Effect of Antacid on the Bioavailability of Cefprozil

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The effect of antacid on the bioavailability of cefprozil was investigated in a two-way crossover study. Eight healthy male subjects received a single 500-mg oral dose of cefprozil with and without coadministration of 30 ml of an antacid suspension containing magnesium hydroxide and aluminum hydroxide (Maalox). Cefprozil consists of cis and trans isomers in an approximate 90:10 ratio. When cefprozil was administered alone (treatment A), the mean maximum concentrations (Cmax) of the cis and trans isomers were 9.2 and 1.2 μg/ml, respectively. When cefprozil was coadministered with Maalox (treatment B), the Cmax values of the cis and trans isomers were 8.7 and 1.3 μg/ml, respectively. The mean values of the area under the curve from time zero to infinity (AUC0-∞) were 27.7 and 3.5 μg·h/ml for treatment A and 27.5 and 3.5 μg·h/ml for treatment B for the cis and trans isomers, respectively. The other pharmacokinetic parameters, time to Cmax, elimination half-life, mean residence time, renal clearance, and percent urinary excretion, were essentially the same for the two isomers. The respective values of the elimination half-life for the cis and trans isomers were 1.36 and 1.32 h for treatment A and 1.36 and 1.42 h for treatment B. Mean urinary excretion was 63 and 60% for treatment A and 55 and 56% for treatment B for the cis and trans isomers, respectively. No significant differences between the two treatments were found for any of the pharmacokinetic parameters for either isomer. For the cis isomer, bioavailability point estimates (90% confidence intervals) of the mean Cmax and AUC0-∞ values for the Maalox treatment relative to those for the reference treatment were 95% (87%, 103%) and 99% (95%, 104%), respectively. For the trans isomer, the values were 109% (92%, 126%) for Cmax and 97% (88%, 106%) for AUC0-∞. On the basis of the results of this study, it is concluded that the bioavailability of cefprozil is not affected by the coadministration of Maalox.

Cefprozil is an oral β-lactam cephalosporin consisting of cis and trans isomers in an approximate 90:10 ratio. Its structure is similar to that of most other oral cephalosporins with a propenyl side chain at the 7 position and a p-hydroxyphenylglycyl substituent at the 7 position. Cefprozil has a broad antimicrobial spectrum and is more active than cefaclor and cephalixin against streptococci (6, 8, 12). All penicillinase-producing strains of Staphylococcus aureus are inhibited by 4 μg or less of cefprozil per ml, whereas they are inhibited by 32 μg of cefaclor and cephalixin per ml (12). Against S. aureus strains that lack penicillinase and Staphylococcus epidermidis, cefprozil is two- to fourfold more active than cefaclor and is about eightfold more active than cephalixin (12).

Cefprozil is essentially completely absorbed (18). It exhibits linear and dose-proportional pharmacokinetics after administration of a single oral or intravenous dose in the range of 250 to 1,000 mg (1, 4, 18). Cefprozil is cleared primarily by the kidneys unchanged, with an elimination half-life (t1/2) of about 1.3 h. The urinary recovery of unchanged cefprozil is about 65% (1-4). The pharmacokinetic characteristics of the two isomers have been shown to be similar after administration by the oral and intravenous routes (17, 18, 20).

Antacids are widely used in clinical practice. Coadministration of antacids and antibiotics has affected the bioavailabilities of some antibiotics (7, 11, 13, 21) but not others (5, 7, 10, 14). This study was designed to investigate the effect of the antacid Maalox on the pharmacokinetics of cefprozil in healthy male volunteers receiving a single 500-mg oral dose of cefprozil.

MATERIALS AND METHODS

Antibiotics. Cefprozil was supplied as opaque white capsules containing approximately 250 mg of cefprozil (lot no. 20823) by Bristol-Myers Squibb Company, Syracuse, N.Y. Each 500-mg dose was individually packaged in a bottle containing two capsules. Maalox was used in its liquid formulation (lot no. 84918; Rorer Consumer Pharmaceuticals, Fort Washington, Pa.) and was purchased commercially. Each milliliter of Maalox contains 60 mg of magnesium hydroxide and 120 mg of aluminum hydroxide.

