Pharmacokinetics of Cefpimizole in Normal Humans after Single- and Multiple-Dose Intravenous Infusions

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The pharmacokinetics of cefpimizole (free acid equivalents of cefpimizole sodium), a broad-spectrum cephalosporin antibiotic, were determined after single- and multiple-dose 20-min intravenous infusions of 1, 2, and 4 g. The kinetics of single-dose administration of cefpimizole correspond to a two-compartment model with an average apparent volume of distribution of 20.0 ± 3.5 liters, a distribution rate constant of 2.24 ± 1.00 h⁻¹, and a terminal rate constant of 0.358 ± 0.036 h⁻¹ (half-life, 1.9 h). The total body clearance was 118.6 ± 20.2 ml/min. The primary route of elimination for cefpimizole was the renal route, with approximately 80% of the administered dose excreted as the parent compound. The elimination rate constant, as calculated from urinary excretion data, was 0.339 ± 0.043 h⁻¹, which is in close agreement with the terminal rate constant for plasma. Renal clearance of cefpimizole was 96.2 ± 17.3 ml/min. Dose proportionality over the three dose levels was obtained from area under the plasma curve and cumulative urinary excretion data. The results of the multiple-dose study indicated that no apparent change in the distribution or elimination kinetics of cefpimizole occurred after the administration of 1-, 2-, and 4-g doses for 7 days, three times a day. The kinetics from the multiple-dose study were in close agreement with those from the single-dose study. No accumulation of cefpimizole occurred, and nondetectable levels were observed 24 h after administration of the last dose. Peaks that could be attributed to metabolites of cefpimizole were not observed during high-pressure liquid chromatographic analysis of either plasma or urine specimens.

Cefpimizole sodium (U-63196E, AC-1370), 7-[β-d(-)-α-[4(5)-carboxy-imidazole-5(4)-carboxamido]phenylacetamido]-3-(4-β-sulfoethylpyridinium)methyl-3-cepham-4-carboxylic acid, sodium salt (19) is a cephalosporin with activity against a broad spectrum of gram-negative bacteria, including Pseudomonas aeruginosa. Cefpimizole (free acid equivalents of cefpimizole sodium) is reported to have greater activity in vivo than in vitro (19). Results of a report on the in vitro activity of cefpimizole (12) have indicated that this cephalosporin inhibited many ampicillin-resistant bacteria, had in vitro activity similar to cefoperazone against gram-negative species, and was stable against hydrolysis by chromosomal β-lactamases. It was also stated that the in vitro activity of cefpimizole was less than that of other broad-spectrum cephalosporins. However, in vivo comparisons of activities of cefpimizole with other cephalosporins were not made. In addition, cefpimizole has been shown (13) to augment phagocyte function by human neutrophils, which may partially explain differences in in vivo and in vitro activities. Thus, the antibacterial activity in vivo and the potential increase in the host defense system caused by cefpimizole may provide an important addition in the treatment of bacterial infections.

This report presents the pharmacokinetics of cefpimizole after single- and multiple-dose intravenous infusions to normal adult humans. The analytical methods used to determine cefpimizole levels in plasma and urine specimens have been described previously (8), and high-pressure liquid chromatography (HPLC) for separation and UV detection at 254 nm were used. Pharmacokinetic evaluation was performed by noncompartmental and compartmental NONLIN (11) techniques.

MATERIALS AND METHODS

Single-dose study. Six normal adult male volunteers participated in the cefpimizole single-dose intravenous study. Informed consent was obtained from each subject. During the 2 weeks before drug administration, a history physical, electrocardiogram, and laboratory tests (hematology, serum chemistry, urinalysis) were performed. The laboratory studies, including the additional tests of creatinine clearance, urinary β-2-microglobulin concentration, and urinary excretion of N-acetyl-β-glucosaminidase, were repeated the day before and the day after each drug administration and 6 days after administration of the 4-g dose. The subjects ranged in age from 18 to 37 years and were within 20% of their ideal weights.

Cefpimizole sodium, freeze-dried in vials containing 1,000 mg of free acid equivalents, was reconstituted in an adequate volume of normal saline to be delivered over 20 min by intravenous infusion with Vicker infusion pumps. Each subject received three doses (1, 2, and 4 g) with a 7-day washout period between doses.

