Pharmacokinetic Study of an Oral Cephalosporin, Cefdinir, in Hemodialysis Patients

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The pharmacokinetics of cefdinir were investigated in six hemodialysis patients. For the present study, two tests were carried out, one with 4 h of hemodialysis and the other without hemodialysis. Cefdinir was given orally to each patient in a dose of 100 mg, and blood was collected serially for 48 h after dosing in the test without dialysis and for 72 h in the test with dialysis. In the test without dialysis, the maximum plasma concentration (Cmax) was 2.36 ± 0.53 μg/ml (mean ± standard deviation) and the time to Cmax was 9.00 ± 2.45 h. The terminal elimination half-life (t1/2) and area under the concentration-time curve (AUC) were 16.95 ± 1.20 h and 69.05 ± 14.84 μg · h/ml, respectively. In the test with dialysis, t1/2 during hemodialysis decreased approximately to one-sixth of that obtained in the test without dialysis, although t1/2 in the latter elimination phase did not differ from that in the nondialysis test. AUC was reduced to 43% of that in the test without dialysis. The fractional removal of cefdinir by hemodialysis was 61%. These findings indicate that clearance of cefdinir is prolonged in patients with renal failure, and cefdinir is well removed by introduction of hemodialysis, although the elimination of cephalosporin is significantly prolonged in patients with renal failure, and cefdinir is well removed by introduction of hemodialysis.

The present study was carried out with and without hemodialysis. The fractional removal of cefdinir by hemodialysis was 61%. These findings indicate that clearance of cefdinir is prolonged in patients with renal failure, and cefdinir is well removed by introduction of hemodialysis. In addition, the elimination of cephalosporin is significantly prolonged in patients with renal failure, and cefdinir is well removed by introduction of hemodialysis.

Cefdinir is a broad-spectrum oral cephalosporin which is highly active against many gram-positive and gram-negative bacteria (6, 11–14). The drug has been launched in Japan and approved in the United States, the United Kingdom, and other countries in Europe.

It is well known from clinical studies carried out so far that the elimination of cephalosporin is significantly prolonged in patients with impaired renal function, and the usual recommended dose for hemodialysis patients is reported for each cephalosporin (1–5, 7, 8, 10, 18–20).

A previous study with healthy volunteers demonstrated that cefdinir is excreted primarily by the kidney in an unchanged form (17). Linear increases were observed in the maximum plasma concentration (Cmax) and the area under the concentration-time curve (AUC) after a single oral dose of 50 to 200 mg of cefdinir. Cmax, time to Cmax (Tmax), AUC, and renal clearance (CL) did not significantly differ between the first and last doses in the multiple-dose study (17), and a steady-state trough of concentration in plasma and urinary excretion were attained within 2 days. However, the pharmacokinetics of cefdinir in patients undergoing hemodialysis have not been examined. The present study was carried out with and without hemodialysis to evaluate the pharmacokinetics of cefdinir after a single oral dose to patients with chronic renal failure.

MATERIALS AND METHODS

Subjects. Six adult male hemodialysis patients aged 38 to 60 years and weighing 45.3 to 64.4 kg gave written informed consent to be included in this study. The study was approved by the Ethical Committee of Shitoro Clinic. Serum creatinine concentrations ranged from 10.0 to 13.9 mg/dl, and urine output was less than 100 ml/day. Patients had been on maintenance hemodialysis for 4 h three times a week for more than 6 years (6 to 17 years). The dialyzer used was hollow fiber cartridges with a 1.5-, 1.8-, or 2.0-m² cuprammonium rayon membrane. Flow rates were maintained at 200 and 500 ml/min for the blood and dialysate, respectively, throughout the dialysis procedure. Subjects who had a history of heart disease, hepatic disease, and sensitivity to penicillin or cephalosporin were not included in this study. Patients did not take any drug except insulin for diabetes mellitus on days when the study was performed. The absence of hepatic and hematological disease was confirmed by physical examination and blood chemistry tests.

