Pharmacokinetics of Cefpiramide (SM-1652) in Humans

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Received 1 August 1983/ Accepted 2 November 1983

The pharmacokinetics of cefpiramide (SM-1652) were studied after the intravenous administration of single or multiple doses to 21 healthy volunteers. The cefpiramide concentration in plasma at time zero after a bolus intravenous injection of 500 or 1,000 mg was 152 or 303 μg/ml, respectively. The maximum cefpiramide level in plasma at the end of a 1-h infusion of 1,000 or 2,000 mg was 166 or 317 μg/ml, respectively. The mean plasma half-life of cefpiramide in 15 subjects who received a single dose of 500 or 1,000 mg was 4.44 h. There was no evidence of drug accumulation in plasma when 500 or 1,000 mg of cefpiramide was administered 11 times at 12-h intervals. Urinary excretion of cefpiramide over a 24-h period was ca. 22.5%, regardless of the intravenous administration technique and the dosage. Fecal recoveries of cefpiramide varied from 0 to 36.9% in different subjects.

As has been shown by Kato and Fukasawa, cefpiramide (SM-1652) has a broad spectrum and high levels of activity against gram-positive and gram-negative bacteria including Pseudomonas aeruginosa (3, 5). As shown by Matsui et al., plasma half-lives of cefpiramide in rabbits, dogs, and rhesus monkeys were much longer than those of cefoperazone and cefazolin (7). The present communication describes the pharmacokinetics of cefpiramide administered intravenously to healthy volunteers. (The results of these studies were presented in part at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., 22 to 24 September 1980 [K. Nakagawa, M. Koyama, N. Nakatsuru, K. Yoshinaga, H. Matsui, C. Ikeda, K. Yano, and T. Noguchi, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 1980, abstr. no. 149].)

MATERIALS AND METHODS

Subjects. Twenty-one healthy male volunteers, aged 27 to 50 (mean, 38) years and weighing from 48 to 75 (mean, 61) kg, participated in these studies after informed consent. All subjects were normal as determined by physical examinations, hematological (leukocyte count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count) and biochemical (total protein, albumin/globulin ratio, blood urea nitrogen, glumatic-oxalacetate transaminase, glumatic-pyruvic transaminase, lactate dehydrogenase, alkaline phosphatase, leucine aminopeptidase, γ-GTP, total cholesterol, blood glucose, Na, K) profiles, Coombs tests and urinalyses. Subjects with a history of allergy to penicillins or cephalosporins were excluded. None of the subjects was on any drug therapy for at least 1 week before the start of the study. These subjects were divided into seven groups of three men each for tests mentioned below.

Administration of drug. The following doses of cefpiramide were administered intravenously: tests I and II, single bolus injection of 500 and 1,000 mg, respectively; tests III and IV, 1-h infusion of 1,000 and 2,000 mg, respectively; tests V and VI, multiple bolus injections of 500 and 1,000 mg, respectively, 11 times at 12-h intervals; test VII, multiple bolus injections of 1,000 mg 6 times at 24-h intervals.

Collection of blood, urine, and feces. In tests I and II, blood samples were withdrawn at 1/12, 1/4, 1/2, 1, 2, 4, 6, 8, 12, and 24 h after the administration of the drug. In tests III and IV, blood samples were taken at 1/3, 1/2, 1, 2, 4, 6, 8, 12, 18, and 24 h after the start of the infusion. In test V, blood specimens were obtained at 1/12, 1/4, 1/2, 1, 2, 4, 6, 8, and 12 h after the 1st dosing; 12 h after the 3rd and 7th dosings; 2 and 12 h after the 5th and 9th administrations; and 1/2, 1, 2, 4, 8, and 12 h after the 11th dosing. In test VI, bleedings were performed at the same hours as in test V except that blood was collected at 2 and 12 h after the third and seventh dosings and 2 h after the fifth and ninth administrations. In test VII, blood specimens were taken at 1/12, 1/4, 1/2, 1, 2, 4, 6, 8, 12, 18, and 24 h after the first injection; 24 h after the second, fourth, and fifth dosings; 2 and 24 h after the third dose; and 1/12, 1/2, 2, 8, 12, and 24 h after the sixth administration. Time intervals for urine collection after the injection or onset of infusion were as follows: test I, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h; tests II, III, and IV, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 22 to 24 h (24 to 48 h only in test II); tests V and VI, 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 12 h after the 1st, 5th, and 11th dosings (12 to 24 h only after the last dose); and test VII, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after the 1st, 3rd, and 6th injections. In test VII, feces were collected from subject 16 at 22 h after the first dosing and at 4 and 21 h after the third dose; from subject 17 at 22 h after the first, third, and sixth injections; and from subject 18 at 22 h after the first and third administrations and at 8 and 22 h after the sixth treatment. These biological materials were stored at −20°C until assayed for the antibiotic concentrations, usually within 1 week.