Sample collection of single doses. Blood samples (10 ml) were collected in tubes containing EDTA as anticoagulant and preservative and were obtained before the dose was administered (0 h) and at 0.33 (end of infusion), 0.67, 1.0, 2.0, 4.0, 6.0, 8.0, 12, and 24 h. Samples were centrifuged, and plasma was harvested, frozen immediately, and maintained at −30°C or lower until analysis. Urine collection intervals were predose, 0 to 0.5 (infusion time and 10 min after infusion), 0.5 to 0.75, 0.75 to 1.0, 1.0 to 2.0, 2.0 to 6.0, 6.0 to 12, 12 to 24, and 24 to 48 h. Urine samples were collected in flasks containing EDTA as preservative and refrigerated during the collection interval. After each collection period, the urine specimens were mixed thoroughly, the volume was measured, and a portion was frozen and maintained at −30°C or lower until analysis.
**Multiple-dose study.** Eighteen healthy adult male volunteers participated in the cefpimizole multiple-dose intravenous study. Informed consent, medical history, and laboratory tests for each volunteer were similar to those described above for the single-dose study. The laboratory tests were performed on days −1, 1, 3, 7, and 14.

Cefpimizole was administered as described above for the single-dose study. Doses of 1, 2, and 4 g were given three times a day (i.e., 7 days, resulting in total daily doses of 3, 6, and 12 g.

**Sample collection of multiple doses.** Blood samples (10 ml) were collected as described above for the single-dose study at the following times: on days 0 and 6, at predose, 0.333 (end of infusion), 0.67, 1.0, 2.0, 4.0, 6.0, and 8.0 h; on days 2 and 4, before the first daily dose. Urine was collected as described above for the single-dose study for the following collection intervals: on days 0 and 6, at predose, 0 to 0.5, 0.5 to 0.75, 0.75 to 1.0, 1.0 to 2.0, 2.0 to 4.0, 4.0 to 6.0, 6.0 to 8.0, 8.0 to 16, and 16 to 24 h.

**Analytical methods.** The levels of cefpimizole in plasma and urine specimens were determined by HPLC-UV (254 nm) methods reported previously (8). The sample preparation procedure for plasma consisted of combining a 1.0-ml fraction of plasma with 1.0 ml of 0.01 M EDTA–0.05 M tetrabutylammonium hydroxide (pH 5.0) and precipitating the protein with 4.0 ml of acetonitrile. After centrifugation, the supernatant was transferred, and the precipitate was washed with 2.0 ml of 75:25 (vol/vol) acetonitrile–0.01 M EDTA–0.05 M tetrabutylammonium hydroxide (pH 5.0). The wash was combined with the supernatant, and 200 μl of methylene chloride was added. The sample was allowed to undergo phase separation at −30°C, and the organic layer was aspirated and discarded. The internal standard, acetonaphone (50 μl of a 200-μg/ml solution), was added; the sample was filtered through a 0.45-μm Gelman Acrodisc-CR filter and stored at 4°C until analysis. For urine, the samples were prepared by adding 100 μl of urine to 4.0 ml of HPLC eluent containing 10 μg of internal standard per ml filtering, and storing at 4°C until analysis.

HPLC-UV analysis of prepared plasma and urine samples was performed on a column (Supelcosil LC-18; 5 μm, 250 by 4.6 mm [inner diameter]) with a guard column (C8-Partisil ODS; 35 μm, 50 by 2.1 mm [inner diameter]) with an eluent of methanol-water (35:65 [vol/vol]) containing 0.001 M EDTA and 0.005 tetrabutylammonium hydroxide (pH 6.0). The flow rate was 1.0 ml/min, and the UV detector was set at 254 nm.

The analytical methods had the necessary precision, accuracy, specificity, and sensitivity to provide quantitative data from 1 to 400 μg/ml for plasma and 10 to 800 μg/ml for urine.

**Pharmacokinetic evaluation.** The levels of cefpimizole in plasma and urine from the single-dose study subjects were subjected to pharmacokinetic evaluation by noncompartmental and compartmental techniques. Pharmacokinetic parameters included the apparent volume of distribution (V); area under the curve from zero to infinity (AUC_{0→∞}); using the trapezoidal rule from zero to the last quantifiable plasma level [C(t)] and C(t)/β, where β is the terminal (elimination) rate constant, for the remaining area to infinity; the total body clearance (CL_t); cumulative urinary excretion (U_t); elimination rate constant (k_e) from urine data; and renal clearance (CL_R). The value for V for each subject was calculated by the equation dose/AUC_{0→∞}; CL_t was determined from the equation dose/AUC_{0→∞}; and CL_R was determined from U_t/AUC for each subject. In addition, composite CL_T and CL_R values were obtained from the slopes of AUC_{0→∞} versus dose and AUC_{0→∞} versus U_t plots. Plots of log (U_t−U) versus time, i.e., log (cumulative urinary excretion−urinary excretion to a given time), were employed to determine k_e values which were compared with the results for the elimination of the drug from plasma. Model-dependent pharmacokinetic parameters were the distribution rate constant (α) and β and were obtained by NONLIN (11) for a two-compartment model with a constant rate of infusion.

