Pharmacokinetics of Cefpiramide in Volunteers with Normal or Impaired Renal Function

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The pharmacokinetics of a single 2.0-g intravenous dose of cefpiramide in patients with normal or impaired renal function were studied. Serial concentrations in serum and urine were measured by using high-performance liquid chromatography, and the effect of the concentration in serum on protein binding was assessed. Thirty patients (ten with creatinine clearances of >80 ml/min, ten with creatinine clearances between 10 and 80 ml/min, and ten on dialysis) were studied. The concentration-time curve of cefpiramide was best described by an open two-compartment model. The elimination half-lives in patients with normal or impaired renal function or those on dialysis were 5.41 ± 1.44, 8.3 ± 2.82, and 8.38 ± 4.06 h, respectively, and the serum clearances in the same groups were 2.0 ± 0.84, 1.29 ± 0.45, and 2.04 ± 1.10 liters/h, respectively. There were no significant differences in any of the parameters among the three groups of patients. In patients with normal or impaired renal function, protein binding varied between 93.0 ± 1.3% at 304.4 µg/ml and 99.3 ± 0.8% at 41.1 µg/ml and was linearly and inversely related to the cefpiramide concentration in serum. In patients on dialysis, protein binding was significantly lower (P < 0.05) and varied between 88.5 ± 7.1% at 173.4 µg/ml to 94.9 ± 4.8% at 46.8 µg/ml. In patients with normal or abnormal renal function, renal cefpiramide clearance decreased linearly with declining renal function, whereas plasma clearance was maintained. Therefore, nonrenal elimination becomes more important as renal impairment progresses.

Cefpiramide is an investigational cephalexin with broad-spectrum in vitro antibacterial activity (1, 4, 8). It is highly protein bound (96.3% at 100 µg/ml) and has a reported half-life of 4.4 h in volunteers with normal renal function (6, 7). High and prolonged concentrations in blood are achieved after intravenous infusion.

The purpose of this study was to define further the pharmacokinetics of cefpiramide in patients with normal or impaired renal function and determine the effect of the concentration of the antibiotic on its binding to serum proteins.

MATERIALS AND METHODS

Written informed consent was obtained from all subjects. Sixteen subjects were men, and fourteen were women. The subjects ranged in age from 18 to 62 years, with a mean of 42 years. Individuals with stable renal function were recruited according to the following categories: group 1 (10 volunteers), normal renal function and creatinine clearance (CLCR) of ≥90 ml/min; group 2 (10 volunteers), impaired renal function categorized as follows: group 2a (mild), 50 ≤ CLCR ≤ 70 ml/min; group 2b (moderate), 30 ≤ CLCR ≤ 50 ml/min; group 2c (severe), 10 ≤ CLCR ≤ 30 ml/min; group 3 (10 volunteers), individuals requiring chronic hemodialysis. Subjects from group 3 were studied on interdialysis days. CLCR measurements were made in all patients within 2 weeks and in most within a few days of the study. There were no significant differences when the three groups of subjects were compared for age, weight, height, or body surface area (P > 0.05).

Tobacco or alcohol use or ingestion of caffeine-containing food or beverage was not permitted during the study period. Subjects were excluded if there was a history of antibiotic treatment within the week before admission or a history of cephalosporin allergy. Subjects with impaired renal function were taking prescribed medications necessary for their chronic care. All participants fasted for 4 h before receiving the drug and for 2 h after completion of the infusion; thereafter, food and water were allowed ad libitum.

Cefpiramide was obtained from Wyeth Laboratories, Philadelphia, Pa. Two grams diluted in 100 ml of 5% glucose in water was infused during 30 min using a timed infusion pump (AVI, Inc., St. Paul, Minn.). Blood samples (5 ml) for cefpiramide assay were collected in tubes without anticoagulant before drug infusion and at 0.25, 0.5, 0.53, 0.58, 0.75, 1, 1.5, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48 h after the initiation of the infusion. Blood samples (5 ml) for protein-binding assay were collected at 1, 2, 4, and 8 h after the initiation of the infusion. Samples were placed in ice and then centrifuged. Serum was frozen at −70°C until assay by

FIG. 1. Typical cefpiramide concentration-time curve in a patient with normal renal function.
**TABLE 2. Cefpiramide urinary excretion and renal clearance**

