Comparative Pharmacokinetics of Oral Ceftibuten, Cefixime, Cefaclor, and Cefuroxime Axetil in Healthy Volunteers

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Study Objective. To compare the pharmacokinetics of ceftibuten, cefixime, cefuroxime axetil, and cefaclor after oral administration.

Design. Randomized, four-period, crossover study.

Setting. Hospital-based clinical research center.

Subjects. Healthy adult men and women volunteers.

Interventions. Single 400-mg doses of cefixime and ceftibuten, and 500-mg doses of cefuroxime axetil and cefaclor.

Measurements and Main Results. Serum concentrations were determined by high-performance liquid chromatography methods. The mean oral clearances of cefixime, cefuroxime axetil, and cefaclor were similar, ranging from 20.4–27.0 L/hour; clearance of ceftibuten was approximately 4-fold less, 5.45 L/hour. The serum half-lives of ceftibuten (2.35 hrs) and cefixime (2.38 hrs) were prolonged compared with those of cefuroxime axetil (1.30 hrs) and cefaclor (0.693 hr). These agents also differed in terms of time to maximum concentration, time to peak plasma level, area under the curve, and apparent volume of distribution, the last reflecting differences in bioavailability.

Conclusion. Ceftibuten had a relatively high time to maximum concentration and long half-life, resulting in a 3.5-fold higher area under the curve than cefixime, cefuroxime axetil, and cefaclor. These pharmacokinetic data can be used as a basis to compare the four oral cephalosporins; however, comparative susceptibility data must also be considered.

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Ceftibuten is a third-generation cephalosporin antibiotic with good oral bioavailability and in vitro activity against gram-negative bacteria and common respiratory pathogens such as Streptococcus pneumoniae, Streptococcus pyogenes, and Moraxella catarrhalis.1,2 It does not have useful activity against staphylococci, enterococci, obligate anaerobes, or Pseudomonas species. Ceftibuten is classified as a third-generation cephalosporin because of its stability in the presence of plasmid-mediated and extended-spectrum β-lactamases produced by some Enterobacteriaceae.2,3 The extended-spectrum β-lactamases hydrolyze many cephalosporins including cefaclor, cefixime, and cefuroxime, which are considered β-lactamase stable due to

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their stability in the presence of class I and IVc enzymes. However, ceftibuten is hydrolyzed by type I chromosomal-encoded β-lactamases of *Pseudomonas aeruginosa* and *Enterobacter* sp. The in vitro activity of ceftibuten against *Enterobacteriaceae* is generally better than that of cefaclor, cefixime, cefpodoxime, and cefuroxime.

The pharmacokinetics of ceftibuten have been described extensively,4,5 but comparative studies with other oral cephalosporins have not been published; one group summarized the comparative pharmacokinetics based on a literature review.6,7 Our crossover study was performed to compare directly the pharmacokinetics of ceftibuten with those of cefaclor, cefixime, and cefuroxime in healthy adult volunteers.

**Methods**

**Subjects and Study Design**

Twelve healthy volunteers (7 men, 5 women) between 18 and 45 years of age were enrolled. They were randomized to receive four treatments in a randomized, open-label, four-way, crossover design. The treatments were separated by a 7-day washout period. Before enrollment a screening evaluation was performed, including complete history and physical examination, 12-lead electrocardiogram, hepatitis B surface antigen screen, human immunodeficiency virus (HIV) antibody test, urine drug screen, and clinical laboratory profiles. Subjects who were found to be healthy based on these procedures were eligible. Exclusion criteria were history of major organ disease, presence of active infection within 4 weeks, use of prescription or over-the-counter drugs within 2 weeks, use of alcohol within 72 hours, history of drug abuse, use of investigational drugs within 60 days, receipt of radiolabeled material within 6 months, history of β-lactam allergy, positive hepatitis B surface antigen or HIV antibodies, and positive urine drug screen.

The study was reviewed and approved by the Millard Fillmore Hospital human research committee, and written informed consent was obtained from all subjects.

Each subject received the following single oral doses with 240 ml of water: ceftibuten 400 mg (Schering Plough Research), cefixime 400 mg (Wyeth-Lederle, Pearl River, NY), cefaclor 500 mg (Eli Lilly & Co., Indianapolis, IN), and cefuroxime axetil 500 mg (Allen & Hanburys, Research Triangle Park, NC). The subjects fasted overnight and received only water until 4 hours after dosing, at which time light lunch was served. No beverages containing caffeine were permitted during the study.