Similar pharmacokinetic evaluations were performed on the results from the multiple-dose study. Since dosing occurred three times a day, the AUC was determined from 0 to 8 h. The values of α and β were determined by NONLIN from plasma levels after the first dose of days 0 and 6. The k_e value in urine and the percentage of the dose excreted from 0 to 8 h (one dose) and 0 to 24 h (three doses) was calculated for days 0 and 6. The k_e values from the multiple-dose study were employed to evaluate the uniformity of cefpimizole elimination in the urine after 7 days of treatment and are not directly comparable with the β value in plasma since the total urinary elimination profile was not available for each dose.

**RESULTS**

The results for the evaluation of cefpimizole in humans receiving a single 20-min intravenous infusion of drug are shown for plasma and urine in Fig. 1 and 2, respectively. The pharmacokinetic evaluation of the data from each volunteer in the single-dose study is summarized in Table 1. The semilogarithmic plots of the average plasma concentration versus time curves for the six subjects in each dose group are shown in Fig. 1. The curves are drawn from the time of the end of infusion to the last quantifiable plasma level. Each of the doses had a rapid distribution phase followed by a log-linear terminal phase. The average terminal phases appear to be parallel among the dose groups, indicating that the distribution and elimination of cefpimizole are similar for 1-, 2-, and 4-g doses. The average U_t of the parent compound for the three dose levels is shown in Fig. 2. The curves indicate that the drug is rapidly excreted in the urine, with about 75% of the dose excreted in the first 6 h and small amounts excreted after 12 h. The results of the pharmacokinetic parameters (Table 1) show excellent correlation over
the dose levels and between individuals. The average values for $V$, $\alpha$, $\beta$, $\text{CLR}_T$, $k_{\text{al}}$, and $\text{CLR}_R$ are presented, and only $\alpha$ has a relative standard deviation greater than 20%. The value of $V$ of 20.0 ± 3.5 liters was greater than that of the extracellular fluid (approximately 14 liters for a 70-kg human), indicating that cefpimizole may be distributed into some tissues. The distribution phase was rapid, with an average half-life of 0.3 h, and the terminal phase had an average half-life of 1.9 h. The $\text{CLR}_T$ and $\text{CLR}_R$ averages of 118.6 ± 20.2 and 96.2 ± 17.3 ml/min, respectively, indicate that cefpimizole is excreted mainly as the parent compound in the urine. The difference between $\text{CLR}_T$ and $\text{CLR}_R$ represents the amount of drug cleared from body by metabolism, degradation, or other routes of elimination, i.e., biliary, or by all three routes. No peaks that could be attributed to either metabolites or degradation products were observed on the chromatograms. The average value for $k_{\text{al}}$ from the urine data, determined from the slope of log($U_T - U$) versus time plots, was 0.339 ± 0.043 h$^{-1}$, which is statistically not different ($P > 0.2$ for Student $t$ test comparison of the means) than the average value of $\beta$ of 0.358 ± 0.036 h$^{-1}$ in plasma. Thus, the rate of cefpimizole clearance from plasma and the rate of urinary excretion were similar.

Plots of $\text{AUC}_{0-\infty}$ versus dose, $U_T$ versus dose, and $\text{AUC}_{0-\infty}$ versus $U_T$ are given in Fig. 3. The $\text{AUC}_{0-\infty}$-dose plot shows dose proportionality for the plasma levels of cefpimizole. Least-squares linear regression analysis of the data gave an equation of $y = (0.143 ± 0.011)x + (3 ± 29)$ and a correlation coefficient of 0.955. The reciprocal of the slope,