Subjects. Eight healthy male subjects were selected for the study and signed written informed consent forms prior to entering the study. The criteria for selecting subjects were no history or evidence of chronic infectious disease, heart disease, renal disease, hepatic disease, pulmonary obstructive disease, bronchial asthma, hypertension, or glaucoma. Subjects did not have a history of drug hypersensitivity or intolerance. These subjects also had negative laboratory results for human immunodeficiency virus antibodies, hepatitis B surface antigen, or drug abuse. No concurrent medication was allowed. Subjects were not allowed to ingest alcohol within 24 h prior to the administration of each dose. The subjects had a mean ± standard deviation age of 22 ± 2 years, a mean body weight of 75 ± 8 kg, and an average height of 181 ± 7 cm.

Study design. This was an open, two-way crossover study designed to evaluate the bioavailability of cefprozil when it is administered with and without an antacid. After each subject

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signed an informed consent, each subject was assigned to one of two randomization sequences. Each subject received a single oral 500-mg dose of cefprozil with or without coadministration of 30 ml of Maalox. Subjects entered the test facility the evening before each dosing session and stayed until 24 h after dosing. All subjects fasted overnight prior to dosing and continued fasting until 4 h postdose. After a 3-day washout period, each subject received the appropriate alternate treatment.

Drug administration. Each subject swallowed two 250-mg capsules of cefprozil with 100 ml of tap water without chewing or crushing the dosage form. Subjects who received cefprozil with the antacid drank 30 ml of Maalox 5 min prior to receiving cefprozil. The 30-ml volume of Maalox was accurately measured and was dispensed in a medicine dosing cup. The subjects remained ambulatory for at least 10 min every half-hour during the first 2 h after drug administration.

Sample collection. Approximately 5 ml of blood was collected at each sampling time in a heparinized tube. Blood samples were collected at predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 h after cefprozil administration. The plasma was immediately separated, frozen, and stored at −20°C pending drug analysis.

Urine samples were collected from each subject at predose and over the intervals of 0 to 4, 4 to 8, and 8 to 24 h after cefprozil dosing. Urine specimens were kept refrigerated during the collection period. The volume and pH of each sample were measured to the closest 1 ml and 0.1 pH units, respectively. Exactly 5 ml of urine was transferred to a screw-cap polypropylene tube containing 5 ml of 0.02 M acetate buffer (pH 3.8). The buffered urine was mixed thoroughly and stored at −20°C pending drug analysis.

Sample analyses. Plasma and urine samples were analyzed for intact cis and trans isomers of cefprozil by validated high-performance liquid chromatography methods (19). Plasma and urine quality control (QC) samples were prepared prior to initiation of the study. The QC samples were stored and assayed with the study samples to verify the accuracy, precision, and reproducibility of the assay and the stability of the cis and trans isomers during shipment and storage.

All standard curves for the cis and the trans isomers in plasma and urine were linear. The standard concentrations of both isomers ranged from 0.1 to 20 μg/ml in the plasma assay and from 5 to 500 μg/ml in the urine assay. The between-day and within-day errors for the plasma and urine QC samples were less than 5 and 11% for both isomers, respectively. The mean observed QC concentrations in plasma and urine deviated less than 9 and 10% from the corresponding nominal concentrations of both isomers, respectively. The accuracy, precision, and reproducibility of the QC results demonstrated the excellent performance of the assay and that both isomers are stable in human plasma and urine during sample shipment and storage.

Pharmacokinetic analyses. Noncompartmental pharmacokinetic parameters were calculated by standard methods (9, 15). The highest observed concentration and the corresponding sampling time were defined as $C_{\text{max}}$ and $T_{\text{max}}$, respectively. $t_{1/2}$ was determined from the slope of the regression line which best fit the terminal portion of the log-linear concentration-time curve. The data were fitted to the function $\ln C = \ln B - \beta t$ (where $C$ is concentration, $B$ is the intercept, $\beta$ is the elimination rate constant, and $t$ is time), starting with the last three concentrations-versus-time datum points. The procedure continued by adding the preceding datum points one at a time until $C_{\text{max}}$ was reached. The terminal log-linear portion was defined by the data set for which the mean square error term from the regression was minimized.