Microbiological assay. Cefpiramide concentrations in plasma, urine, and feces were determined by an agar-well diffusion technique, using Escherichia coli NIHJ as the test organism. The procedures of the technique were as follows. Melted and autoclaved agar medium (19 ml; Sensitivity Test Agar, Eiken, Tokyo) was added to each sterilized plastic petri dish (15 by 90 mm; TERUMO, Tokyo) and spread evenly on the plate. After the agar solidified, 5 ml of the agar

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medium inoculated with *E. coli* NIHJ was poured onto each plate containing 19 ml of the uninoculated agar and distributed evenly. After the inoculated agar solidified, four wells (diameter, 8 mm; depth, 3.8 mm) per plate were perforated by a model SE-4 Agar Perforator (Yamato Scientific, Tokyo). A precise volume (100 μl) of the standard solutions or samples was added into one well of each plate so that each standard solution or sample might be distributed to four plates. The plates were kept at 4°C for 2 h for preliminary diffusion and subsequently incubated overnight at 37°C. Plasma samples were subjected to assays without any treatment, and urine specimens were usually diluted with 0.067 M phosphate buffer (pH 7.0) to bring the drug concentrations within the range of standard curves. Samples of thoroughly mixed feces were homogenized in nine volumes of phosphate buffer and centrifuged at 4°C. The supernatants were supplied for analyses. Calibration curves from the spiked plasma of humans were used for plasma analyses. Standard solutions of cepfiramide were prepared in phosphate buffer for assays of urine and supernatants of fecal homogenates.

**Pharmacokinetic analysis.** The plasma concentration-time curves after the bolus intravenous injection were analyzed by a two-compartment open model (11). The cepfiramide concentration in plasma (*C*ₜ) at time *t* postdosing is expressed by the following equation: *C*ₜ = *Ae*⁻ᵃᵗ + *Be*⁻ᵇᵗ (equation 1), in which *A* and *B* are the zero time intercepts of the two components of the biexponential curves and *a* and *b* are the hybrid rate constants for the distribution and elimination phases, respectively. Other pharmacokinetic parameters, *C*₁₀₀, *k₁₂*, *k₂₁*, *k₉₁*, *t₁/₂a*, *t₁/₂b*, *V₁*, *V₂*, and *V₃₁₂* were calculated by equations based on the model (10, 11). Body clearance ([Cl(body)]) and renal clearance ([Cl(renal)]) were obtained by equations devised by Gibaldi and Perrier (4). The area under a plasma concentration curve (AUC) was obtained by integration of the curve from zero to infinite time, giving the following equation: AUC = *A/a + B/b* (equation 2). The nonlinear least-square program NONLIN (8), in which the inverse of concentrations was chosen as the weighting factor, was employed for regression analyses of plasma concentration-time curves. Student's t-test was used for statistical analysis of the difference between pharmacokinetic values; *P* < 0.05 was regarded as significant.

**Simulation of plasma concentration-time curve.** When cepfiramide was administered by a 1-h intravenous infusion (tests III and IV) or by multiple bolus intravenous injections (tests V, VI, and VII), plasma concentration-time curves were simulated by the following equations. During infusion,

\[
C_t = \frac{K(k_{21} - \alpha)}{V_1(\alpha - \beta)} \left( e^{-\alpha T} - 1 \right) + \frac{[K(\beta - k_{21})]}{V_1(\alpha - \beta)} \left( e^{-\beta T} - 1 \right)
\]

and after infusion,

\[
C_t = \frac{[K(k_{21} - \alpha)]}{V_1(\alpha - \beta)} \left( e^{-\alpha t'} - 1 \right) e^{-\alpha t'} + \frac{[K(\beta - k_{21})]}{V_1(\alpha - \beta)} \left( e^{-\beta t'} - 1 \right) e^{-\beta t'}
\]

in which *K* is the zero order infusion rate and *T* and *t'* indicate the duration time of infusion and postinfusion time, respectively.

In case of multiple intravenous injections,

\[
C_t^n = \frac{D(\alpha - k_{21})}{V_1(\alpha - \beta)} \left( \frac{1 - e^{-n\alpha t}}{1 - e^{-\alpha t'}} \right) e^{-\alpha t'} + \frac{D(k_{21} - \beta)}{V_1(\alpha - \beta)} \left( 1 - e^{-n\beta t} \right) e^{-\beta t'}
\]

in which *C*ₜᵣ indicates a plasma concentration at *t* after the *n*th dosing. *D* is the dose, and *t* is the dosing interval.