**TABLE 1. Pharmacokinetic parameter estimates for the single-dose intravenous study**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Dose (mg)</th>
<th>$V$ (liters)</th>
<th>$\alpha$ (h$^{-1}$)</th>
<th>$\beta$ (h$^{-1}$)</th>
<th>$\text{AUC}_{0-\infty}$ (mg)</th>
<th>$\text{AUC}_{0-\infty}$ (h/ml)</th>
<th>$\text{Cl}_{T}$ (ml/min)</th>
<th>$\text{Amt}$ excreted (g)</th>
<th>$K_{\text{al}}$ (h$^{-1}$)</th>
<th>$\text{Cl}_{R}$ (ml/min)</th>
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<td>1,000</td>
<td>16.1</td>
<td>2.31</td>
<td>0.366</td>
<td>169.8</td>
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<td>0.322</td>
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<td>0.352</td>
<td>89.8</td>
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<td>0.400</td>
<td>150.4</td>
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<td>528</td>
<td>0.279</td>
<td>58.5</td>
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<td>336.2</td>
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<td>0.364</td>
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<td>0.359</td>
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<td>0.380</td>
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<td>3.76</td>
<td>0.351</td>
<td>120.8</td>
<td>138.0</td>
<td>773</td>
<td>0.311</td>
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<td>118.0</td>
<td>3,527</td>
<td>0.290</td>
<td>104.0</td>
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<td>1,000</td>
<td>17.7</td>
<td>1.70</td>
<td>0.368</td>
<td>153.7</td>
<td>108.4</td>
<td>925</td>
<td>0.329</td>
<td>100.3</td>
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<td>0.95</td>
<td>0.281</td>
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<td>3,488</td>
<td>0.329</td>
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<td>128.8</td>
<td>129.4</td>
<td>649</td>
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<tr>
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<td>2,000</td>
<td>24.7</td>
<td>1.45</td>
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<td>245.9</td>
<td>135.6</td>
<td>1,744</td>
<td>0.368</td>
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<td>1.58</td>
<td>0.387</td>
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<td>138.1</td>
<td>3,100</td>
<td>0.438</td>
<td>107.0</td>
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</table>

| Mean ± SD  | 20.0 ± 3.5 | 2.24 ± 1.00 | 0.358 ± 0.036 | 118.6 ± 20.2 | 0.339 ± 0.043 | 96.2 ± 17.3 |

| RSD (%)    | 17.7       | 44.6        | 10.1           | 17.0          | 12.8          | 18.0         |

* The fact that the amount excreted is greater than the dose level is attributable to possible error in the collection interval volumes, in particular collection at 0 to 0.5 h.
when converted to the proper units, is a measure of $CL_T$ of all subjects and was 116.6 ml/min. This composite $CL_T$ value is very close to the average $CL_T$ of all subjects (118.6 ml/min). The $U_T$-dose plot shows dose proportionality for the urinary excretion of cefpimizole. The least-squares linear regression equation of $y = (0.867 \pm 0.039)x - (78 \pm 104)$, with $r = 0.984$, indicates that no apparent change occurred in the urinary elimination pattern over the dose range (1 to 4 g). The $AUC_{0-\infty}-U_T$ plot presents information on the renal clearance of cefpimizole for all subjects. The equation $y = (0.179 \pm 0.014)x + (25 \pm 31)$, with $r = 0.955$, shows linearity for renal elimination, and the reciprocal of the slope (93.1 ml/min), is very close to the average $CL_R$ (96.2 ml/min) for all subjects.

The multiple-dose evaluations of cefpimizole, given as 20-min intravenous infusions t.i.d. for 7 days at doses 1, 2, and 4 g, demonstrated that no apparent changes in the plasma kinetics or urinary elimination of cefpimizole were present, and no accumulation of the drug was apparent after drug administration for 7 days. The average levels of cefpimizole in plasma after the first dose on days 0 and 6 for each of the dose groups are shown in Fig. 4. The average cumulative urinary elimination for days 0 and 6 for the three dose groups is given in Fig. 5. The pharmacokinetic parameter averages obtained from the six volunteers in each dose group on days 0 and 6 are summarized in Table 2. The pharmacokinetic parameter averages are statistically equal ($P > 0.2$) for days 0 and 6 and are very similar, with the exception of $k_{el}$, to the values for the single-dose study. The increase in $k_{el}$ for the multiple-dose study may be attributed to the t.i.d. dosing regimen which prevented collection of data from urine after 8 h. The early collection intervals represent a combination of the plasma distribution and elimination phases. Thus, the slope of the log($U_T-U$)-time plots from the multiple-dose study are greater than observed in the single-dose study plots, in which the collection intervals from 6 to 12 and 12 to 24 h were included. When the intervals through 6 h from the single-dose study were used to calculate $k_{el}$ for urine, the $k_{el}$ value from the urine data for the two studies were similar. The $k_{el}$ values for days 0 and 6 were the same, indicating that no apparent change in the rate of urinary elimination occurred after 7 days of dosing.