Clinical laboratory tests were repeated 24 hours after dosing during each study phase. Vital signs were monitored before dosing and 2, 4, 8, 16, and 24 hours after dosing. Physical examinations were repeated before final discharge. Volunteers were monitored throughout each study period for the possible occurrence of adverse events.

**Pharmacokinetic Assays**

Venous blood samples (7 ml) were obtained through an indwelling catheter before dosing and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours after dosing. The samples were allowed to clot for 30 minutes and were centrifuged. The serum was withdrawn and frozen at -70°C for later assay of drug concentrations.

The samples were analyzed on site using validated high-performance liquid chromatography (HPLC) methods. For cefuroxime, the limit of detection was 0.05 µg/ml. The overall precision for quality control samples was 3.2%, with the 1.80-pg/ml control having the highest variability of 4.39%. The assay for ceftibuten required a solid-phase extraction before HPLC analysis. The detection limit was 0.140 µg/ml. The overall precision was 5.22 µg/ml with maximum variability of 6.25% observed with a 2.0-µg/ml quality control sample.

For cefixime, the limit of quantification was 0.008 µg/ml and the overall precision was 6.94% for the quality control samples. Maximum variability was 7.63% with the 0.03-µg/ml quality control sample. The assay for cefaclor had a limit of detection of 0.05 µg/ml and overall precision of 8.55%. Maximum variability was seen with the 4.35-µg/ml quality control sample.

**Statistical Analyses**

The pharmacokinetic analysis was done with noncompartmental methods and Lotus 1-2-3, version 2.2. For each volunteer the concentration versus time profile was examined by treatment. Summary pharmacokinetic parameters were time to maximum concentration among all the plasma samples for a given subject on the test day (C<sub>max</sub>), time at which C<sub>max</sub> occurred (T<sub>max</sub>), terminal elimination rate constant (k<sub>e</sub>), the area under the plasma concentration versus time profile from time zero until the time of the last measured concentration (AUC<sub>0-7</sub>), the area
Table 1. Mean (CV%) Pharmacokinetic Parameters for 12 Healthy Subjects

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>$\text{AUC}_{0-T}$ (µg•hr/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (µg•hr/ml)</th>
<th>$k_e$ (hr⁻¹)</th>
<th>$T_{1/2}$ (hrs)</th>
<th>$V/F$ (L)</th>
<th>$Cl/F$ (L/hr)</th>
<th>$T_{\text{max}}$ (hrs)</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefituben</td>
<td>73.6 (19.6)</td>
<td>76.0 (19.3)</td>
<td>0.297 (8.75)</td>
<td>2.35 (8.94)</td>
<td>18.3 (15.0)</td>
<td>5.45 (19.4)</td>
<td>2.63 (50.2)</td>
<td>13.9 (14.8)</td>
</tr>
<tr>
<td>Cefixime</td>
<td>19.8 (21.8)</td>
<td>20.4 (21.0)</td>
<td>0.299 (16.7)</td>
<td>2.38 (16.0)</td>
<td>69.9 (28.2)</td>
<td>20.4 (20.0)</td>
<td>5.08 (39.8)</td>
<td>2.64 (26.5)</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>20.0 (16.6)</td>
<td>20.6 (16.4)</td>
<td>1.06 (25.2)</td>
<td>0.693 (24.5)</td>
<td>24.9 (30.5)</td>
<td>24.9 (17.6)</td>
<td>0.917 (46.9)</td>
<td>15.9 (36.0)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>19.6 (27.6)</td>
<td>19.9 (26.8)</td>
<td>0.541 (12.9)</td>
<td>1.301 (13.1)</td>
<td>50.0 (28.0)</td>
<td>27.0 (30.0)</td>
<td>2.46 (47.2)</td>
<td>5.24 (19.5)</td>
</tr>
</tbody>
</table>

p Values for ceftibuten vs comparative agent
- Cefixime <0.001 <0.001 NS NS <0.001 <0.001 <0.001 <0.001
- Cefaclor <0.001 <0.001 <0.001 <0.001 NS <0.001 <0.019 NS
- Cefuroxime axetil <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 NS <0.001

*Doses of ceftibuten and cefixime were 400 mg. Doses of cefaclor and cefuroxime axetil were 500 mg each.

under the plasma concentration versus time curve over the time interval zero to infinity ($\text{AUC}_{0-\infty}$), apparent total body clearance ($Cl/F$), apparent volume of distribution ($V/F$), and elimination half-life ($T_{1/2}$).