The accumulation factor was also calculated: *R* = 1/(1 - *e*⁻ᵇᵗ) (equation 6), in which *R* is the accumulation factor.

**RESULTS**

**Concentration in plasma.** The average cepfiramide concentrations in plasma after a bolus intravenous injection of 500 or 1,000 mg are illustrated in Fig. 1. The antibiotic concentration at 5 min after the dosing of 500 or 1,000 mg was 145 or 272 μg/ml, respectively. The concentrations slowly declined to 10.3 μg/ml (500-mg dose) and 25.0 μg/ml (1,000-mg dose) at 12 h and to 2.9 μg/ml (500-mg dose) and 8.2 μg/ml (1,000-mg dose) at 24 h.

The pharmacokinetic parameters obtained by analyzing each plasma concentration-time curve from 5 min up to 12 h are expressed as the mean value ± the standard deviation (Table 1). The calculated cepfiramide concentration at time zero (*C*₀) after the intravenous administration of 500 or 1,000 mg was 152.1 or 303.2 μg/ml, respectively, being proportional to the dose. The plasma half-life (*t₁/₂a*) was 3.89 h for the 500-mg dose and 5.05 h for the 1,000-mg dose, being statistically different (*P* < 0.01). The volume of the peripheral compartment (*V₂*) for the 1,000-mg dose exceeded *V₂* for the 500-mg dose by twofold (*P* < 0.001). These differences will be discussed below. The area under the plasma concentration curve for the 500-mg dose was 539.6 μg · h/ml and for the 1,000-mg dose was 966.0 μg · h/ml; the values were approximately proportional to the doses. The elimination rate constants (*k₉₁*), the volumes of the central compartment (*V₁*), and the body and renal clearances ([Cl(body)] and [Cl(renal)]) for the two doses were nearly equal.

The observed concentration of cepfiramide in plasma during and after a 1-h infusion of 1,000 or 2,000 mg was

**FIG. 1.** Average concentrations of cepfiramide in plasma after a single intravenous administration of 500 or 1,000 mg. Data points without fiducial limits show that the standard deviations are smaller than the size of the points.
TABLE 1. Pharmacokinetic parameters of cefpiramide after a single bolus intravenous administration of 500 or 1,000 mg

| Parameter (measurement) | Mean ± SD after dose (mg) of:
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>500 (test I)</td>
</tr>
<tr>
<td>C₀ (µg/ml)</td>
<td>152.1 ± 13.6 (A + B) = 4.05 ± 0.49</td>
</tr>
<tr>
<td>A (µg/ml)</td>
<td>62.3 ± 2.9</td>
</tr>
<tr>
<td>B (µg/ml)</td>
<td>89.8 ± 16.6 (α (h⁻¹))</td>
</tr>
<tr>
<td>α (h⁻¹)</td>
<td>1.40 ± 0.235</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.038 ± 0.0045</td>
</tr>
<tr>
<td>k₁₂ (h⁻¹)</td>
<td>1.59 ± 0.143</td>
</tr>
<tr>
<td>k₂₁ (h⁻¹)</td>
<td>1.03 ± 0.43</td>
</tr>
<tr>
<td>kₑ (h⁻¹)</td>
<td>0.285 ± 0.024</td>
</tr>
<tr>
<td>t₁/₂α (h)</td>
<td>0.377 ± 0.097</td>
</tr>
<tr>
<td>t₁/₂β (h)</td>
<td>3.89 ± 0.10</td>
</tr>
<tr>
<td>V₁ (ml/kg)</td>
<td>54.6 ± 1.7</td>
</tr>
<tr>
<td>V₂ (ml/kg)</td>
<td>27.5 ± 2.2</td>
</tr>
<tr>
<td>Vₐss (ml/kg)</td>
<td>85.9 ± 5.2</td>
</tr>
<tr>
<td>AUC (µg · h/ml)</td>
<td>539.6 ± 93.8</td>
</tr>
<tr>
<td>Cl(body) (ml/h per kg)</td>
<td>15.6 ± 0.9</td>
</tr>
<tr>
<td>Cl(renal) (ml/h per kg)</td>
<td>3.66 ± 0.77</td>
</tr>
</tbody>
</table>

