit, which allows more complete drug dissolution and/or prolonged residence at the intestinal site from which absorption is optimal (16). Additionally, and in support of our findings, some recent work indicates that a decreased rate of hydrolytic degradation may also be involved (8).

The reasons explaining the discrepancies between results found in dogs and those found in our investigation are unclear at present but may include one or several of the following: species differences in gastrointestinal tract physiology (11); pH-related differences in the rate of intestinal uptake of cefixime (15); differences in the rate of cefixime hydrolysis (8); the presence of a saturable renal tubular reabsorption process in dogs (14); and differences in the dose size and formulation of cefixime and antacid used. Regardless of the exact mechanism(s) responsible for the differences observed, these data underscore the importance of confirming preliminary antacid interaction data derived from animals with clinical trials in humans.

In summary, we conclude that single-dose administration of antacids containing aluminum hydroxide and magnesium hydroxide does not decrease the extent of cefixime absorption and that separation of doses is not necessary. In addition, the unpredictable influence of antacids on the oral bioavailability of newer expanded-spectrum cephalosporins and the lack of correlation between dogs and humans necessitate the study of individual agents in clinical trials.

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LITERATURE CITED