Study design. The kinetic studies after single oral dosing with 100 mg of cefdinir were carried out in patients with chronic renal failure with and without hemodialysis for 4 h. Two tests were performed separately 4 weeks apart, and the test without hemodialysis was started first. Cefdinir was given 30 min after breakfast (601 kcal of energy, 31 g of protein, 16.3 g of lipid, and 79 g of carbohydrate). Blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h (samples at 10 and 72 h were added in the test with hemodialysis) after administration. In the test with dialysis, hemodialysis was started 8 h after drug administration, since the median Tstop in the test without dialysis was 8 h. Blood was centrifuged to separate the plasma, and plasma was stored at −20°C until being assayed. The concentrations of cefdinir in plasma were measured by high-performance liquid chromatography (HPLC) at Mitsubishi Kagaku Bio-Clinical Laboratories, Inc. (Tokyo, Japan). Plasma (0.5 ml) was mixed with 1/15 M phosphate-buffered saline (pH 7.0) (0.05 ml) with an internal standard solution (0.05 ml) of cefizoxime sodium. The mixture was vortexed for 5 s with 1 M H3PO4 (0.4 ml). The mixture solution (0.9 ml) was transferred to Bond Elut SCX cartridges with a 1.5-, 1.8-, or 2.0-m² cuprammonium rayon membrane. Flow rates were maintained at 200 and 500 ml/min for the blood and dialysate, respectively, throughout the dialysis procedure. The absence of hepatic and hematological disease was confirmed by physical examination and blood chemistry tests.

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Pharmacokinetic analysis. Pharmacokinetic parameters were calculated by a model-independent method. \( C_{\text{max}} \) and \( T_{\text{max}} \) were determined by plasma concentration-time data, and the elimination rate constant (\( b \)) was determined by linear least-squares regression analysis. The terminal elimination half-life (\( t_{1/2} \)) was calculated as \( \ln 2/ b \). \( t_{1/2} \) during hemodialysis was calculated by data at 8, 10, and 12 h in the test with dialysis, and post-hemodialysis \( t_{1/2} \) was calculated from plasma cefdinir concentrations at 12, 24, and 48 h.

Plasma cefdinir area under the concentration-time curve from time zero to infinity (\( \text{AUC}_{0-\infty} \)) was estimated by using the plasma concentrations from time zero to the last time measured by the trapezoidal rule for time zero to the last measurement and then extrapolating to infinity by adding the last measured plasma concentration divided by \( b \).

The fractional removal of cefdinir (\( f_d \)) by hemodialysis was calculated by the equation

\[
\text{fd} = \frac{1 - \text{CL}_{\text{HD}}(\text{HD})}{1 - \exp(-0.693\text{CL}_{\text{HD}}(\text{HD}))} \times 100
\]

where \( t_{1/2} \) (HD) is \( t_{1/2} \) in the test with hemodialysis and \( t_{1/2} \) (HD) is \( t_{1/2} \) in the test without dialysis.

During hemodialysis, cefdinir, creatinine, urea nitrogen levels, as well as hematocrit, were determined in plasma from both venous and arterial lines. The hemodialysis CL of these items was calculated by the equation

\[
\text{CL} = \frac{\text{QB} \times (1 - Ht)}{V}
\]

where \( \text{CL} \) is the clearance in plasma (ml/min) in venous lines, \( \text{QB} \) is the dialyzer blood flow rate, \( B \) is the concentration in plasma (mg/ml) in arterial lines, \( V \) is the volume of distribution (liters), and \( Ht \) is hematocrit.

Statistical analysis. Results are expressed as means ± standard deviations (SD). For statistical comparisons, a paired \( t \) test was used; a \( P \) value of less than 0.05 was considered significant statistically.

RESULTS

The pharmacokinetic data for each patient is shown in Tables 1 through 3, and the mean plasma cefdinir concentration-time curves in the tests with and without dialysis are shown in Fig. 1. In the test without dialysis, the mean \( C_{\text{max}} \) of cefdinir was 2.36 ± 0.53 µg/ml and the mean \( T_{\text{max}} \) was 9.00 ± 2.45 h, with a median \( T_{\text{max}} \) of 8 h. The mean \( \text{AUC}_{0-\infty} \) was 69.05 ± 14.84 µg ⋅ h/ml, and the mean \( t_{1/2} \) was 16.95 ± 1.2 h. The plasma cefdinir concentrations at 24 and 48 h after dosing were 1.29 ± 0.34 and 0.50 ± 0.12 µg/ml, respectively.

In the test with dialysis, the mean \( C_{\text{max}} \) of cefdinir was 2.03 ± 0.54 µg/ml. No significant difference was observed in the mean \( C_{\text{max}} \) of cefdinir between the tests with and without dialysis. The mean \( t_{1/2} \) was 2.76 ± 1.01 h during 4 h of hemodialysis and 15.59 ± 2.42 h after hemodialysis. The mean \( t_{1/2} \) during hemodialysis was significantly less than that in the test without dialysis (\( P < 0.0001 \)). In contrast, no significant difference was found between the posthemodialysis \( t_{1/2} \) in the test with and \( t_{1/2} \) in the test without dialysis. Mean \( \text{AUC}_{0-\infty} \) in the test with dialysis (30.18 ± 12.03 µg ⋅ h/ml) was significantly less than that in the test without dialysis (\( P < 0.0001 \)). The plasma cefdinir concentrations at 24, 48, and 72 h were 0.52 ± 0.29, 0.16 ± 0.12 and 0.03 ± 0.03 µg/ml, respectively, and those at 24 and 48 h were significantly lower than in the test without dialysis (\( P < 0.001 \)).