* Cₐ₀ = A + B (A and B are the zero time intercepts of the two components of the biexponential curves; k₁₂, intercompartmental distribution rate constants; kₑ, elimination rate constant; t₁/₂α and t₁/₂β, plasma half-lives at α- and β-phases; V₁ and V₂, distribution volumes per kilogram of body weight for central and peripheral compartments; Vₐss, distribution volume per kilogram of body weight at steady state; AUC, area under plasma concentration-time curve; Cl(body), and Cl(renal), body and renal clearances per kilogram of body weight.

compared with the predicted concentration curves, which were calculated by using equations 3 and 4, and the average pharmacokinetic parameters for the 1,000-mg dose in Table 1, α, β, k₁₂, and V₁ (Fig. 2). The maximum observed concentration and predicted concentration of cefpiramide in plasma at the end of a 1-h infusion of 1,000 mg were 166 and 157 µg/ml, respectively; they were 317 µg/ml (observed) and 314 µg/ml (predicted) with the 2,000-mg dose. The other observed concentrations were also close to the expected values. This means that cefpiramide, administered either by a bolus intravenous injection or by intravenous infusion, obeys a linear pharmacokinetic system.

Figure 3 shows cefpiramide concentrations in plasma after the 1st, 3rd, 5th, 7th, 9th, and 11th bolus intravenous injections of 1,000 mg of the antibiotic at 12-h intervals (test VI). The observed concentrations in plasma 2 h after the 1st, 3rd, 7th, and 11th doses averaged 108, 125, 126, and 121 µg/ml, respectively. The average minimum concentrations after the 1st, 3rd, 5th, 7th, 9th, and 11th injections were 24, 29, 27, 32, 31, and 34 µg/ml, respectively. The observed accumulation factor after the 11th dose, calculated as the ratio of 34 to 24 µg/ml, was 1.42. The pharmacokinetic analysis of the plasma concentration-time curve after the first administration yielded the following equation as the average: C₁ = 179.1e⁻2.81t + 149.2e⁻0.13t (equation 7), displayed as the dotted line in Fig. 3. The plasma concentration-time curve after the nth dosing was predicted by using equation 5 and the parameters, α, β, k₁₂, and V₁, obtained directly or indirectly from equation 7, and are shown as solid lines in Fig. 3. The observed cefpiramide concentrations in plasma after the 3rd, 5th, 7th, 9th, and 11th administrations were on or close to the simulated curves. This means that cefpiramide given by multiple bolus intravenous injections obeys the same linear pharmacokinetics as it does in the case of a single intravenous administration. Similar results were obtained in tests V and VII, in which 500 or 1,000 mg of cefpiramide were given 11 and 6 times at 12- and 24-h intervals, respectively.

Urinary excretion. Urinary concentrations and excretions of cefpiramide, delivered by a bolus intravenous injection of 500 or 1,000 mg (test I or II, respectively) are demonstrated in Fig. 4. The highest concentration of 377 or 1,087 µg/ml was achieved in the first 2-h urine after the dosing of 500 or 1,000 mg, respectively. Owing to the long plasma half-lives of cefpiramide, the concentrations of 41.0 µg/ml (500-mg dose) and 55.8 µg/ml (1,000-mg dose) were detected in urine between 12 and 24 h and between 12 and 22 h, respectively. The cumulative urinary excretion at 24 h postdosing of 500 or 1,000 mg was 23.8 ± 6.2% or 24.3 ± 3.9% (mean value ± standard deviation) of the doses, respectively. In test II, the urinary excretion of cefpiramide between 24 and 48 h postdosing was 0.96 ± 0.30% (mean value ± standard deviation). The 24-h urinary recovery after a 1-h infusion of 1,000 or 2,000 mg (test III or IV) was 18.7 ± 2.7% or 23.4 ± 8.5% (mean value ± standard deviation). Therefore, the 24-h average urinary recovery of cefpiramide in 12 normal subjects who received a single intravenous administration was 22.5 ± 5.5% (mean value ± standard deviation).

Fecal recovery. Table 2 indicates the recoveries and concentrations of cefpiramide in feces obtained during the sixtimes multiple dosing test (test VII). The fecal recoveries varied from subject to subject. In subject 16, cefpiramide was not detected in the feces after the first dose, but a total of 35.6% was recovered after the third dose. Consistent fecal recoveries from 28.1 to 36.9% were observed for subject 17. In contrast, no cefpiramide was found in the feces of subject 18. Cefpiramide concentrations in feces, when detectable, ranged from 820 to 1,550 µg/g with the exception of the second feces from subject 16 after the third dosing.