<table>
<thead>
<tr>
<th>Renal status</th>
<th>$A_{\infty}$ (mg/24 h)</th>
<th>% of dose eliminated in 24 h</th>
<th>CLr (liters/h per 1.73 m²)</th>
<th>CLr/CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (group 1)</td>
<td>341.5 ± 127.8</td>
<td>17.1 ± 6.4</td>
<td>0.32 ± 0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>Impaired (group 2)</td>
<td>232.3 ± 165</td>
<td>11.6 ± 8.3</td>
<td>0.15 ± 0.10</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Abbreviations and parameters: $A_{\infty}$, amount of cefpiramide excreted in urine from 0 to 24 h; CLr, renal clearance = $A_{\infty}(\text{dose}/\text{AUC}_{\text{inj}})$, where $\text{AUC}_{\text{inj}}$ is the area under the concentration in serum-time curve from 0 to 24 h; CLr/CL, serum clearance = dose/area under the concentration-time curve (extrapolated to infinity by dividing the last predicted concentration by the slower of two disposition rate constants [log trapezoidal rule]). Values are means ± standard deviation.

**RESULTS**

The mean peak cefpiramide concentrations (± standard deviation) and concentrations at 12 and 24 h in the three groups were: group 1, 307 ± 32.9, 22.2 ± 12.9, 5.8 ± 5.0; group 2, 316 ± 58.3, 37.3 ± 19.8, 14.3 ± 11.0; group 3, 254 ± 56.0, 29.4 ± 24.6, 9.6 ± 13.4 μg/ml, respectively.

The concentration-time curves for a patient with normal renal function and for a dialysis patient are depicted in Fig. 1 and 2. They are virtually superimposable, demonstrating that renal impairment has little or no effect on the elimination of cefpiramide.

The pharmacokinetic parameters in subjects with normal renal function are similar to those previously reported (Table 1)(7). All of the parameters (Table 1), including the terminal half-life, were poorly correlated ($V_1$, $r = 0.271$; Ex2, $r = -0.012$; Ex2, $r = -0.033$; CL, $r = -0.089$) with CLCR. When the three groups were compared, the mean elimination of cefpiramide appears to be similar in all groups.

**TABLE 1. Pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>$V_1$ (liters/kg)</th>
<th>$V_v$ (liters/kg)</th>
<th>$L_1$ (h⁻¹)</th>
<th>$L_Z$ (h⁻¹)</th>
<th>Ex2 (h⁻¹)</th>
<th>$t_{1/26}$ (h)</th>
<th>$t_{1/28}$ (h)</th>
<th>CLr (liters/h per 1.73 m²)</th>
<th>AUC (μg · h/ml)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.09 ± 0.02</td>
<td>0.15 ± 0.03</td>
<td>0.73 ± 0.13</td>
<td>0.14 ± 0.03</td>
<td>0.33 ± 0.1</td>
<td>0.98 ± 0.22</td>
<td>5.41 ± 1.44</td>
<td>2.00 ± 0.84</td>
<td>1.148 ± 382</td>
<td>1.148</td>
</tr>
<tr>
<td>2</td>
<td>0.10 ± 0.02</td>
<td>0.16 ± 0.04</td>
<td>0.54 ± 0.21</td>
<td>0.09 ± 0.03</td>
<td>0.24 ± 0.08</td>
<td>1.51 ± 0.69</td>
<td>8.3 ± 2.82</td>
<td>1.29 ± 0.45</td>
<td>1.704 ± 682</td>
<td>1.704</td>
</tr>
<tr>
<td>3</td>
<td>0.11 ± 0.02</td>
<td>0.20 ± 0.04</td>
<td>0.73 ± 0.37</td>
<td>0.11 ± 0.07</td>
<td>0.33 ± 0.22</td>
<td>1.28 ± 0.79</td>
<td>8.38 ± 4.06</td>
<td>2.04 ± 1.10</td>
<td>1.277 ± 838</td>
<td>1.277</td>
</tr>
</tbody>
</table>

* $V_1$, Ex2, and $t_{1/26}$ are defined in Materials and Methods. $V_v$, Apparent volume of distribution at steady state = (dose x AUCM)/AUC, where $T$ equals length of infusion. AUCM, Area under the first moment of the concentration-time curve (log trapezoidal rule) extrapolated to infinity by the following formula: $(t(C/L_Z)Z + (C/L_Z))$, where $C$, represents the value for the predicted concentration at the last sampling time ($t$). $L_Z$, Slover of two disposition rate constants. $AUC$, Area under the time-concentration curve extrapolated to infinity by dividing the last predicted concentration by $L_Z$ (log trapezoidal rule). $L_1$, Faster of two disposition rate constants. $t_{1/26}$, Half-life during the terminal elimination phase $= \ln(2)/L_Z$. CLr, Plasma clearance (dose/AUC). AUC, AUMC, CLr, and $V_v$ were derived from noncompartmental analysis. Values are means ± standard deviation.