Hemodialysis CL of cefdinir was 75.7 ± 7.9 (68.1 to 85.6) ml/min. The hemodialysis CL of blood urea nitrogen and creatinine were 128.6 ± 5.8 and 105.0 ± 6.2 ml/min, respectively. The fractional removal of cefdinir by hemodialysis was 61%.

Cefdinir was well tolerated by the hemodialysis patients. No significant changes attributable to cefdinir were observed in laboratory test results or physical findings during this study.

DISCUSSION

In the present study, the pharmacokinetics of cefdinir were examined in hemodialized patients with and without hemodialysis.

The pharmacokinetics of this drug in subjects with normal renal function were evaluated in a previous study (16, 17). The degree of protein binding was 73.1% ± 2.2% in normal human serum (15). Following a single administration of 100 mg of cefdinir, \( C_{\text{max}} \), \( T_{\text{max}} \), \( t_{1/2} \), and \( \text{AUC}_{0-\infty} \) of cefdinir were 0.79 ± 0.19 µg/ml, 4.3 ± 0.5 h, 1.48 ± 0.12 h, and 4.04 ± 0.72 µg ⋅ h/ml, respectively (16). Renal CL in healthy subjects was 89.2 ± 6.0 ml/min, and 30.8% ± 8.2% of each administered dose was excreted unchanged in the urine during the first 24 h.

Since cefdinir is excreted primarily through the kidney, it is expected that \( C_{\text{max}} \) and AUC would be increased and \( t_{1/2} \) prolonged in patients with renal dysfunction. In this study, the mean \( C_{\text{max}} \) and the mean AUC of cefdinir in the test without dialysis increased to 3 and 17 times the respective values obtained previously with healthy subjects (16), and \( T_{\text{max}} \) and \( t_{1/2} \) for these patients were prolonged to 2 and 11 times those for subjects with normal renal function.

The results of this study are in agreement with previous findings on the other cephalosporins (1–5, 7, 8, 10, 18–20). For example, \( C_{\text{max}} \) and AUC of cepodoxime proxetil, cefixime, cefadroxil, and cefprozil in hemodialysis patients are increased to 1.3 to 3 times and 2.4 to 10 times those in healthy subjects, respectively. \( T_{\text{max}} \) and \( t_{1/2} \) are also prolonged, to 1.9 to 3 times and 2.6 to 18.3 times the respective values obtained in subjects.
with normal renal function, except for the $T_{\text{max}}$ of cefdinir, which was not affected by the decrease in renal function. AUC in the test with dialysis decreased from 69 μg · h/ml in the test without dialysis to 30 μg · h/ml. This was effected by the removal of the drug through hemodialysis, since the posthemodialysis $t_{1/2}$ was almost the same as that obtained in the test without dialysis. The hemodialysis CL of cefdinir calculated from the blood flow rate and concentrations in plasma of both arterial and venous lines was 76 ml/min during hemodialysis. The hemodialysis CL of this drug was 72 and 59% of the hemodialysis CL of creatinine and urea nitrogen, respectively. The fractional removal of cefdinir by hemodialysis was 61%. These findings indicate that cefdinir is well removed by hemodialysis. $t_{1/2}$ during 4 h of hemodialysis was 2.76 h, which was about one-sixth of that in the test without dialysis.

Hemodialysis significantly removed plasma cefdinir, but $t_{1/2}$ during hemodialysis was still two times longer than that reported in subjects with normal renal function. Moreover, AUC in the test with dialysis was still eight times higher than in subjects with normal renal function. The plasma concentrations of this drug at 24 and 48 h after the administration of 100 mg of cefdinir in the test with dialysis were 0.52 ± 0.29 and 0.16 ± 0.12 μg/ml and were much higher than that observed at 12 h in subjects with normal renal function (0.03 ± 0.02 μg/ml). These data indicate the need for a reduction of the dose of cefdinir in patients on hemodialysis.

The plasma cefdinir concentration (0.52 ± 0.29 μg/ml) at 24 h after the administration of 100 mg of cefdinir in the test with dialysis was higher than that drug’s reported MIC at which 80% of isolates were inhibited against clinical isolates of *Staphylococcus aureus* (0.5 μg/ml), *Streptococcus pyogenes* (≤0.03 μg/ml), *Haemophilus influenzae* (0.5 μg/ml), and *Escherichia coli* (0.25 μg/ml) (9). Since the dialysis clearance of cefdinir was evaluated when the peak concentration of the drug was achieved, the fractional drug removal observed in our study would be the highest that we have seen in clinical practice settings. Thus, we can expect a sufficient plasma cefdinir concentration with 100 mg of oral cefdinir once a day in hemodialysis patients.