To obtain $k_e$, the natural log concentration versus time values were plotted. The number of points for the terminal slope determination was defined by visual examination of the linear portion of the plot. The slope obtained from linear regression of the selected points on the natural log concentration versus time plot was defined as $k_e$. The $\text{AUC}_{0-\infty}$ was estimated using the linear trapezoidal rule. The $\text{AUC}_{0-T}$ was calculated using the equation: $\text{AUC}_{0-T} + C(t^*)/k_e$, where $C(t^*)$ is the last measured concentration. The $T_{1/2}$, $Cl/F$, and $V/F$ were calculated from the above parameters using standard equations.

Descriptive statistics (mean, SD, coefficient of variation, CV%) were calculated for each treatment using the individual parameters. Differences in pharmacokinetics were determined using a general linear model for repeated measures with treatment, period, and subject effects. This testing is equivalent to a multi-factorial analysis of variance given the equal sample sizes and lack of missing data. The program Systat (Systat Inc., Evanston, IL) was used for this analysis. Pairwise comparisons were made using Bonferroni's multiple comparison test with respect to treatment effects. Linear regression analysis was applied to the pharmacokinetics to determine significant associations with body weight ($t$ test, p<0.05). Where significant associations were found, the parameters were normalized by body weight.

Results

All subjects completed the study. The mean (CV%) age was 24.8 (22.2%) years and the overall mean weight was 75.2 (18.0%) kg (82.2 kg for men, 65.3 kg for women). The mean concentration versus time data for all four treatments are shown in Figure 1. Table 1 provides the mean (CV%) calculated pharmacokinetic parameters for each study treatment. A significant relationship (p<0.05) was identified between some parameters and body weight. For ceftibuten, body weight explained some of the intersubject variability in $\text{AUC}$, $Cl/F$, and $V/F$. The normalized mean (CV%) values were 1.06 µg•hour/L/kg for $\text{AUC}_{0-\infty}$, 0.0732 L/hour/kg for $Cl/F$, and 0.246 L/kg for $V/F$. For cefixime, only $Cl/F$ (0.275 L/hr/kg), and $C_{\text{max}}$ (0.0371 µg/ml/kg) were normalized. Significant associations between body weight and $\text{AUC}$ and $Cl/F$ were identified for cefaclor. The normalized values were 0.289 µg•hour/ml/kg for $\text{AUC}_{0-\infty}$ and 0.334 L/hour/kg for $Cl/F$. Normalized parameters for
Cefuroxime axetil included AUC\textsubscript{0-\infty} of 0.281 pg\textbullet{}hour/ml/kg, Cl/F 0.359 L/hour/kg, and \( k_e \) 0.00731/hour/kg.

Cefixime, cefaclor, and cefuroxime axetil all had similar AUC\textsubscript{0-\infty} values of approximately 20 pg\textbullet{}hour/ml, whereas that for ceftibuten (76.0 pg\textbullet{}hr/ml) was significantly higher. This difference also held true for AUC\textsubscript{0-\infty}. Cefaclor attained the highest C\textsubscript{\text{max}}, 15.9 pg/ml, followed by ceftibuten, 13.9 pg/ml. Both of these agents had significantly higher mean C\textsubscript{\text{max}} values compared with cefuroxime axetil, 5.2 pg/ml, and cefixime, 2.6 pg/ml. Cefixime had the longest elimination half-life (2.38 hrs) followed by ceftibuten (2.35 hrs), cefuroxime axetil (1.30 hrs), and cefaclor (0.70 hr). The values for CI/F were similar for cefaclor, cefixime, and cefuroxime axetil at approximately 24 Uhr, whereas the CI/F for ceftibuten was significantly slower at 5.5 L/hour.

No clinically significant laboratory abnormalities were observed during the study. Approximately half of the subjects experienced a slight decrease in hematocrit and hemoglobin by phase 4, due to blood sampling for pharmacokinetic analysis. Vital signs were within acceptable limits for all volunteers.

Eight subjects reported a total of 23 adverse events that were either mild (20) or moderate (3) in intensity. Of the 23 events, 8 were possibly related to the study drugs and 15 were not. The most frequent adverse event was headache (35%). Abdominal pain was reported by one subject each after ceftibuten and cefixime administration. None of the adverse events required interruption in the study procedures and they resolved without medical intervention.