The area under the concentration-versus-time curve (AUC) and the area under the first moment of the concentration-versus-time curve (AUMC) were calculated by using the trapezoidal rule method from time zero to $t_m$, where $t_m$ was the time at which the drug concentration appeared to decline in a log-linear manner. From $t_m$ to $t_n$, the last non-zero datum point, the log-trapezoidal rule method was used (15). The AUC and AUMC values were extrapolated to infinity and are reported as $AUC_{0-m}$ and $AUMC_{0-m}$, respectively. Mean residence time in the body (MRT) was estimated as $AUMC_{0-m}/AUC_{0-m}$.

Total urinary recovery (UR) was calculated as the cumulative amount of drug excreted within the collection period and was expressed as a percentage of the administered dose. The renal clearance ($CL_R$) of the cis and trans isomers was estimated by standard methods (9).

Statistical analyses. The relative bioavailability of cefprozil when it was administered with Maalox was compared with that of cefprozil when it was administered alone by analyzing the values of $C_{\text{max}}$, $t_{1/2}$, $AUC_{0-m}$, MRT, $CL_R$, and UR for the two treatments. An analysis of variance model for a two-period crossover design was used to make the comparison by considering the sequence, the subjects within the sequence, treatment, period, and mean sequence error effects (22). Bioavailability was also assessed by two one-sided tests that compared the $C_{\text{max}}$ and $AUC_{0-m}$ values for the drug after the two treatments (16). All tests of significance were performed at the $P = 0.05$ level. Analyses were conducted separately for the cis and trans isomers of cefprozil.

RESULTS

Safety assessment. Mild headache, nausea, and vomiting were reported by six of the eight subjects. One of the six subjects who reported adverse experiences received cef-
TABLE 1. Pharmacokinetic parameters for the cis and trans isomers of cefprozil following oral administration of 500 mg of cefprozil with or without coadministration of Maaloxa

<table>
<thead>
<tr>
<th>Isomer</th>
<th>Treatment</th>
<th>Cmax (µg/ml)</th>
<th>AUC0.0.0 (µg · h/ml)</th>
<th>Tm (h)b</th>
<th>t1/2 (h)</th>
<th>MRT (h)</th>
<th>CLa (ml/min)</th>
<th>UR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis</td>
<td>Without Maalox</td>
<td>9.2 ± 0.7</td>
<td>27.7 ± 1.9</td>
<td>1.5 (1.5–2.0)</td>
<td>1.36 ± 0.14</td>
<td>2.81 ± 0.22</td>
<td>174 ± 47</td>
<td>63 ± 15</td>
</tr>
<tr>
<td></td>
<td>With Maalox</td>
<td>8.7 ± 1.1</td>
<td>27.5 ± 2.1</td>
<td>1.5 (1.0–2.0)</td>
<td>1.36 ± 0.15</td>
<td>2.79 ± 0.30</td>
<td>160 ± 34</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>Trans</td>
<td>Without Maalox</td>
<td>1.2 ± 0.2</td>
<td>3.5 ± 0.8</td>
<td>1.5 (1.0–2.5)</td>
<td>1.32 ± 0.54</td>
<td>2.91 ± 0.36</td>
<td>152 ± 60</td>
<td>60 ± 15</td>
</tr>
<tr>
<td></td>
<td>With Maalox</td>
<td>1.3 ± 0.4</td>
<td>3.5 ± 0.6</td>
<td>1.75 (1.0–2.5)</td>
<td>1.42 ± 0.60</td>
<td>2.97 ± 0.54</td>
<td>141 ± 38</td>
<td>56 ± 9</td>
</tr>
</tbody>
</table>

a Values are means ± standard deviations, unless indicated otherwise.
b Tm, time to Cmax. Values are reported as median (minimum–maximum).

ciprozil alone, and the rest of the subjects who reported adverse experiences received ciprofloxacin with Maalox. Among all the reported adverse experiences, two episodes of vomiting were observed in one subject who was under the coadministration treatment. These events occurred at 2 and 7 min after drug administration. However, the vomiting did not result in significantly lower values of Cmax, AUC, or UR for this subject. No medication was needed for any of the adverse experiences. No significant laboratory abnormalities occurred during the study. No abnormal findings were noted on poststudy physical examinations.