It is known that a transient increase in the concentration of drug occurs following the end of hemodialysis. This rebound phenomenon should be taken into account when we estimate the serum drug concentration in multiple doses from the single-dose study. Unfortunately, we did not determine whether there was a rebound in the plasma cefdinir concentration.

In conclusion, (i) $t_{1/2}$ of cefdinir increases in patients with chronic renal failure to 11 times that of healthy controls; (ii) hemodialysis effectively removes cefdinir, and $t_{1/2}$ during hemodialysis decreases to one-sixth of that in tests without dialysis but is still longer than in healthy subjects; and (iii) 100 mg of cefdinir once a day is a sufficient dose for hemodialysis patients.

### TABLE 2. Pharmacokinetic parameters of cefdinir after a single oral 100-mg dose in the test with hemodialysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Wt (kg)</th>
<th>SA (m$^2$)</th>
<th>$C_{\text{max}}$ (μg/ml)</th>
<th>$t_{1/2}$ (h)</th>
<th>$t_{1/2}(\text{HD})$ (h)$^a$</th>
<th>AUC$_{0-\infty}$ (μg · h/ml)</th>
<th>fd$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55.2</td>
<td>1.5</td>
<td>1.72</td>
<td>19.52</td>
<td>2.07</td>
<td>21.99</td>
<td>0.69</td>
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<tr>
<td>2</td>
<td>50.6</td>
<td>1.5</td>
<td>1.99</td>
<td>13.95</td>
<td>2.31</td>
<td>24.52</td>
<td>0.66</td>
</tr>
<tr>
<td>3</td>
<td>66.8</td>
<td>2.0</td>
<td>1.18</td>
<td>16.58</td>
<td>2.02</td>
<td>14.09</td>
<td>0.70</td>
</tr>
<tr>
<td>4</td>
<td>54.7</td>
<td>1.5</td>
<td>2.26</td>
<td>13.26</td>
<td>3.53</td>
<td>33.52</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>45.4</td>
<td>1.8</td>
<td>2.23</td>
<td>13.66</td>
<td>4.47</td>
<td>43.19</td>
<td>0.43</td>
</tr>
<tr>
<td>6</td>
<td>53.2</td>
<td>1.5</td>
<td>2.78</td>
<td>16.56</td>
<td>2.18</td>
<td>43.78</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>50.83</td>
<td>1.66</td>
<td>2.03 (0.54)</td>
<td>15.59 (2.42)</td>
<td>2.76 (1.01)</td>
<td>30.18 (12.03)</td>
<td>0.61 (0.11)</td>
</tr>
</tbody>
</table>

$^a$ SA, surface area of dialyzer.

$^b$ $t_{1/2}(\text{HD})$, elimination $t_{1/2}$ during hemodialysis.

$^c$ fd, fractional removal of cefdinir by hemodialysis.

### REFERENCES


### TABLE 3. Hemodialysis CL of cefdinir and indigenous substances$^a$

<table>
<thead>
<tr>
<th>Patient</th>
<th>CL (ml/min)</th>
<th>CL$^{\text{Cef}}$</th>
<th>CL$^{\text{Cr}}$</th>
<th>CL$^{\text{BUN}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69.8</td>
<td>98.7</td>
<td>127.4</td>
<td>0.71</td>
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<tr>
<td>2</td>
<td>74.0</td>
<td>110.3</td>
<td>135.7</td>
<td>0.67</td>
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<tr>
<td>3</td>
<td>85.6</td>
<td>114.2</td>
<td>135.3</td>
<td>0.75</td>
</tr>
<tr>
<td>4</td>
<td>88.6</td>
<td>101.8</td>
<td>122.5</td>
<td>0.84</td>
</tr>
<tr>
<td>5</td>
<td>68.1</td>
<td>104.8</td>
<td>128.4</td>
<td>0.65</td>
</tr>
<tr>
<td>6</td>
<td>70.9</td>
<td>109.9</td>
<td>122.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>75.7</td>
<td>105.0</td>
<td>128.6</td>
<td>0.72</td>
</tr>
</tbody>
</table>

$^a$ CL$^{\text{Cef}}$, cefdinir hemodialysis clearance; CL$^{\text{Cr}}$, creatinine hemodialysis clearance; CL$^{\text{BUN}}$, blood urea nitrogen hemodialysis clearance.