Discussion

Our results indicate that ceftibuten has a higher AUC\textsubscript{0-\infty}, 76.0 pg\textbullet{}hour/ml, than the other oral cephalosporins tested. These findings are consistent with an earlier study in which the AUC\textsubscript{0-\infty} was 79.2 pg\textbullet{}hour/ml after a single 400-mg dose of ceftibuten.\textsuperscript{3} The AUC\textsubscript{0-\infty} of ceftibuten is proportional to the dose with doses ranging from 200–400 mg, and slightly less than proportional with an 800-mg dose.\textsuperscript{4} Food does not affect the extent of absorption of ceftibuten, however, it does reduce the rate of absorption.\textsuperscript{5} The cumulative urinary recovery of ceftibuten and the transisomer metabolite is approximately 70–90% of the dose, indicating excellent bioavailability.

Approximately 20% of ceftibuten is eliminated as a transisomer metabolite. Given the average renal clearance of 49.8 ml/minute and protein binding of approximately 63% in healthy subjects, the unbound renal clearance would be approximately 135 ml/minute. This indicates that ceftibuten is eliminated primarily by glomerular filtration without significant tubular secretion. These pharmacokinetic characteristics result in a relatively high maximum serum concentration and long half-life.

The other three oral cephalosporins all provided AUC\textsubscript{0-\infty} values of approximately 20–21 pg\textbullet{}hour/L, which is more than 70% less than for ceftibuten. In previous studies the AUC\textsubscript{0-\infty} for cefuroxime axetil ranged from 13.5–30.3 pg\textbullet{}hour/L.\textsuperscript{9–11} The higher value of 30.3 was obtained when the dose was administered with food.\textsuperscript{12} In this study, cefuroxime axetil was administered in the fasting state. Some improvement in bioavailability would be expected if it was administered with food; however, the type of food could also affect the results. The AUC\textsubscript{0-\infty} for cefixime was reported to range from 24.6–32.0 mg\textbullet{}hour/L after a 400-mg oral dose\textsuperscript{13–15} and is unaffected by food. The AUC\textsubscript{0-\infty} for cefaclor was 16.1–17.3 mg\textbullet{}hour/L in previous studies.\textsuperscript{16, 17}

Despite their similar AUC\textsubscript{0-\infty} values, cefaclor, cefixime, and cefuroxime axetil have different pharmacokinetic properties. Cefaclor has a relatively high maximum serum concentration due to good oral bioavailability. Cefixime has a relatively low maximum serum concentration resulting from poor bioavailability. The value for cefuroxime axetil is intermediate, but in our study it was 5.24 mg/L in the fasting state. When the drug is administered with food,\textsuperscript{12} the maximum concentration is higher (mean 8.6 mg/L).

The half-life of cefaclor is relatively short. Cefaclor undergoes extensive renal tubular secretion (Cl\textsubscript{R} 315 ml/min),\textsuperscript{17} but only about 54% is recovered in the urine.\textsuperscript{16} It has been hypothesized that this low urine recovery and short half-life may be in part due to degradation in urine since the drug is chemically unstable at body temperature.\textsuperscript{16} Cefixime is eliminated by glomerular filtration since the unbound renal clearance is similar to creatinine clearance. The total and unbound renal clearances are 43 and 130 ml/minute, respectively.\textsuperscript{15} Protein binding averages 67%. The half-life of cefixime is long due to the lack of tubular secretion and moderate protein binding. The mean half life of cefuroxime...
axetil in our study was 1.3 hours. Considering its renal clearance (177 ml/min)\(^9\) and low protein binding (33%), cefuroxime undergoes a small amount of tubular secretion, but considerably less than cefaclor.

Although this investigation provides information on comparative pharmacokinetics, the clinical importance of similarities and differences in the values is complex. The serum half-life is considered for determining dosing intervals. Current intervals are 8 hours for cefaclor, 12 hours for cefuroxime axetil, and 24 hours for cefixime and ceftibuten. In addition, considerable differences in the spectra of activity and relative susceptibilities of bacteria must be considered. Consequently, clinical importance cannot be assigned for differences in a particular pharmacokinetic parameter without considering the dosing intervals and bacterial susceptibilities. One drug may be comparably strong against one pathogen, but weak against another. Finally, therapeutic goals have to be established. It is known that time above minimum inhibitory concentration (MIC) and 24-hour AUC/MIC should be optimum. However, specific targets remain to be defined for most infections.

Summary

Ceftibuten has two pharmacokinetic advantages over the other three oral cephalosporins. Its relatively high \(C_{\text{max}}\) and long half-life lead to a 3.5-fold higher AUC. This pharmacokinetic profile combined with excellent in vitro potency against many common gram-negative and respiratory pathogens suggests a potential advantage in favor of ceftibuten.

These comparative pharmacokinetic data can be used as a basis to compare the four oral cephalosporins; however, comparative susceptibility data must also be considered to determine the best drug for a particular clinical need.

References

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