Pharmacokinetic and statistical analyses. The mean plasma concentration-versus-time profiles for the cis and trans isomers for both treatments are presented in Fig. 1. The mean ± standard deviation pharmacokinetic parameters for the intact cis and trans isomers of ciprofloxacin for oral administration of a 500-mg dose of ciprofloxacin with and without coadministration of Maalox are provided in Table 1. The values of the pharmacokinetic parameters of ciprofloxacin were consistent among the subjects. The coefficients of variation for the pharmacokinetic parameters were generally less than 15%.

The concentrations of the trans isomer in plasma were approximately 1/10th of the values observed for the cis isomer, as indicated by the values of Cmax and AUC0.0.0 for the two isomers. The concentrations of ciprofloxacin in plasma were similar in subjects who received ciprofloxacin either alone or coadministered with Maalox. The other pharmacokinetic parameters, Tm, t1/2, MRT, CLa, and UR, were essentially the same for the two isomers. The effect of the coadministration of Maalox was not detected from the values for any of the pharmacokinetic parameters for the corresponding isomers.

No statistically significant difference between the treatments was found for any parameter for either the cis or the trans isomer. For the cis isomer, the point estimates (90% confidence intervals) estimating the relative bioavailability were 95% (87%, 103%) for Cmax and 99% (95%, 104%) for AUC0.0.0. For the trans isomer, the point estimates (90% confidence intervals) for the relative bioavailability were 109% (92%, 126%) for Cmax and 97% (88%, 106%) for AUC0.0.0.

DISCUSSION

Coadministration of antacids with antibiotics decreases the bioavailability of some antibiotics (7, 11, 13, 21). The bioavailability of doxycycline after coadministration with aluminum magnesium hydroxide is only 15% of that reported for doxycycline administered alone (7). Chelation of doxycycline with Al3+ or Mg2+, leads to the formation of an insoluble six-membered ring structure in a manner analogous to the chelation of tetracycline and reduces the oral absorption. The bioavailability of fluoroquinolones (13) are also decreased when a magnesium-aluminum antacid is coadministered. The mechanism of reduction in the bioavailability of fluoroquinolones is similar to that reported for doxycycline. The values of Cmax and AUC of ciprofloxacin doxycycline also decrease by approximately 35 to 50% after coadministration with aluminum hydroxide or sodium bicarbonate (11). Similarly, the values of Cmax and AUC of cefuroxime axetil dramatically decrease as a result of coadministration with sodium bicarbonate (21). The decrease in bioavailabilities of both produg esters of these cephalosporins are thought to be due to decreased drug dissolution with raised gastric pH. Concurrent administration of an antacid does not significantly affect the pharmacokinetic parameters of some other β-lactam antibiotics such as amoxicillin (7), cephalixin (7), cefixime (10, 14), or cefetamet pivoxil (5).

The solubility of ciprofloxacin remains relatively constant in vitro at pH 2 to 5 (unpublished data). It is stable (<2% degradation) at room temperature for up to 18 h at pH 6 or lower (unpublished data). Ciprofloxacin is well absorbed (1-4, 17-20), and peak levels in plasma are achieved in less than 2 h after dosing. Therefore, a raised pH in the gastrointestinal tract after coadministration of the antacid has no impact on the solubility, stability, or absorption of ciprofloxacin. The narrow range of the 90% confidence interval, 95% (87%, 103%) for Cmax and 99% (95%, 104%) for AUC0.0.0 of the cis isomer, demonstrated that the bioavailability of ciprofloxacin is not affected by the coadministration of Maalox. The overall pharmacokinetic characteristics of ciprofloxacin in this study are consistent with those of both isomers reported previously (1, 4, 17, 18, 20). The pharmacokinetics of ciprofloxacin have small inter- and intrasubject variability. Therefore, the 90% confidence interval for the difference in treatment means is contained within ±20% of the reference means with a probability of 0.90 and can be obtained with a sample size of only eight subjects. The bioavailability of ciprofloxacin is unaffected when it is coadministered with Maalox. This finding is consistent with the physical chemical properties of ciprofloxacin and the results for other β-lactam antibiotics with a phenylglycine side chain, i.e., amoxicillin and cephalixin. Cefprozil can be administered with an antacid, if the need arises, without altering the pharmacokinetics of ciprofloxacin.

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REFERENCES