**DISCUSSION**

The distribution and elimination pharmacokinetics of cefpimizole presented in this report indicate that this cephalosporin has kinetics which are similar to those of other broad-spectrum cephalosporin antibiotics. The single-dose kinetics of cefpimizole in plasma after intravenous administration show an average terminal half-life ($t_{1/2B}$) of 1.9 h, which is similar to the terminal disposition half-life in serum reported for ceftazidime, 1.5 to 1.9 h (4, 17); moxalactam, 2.0 h (7, 9); ceftizoxime, 2.3 h (10, 15); and cefoperazone, 1.0 to 2.6 h (2, 3, 5, 18) but less than the reported $t_{1/2B}$ for ceftriaxone, 6.0 h.

### TABLE 2. Pharmacokinetic parameter estimates for the multiple-dose intravenous study

<table>
<thead>
<tr>
<th>Group (no.)</th>
<th>Dose (mg)</th>
<th>Day</th>
<th>$q$ (h$^{-1}$)</th>
<th>$b$ (h$^{-1}$)</th>
<th>$AUC_{0-\infty}$ (µg · h/ml)</th>
<th>$k_{el}$ (h$^{-1}$)</th>
<th>% dose at 0-8 h</th>
<th>% dose at 0-24 h</th>
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<tr>
<td>I (6)</td>
<td>1,000</td>
<td>0</td>
<td>3.34 ± 1.41</td>
<td>0.39 ± 0.02</td>
<td>120 ± 18</td>
<td>0.56 ± 0.18</td>
<td>69 ± 12</td>
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<td>6</td>
<td>3.01 ± 1.88</td>
<td>0.36 ± 0.03</td>
<td>132 ± 25</td>
<td>0.53 ± 0.13</td>
<td>88 ± 21</td>
<td>82 ± 13</td>
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<tr>
<td>II (6)</td>
<td>2,000</td>
<td>0</td>
<td>2.04 ± 0.82</td>
<td>0.34 ± 0.04</td>
<td>250 ± 39</td>
<td>0.52 ± 0.07</td>
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<td>6</td>
<td>1.53 ± 0.35</td>
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<td>248 ± 35</td>
<td>0.53 ± 0.14</td>
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<td>81 ± 13</td>
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<td>III (6)</td>
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<td>2.16 ± 0.62</td>
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<td>0.52 ± 0.23</td>
<td>78 ± 18</td>
<td>58 ± 20</td>
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<tr>
<td>Avg</td>
<td></td>
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<td>2.50 ± 1.10</td>
<td>0.36 ± 0.05</td>
<td>413 ± 102</td>
<td>0.53 ± 0.16</td>
<td>84 ± 23</td>
<td>74 ± 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>2.23 ± 1.26</td>
<td>0.35 ± 0.04</td>
<td>413 ± 102</td>
<td>0.53 ± 0.16</td>
<td>84 ± 23</td>
<td>74 ± 19</td>
</tr>
</tbody>
</table>

* Values are of the mean ± standard deviation.
(14, 16), and greater than the 1/t/2b reported for cefotaxime, 0.7 to 1.1 h (1, 6). Cefpinizole, like the other broad-spectrum cephalosporins, has plasma distribution and elimination kinetics that correspond to a two-compartment model. The values of V for cefpinizole, 20.0 liters, was higher than that reported for moxalactam, 10 to 14 liters (9); cefotaxime, 16 liters (10); cefoperazone, 15 liters (2); and ceftriaxone, 8.5 to 10 liters (14). The primary route of elimination for cefpinizole is the renal route, with approximately 80% of the administered dose excreted as parent drug. The urinary excretion level of cefpinizole is substantially higher than that reported for cefoperazone, 15 to 37% (5); cefotaxime, 50 to 60% (1); and ceftriaxone, 33 to 44% (14, 16), but it is similar or slightly lower when compared with moxalactam, 82 to 97% (9); ceftazidime, 83 to 90% (17); and cefotaxime, 80% (10). The low urinary excretion level for cefoperazone was attributed to biliary excretion (5) and for cefotaxime it was attributed to metabolite formation (6). Values of CLT and CLR of cefpinizole were similar to clearance values reported for cefotaxime (10), moxalactam (9), and cefoperazone (2) and was considerably greater than those reported for ceftazidime (17) and ceftriaxone (14, 16).

These comparisons of the kinetics of cefpinizole to the kinetics of other broad-spectrum cephalosporins indicate that cefpinizole has distribution and elimination kinetics that are similar to the other compounds of this class.

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LITERATURE CITED