DISCUSSION

The pharmacokinetic disposition of cefpiramide administered intravenously to normal human subjects was described. The t₁/₂α and Vₐ values after a single bolus injection of 500 or 1,000 mg of the antibiotic to three men each were

FIG. 2. Observed and predicted concentrations of cefpiramide in plasma during and after a 1-h intravenous infusion of 1,000 or 2,000 mg. Data points without fiducial limits show that the standard deviations are smaller than the size of the points.
statistically different (Table 1). The plasma concentration-time curves after the first injection in the multiple intravenous dosing tests were analyzed on the basis of similar pharmacokinetics, and the average parameters for six men (500-mg dose) and nine men (1,000-mg dose) were calculated. This handling produced the t1/2b of 4.21 ± 0.39 h (mean of six men ± standard deviation) for the 500-mg dose and 4.59 ± 0.48 h (mean of nine men ± standard deviation) for the 1,000-mg dose. The difference was not statistically significant. Therefore, the overall t1/2b of cefpiramide in the 15 subjects was concluded to be 4.44 h.

The similar calculation for V2 yielded 30.8 ± 6.6 ml/kg (mean of six men ± standard deviation) for the 500-mg dose and 49.8 ± 8.1 ml/kg (mean of nine men ± standard deviation) for the 1,000-mg dose. The difference still remained statistically significant (P < 0.01). Thus, cefpiramide distribution to the periphery compartment appeared dose dependent.

In the multiple dosing test (test VI), the average minimum antibiotic concentration in plasma of 24 μg/ml after the 1st injection was slightly elevated up to 34 μg/ml after the 11th administration. The simulation of the plasma concentration-time curves showed that the trough level of 23.4 μg/ml after the first dosing reached the calculated steady state trough level of 27.7 μg/ml. The accumulation factor of 1.19, computed by using equation 6, was not largely different from the observed value of 1.42.

The average urinary recovery of cefpiramide after the delivery of 500, 1,000, or 2,000 mg by a bolus intravenous injection or a 1-h infusion was 22.5% of the dose. The residual fraction is expected to be excreted in bile if analogous to the experimental results when animals were used (7). However, the fecal recovery of cefpiramide did not exceed 36.9%, so at least half the amount excreted in bile would be inactivated by intestinal flora.

Significant intersubject differences were observed for fecal recoveries of cefpiramide. These intersubject differences in the fecal recoveries, however, were in good agreement with the intestinal flora alternation examined by Nakaya using the same fecal samples (unpublished data). The intestinal flora of subject 16 were unaltered after the first dosing but decreased after the third injection. A few β-lactamase-producing organisms, which required moderate MICs for cefpiramide, were detected in the stool of this subject. The intestinal bacteria in subject 17 were remarkably reduced after the first administration, and this state lasted until the antibiotic injection was stopped. Only a few β-lactamase-producing organisms were present in the feces of this subject, and the MICs of cefpiramide against those organisms were low. In contrast, the enterobacteriaceae in subject 18 were scarcely decreased throughout the test period, and many β-lactamase-producing bacteria, which required high MICs for cefpiramide, were found.

By bioautographic analyses, antibiotically active metabo-

**TABLE 2. Recoveries and concentrations of cefpiramide in feces excreted during multiple intravenous dosings of 1,000 mg at five 24-h intervals**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>First dose</th>
<th>Third dose</th>
<th>Sixth dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First feces</td>
<td>Third dose</td>
<td>Sixth dose</td>
</tr>
<tr>
<td></td>
<td>First feces</td>
<td>Second feces</td>
<td>Total</td>
</tr>
<tr>
<td>16</td>
<td>0 (ND)</td>
<td>32.6 (1,193)</td>
<td>3.0 (248)</td>
</tr>
<tr>
<td>17</td>
<td>35.3 (820)</td>
<td>36.9 (1,550)</td>
<td>36.9</td>
</tr>
<tr>
<td>18</td>
<td>0 (ND)</td>
<td>0 (ND)</td>
<td>0 (ND)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate cefpiramide concentrations in feces (micrograms per gram). ND, Not detected (<2 μg/g); NT, not tested.
lites were not detected in the urine samples or the superna-
tants of fecal homogenates.

The overall $t_{1/2\beta}$ of cefpiramide, 4.44 h, observed in these
studies is much longer than the half-lives of the relatively
long-acting cephalosporins, such as ceftazidime, 1.8 h (1);
cefazolin, 2.0 h (6); cefoperazone, 2.07 h (2); ceforanide, 2.6
h (6); and cefotetan, 3.11 h (9), but it is half the $t_{1/2\beta}$ value
of ceftriaxone (12). This long-acting pharmacokinetic disposi-
tion of cefpiramide suggests once- or twice-daily parenteral
administration, which should suffice for the treatment of
most infectious diseases.

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