* Difference between group 1 and group 3 is statistically significant ($P < 0.05$).
half-lives ($P > 0.05$) and plasma clearances ($P > 0.05$) of total drug were not significantly different. With the exception of the apparent volume of distribution, none of the other parameters was significantly different ($P > 0.05$) when the three groups were compared.

Cefpiramide renal excretion is summarized in Table 2. Renal clearance declined linearly ($r = 0.81$, slope $= 0.05$, $P = 0.0001$) with decreasing CL$_{CR}$ (Fig. 3), whereas total drug plasma clearance remained unchanged ($r = 0.06$, slope $= 0.02$, $P = 0.768$) (Fig. 4). Thus, nonrenal mechanisms of excretion become increasingly important as renal function declines.

Protein binding (Table 3) was high (88.5 $\pm$ 7.1\% to 99.3 $\pm$ 0.8\%) and decreased linearly in group 1 ($r = -0.99$, $P = 0.001$) and group 2 ($r = -0.99$, $P = 0.005$) with increasing concentrations of cefpiramide in serum. Over the range tested (46.8 to 173.4 $\mu$g/ml), protein binding in dialysis patients was less than that in patients with normal or impaired renal function and was not linearly related to cefpiramide concentration ($P = 0.113$).

**DISCUSSION**

The pharmacokinetic disposition of cefpiramide is described in the present report. As previously reported (6, 7), a small volume of distribution and low total drug clearance result in concentrations in serum that are high and prolonged. The half-life (5.41 $\pm$ 1.44 h) of cefpiramide in subjects with normal renal function is shorter than that in patients with impaired renal function (8.3 $\pm$ 2.82 h) or in patients undergoing dialysis (8.38 $\pm$ 4.06 h). The difference, however, is neither statistically nor clinically significant.

Nonrenal (hepatic) mechanisms of excretion are important for cefpiramide. As renal function declines, renal clearance of cefpiramide also declines but plasma total drug clearance is maintained. Since cefpiramide protein binding is less in the dialysis patients and is concentration dependent, free drug clearance may be related to renal function in this group. Further investigation is necessary to clarify this possibility. Thus, no change in dosage is required for patients with impaired renal function as long as hepatic function is normal. It would be anticipated that patients with significant hepatic and renal impairment would have prolongation of the half-life of cefpiramide and therefore dosage reduction or decreased frequency of administration would have to be used.

On the basis of the high concentrations in serum that are achieved and the prolonged half-life, it is likely that infections caused by susceptible pathogens could be treated every 12 h. As has been reported for the long half-life cephalosporins, cefonicid (5) and ceftriaxone (13), many infections can be treated once daily, but such a regimen for cefpiramide would require confirmation in clinical trials.

In patients with normal or impaired renal function, cefpiramide is highly protein bound. For patients with normal or impaired renal function, the binding is linearly related to the concentration of cefpiramide in serum. Protein binding is decreased in patients on dialysis, as has been reported for other cephalosporins (9). Whether this high degree of protein binding will interfere with its antibacterial activity, as has been described for cefonicid (2), requires further investigation.

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**TABLE 3. Cefpiramide protein binding at various concentrations in serum**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Group</th>
<th>CPM* concn (µg/ml)</th>
<th>Protein binding (%)</th>
<th>CPM concn (µg/ml)</th>
<th>Protein binding (%)</th>
<th>CPM concn (µg/ml)</th>
<th>Protein binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>205.3 ± 24.9</td>
<td>95.2 ± 1.4</td>
<td>226.0 ± 36.1</td>
<td>94.1 ± 1.8</td>
<td>173.4 ± 52.3</td>
<td>88.5 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>140.6 ± 25.7</td>
<td>96.8 ± 1.0</td>
<td>154.9 ± 34.9</td>
<td>95.5 ± 1.9</td>
<td>123.5 ± 42.3</td>
<td>89.6 ± 8.3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>82.0 ± 22.8</td>
<td>98.1 ± 1.1</td>
<td>105.8 ± 32.7</td>
<td>97.1 ± 1.1</td>
<td>79.1 ± 34.9</td>
<td>90.5 ± 9.9</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>41.1 ± 17.5</td>
<td>99.3 ± 0.8</td>
<td>61.4 ± 27.8</td>
<td>98.2 ± 0.8</td>
<td>46.8 ± 34.3</td>
<td>94.9 ± 4.8</td>
</tr>
</tbody>
</table>

* All values represent the mean ± one standard deviation. $n = 10$ for each group.

* CPM, Cefpiramide.
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LITERATURE CITED


