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 \( C_{\text{max}} \) was 2.36 \pm 0.53 \mu g/ml (mean \pm standard deviation) and the time to \( C_{\text{max}} \) was 9.00 \pm 2.45 h. The terminal elimination half-life \( t_{1/2} \) and area under the concentration-time curve (AUC) were 16.95 \pm 1.20 h and 69.05 \pm 14.84 \mu g \cdot h/ml, respectively. In the test with dialysis, \( t_{1/2} \) during hemodialysis decreased approximately to one-sixth of that obtained in the test without dialysis, although \( t_{1/2} \) 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 \( t_{1/2} \) (during hemodialysis) and AUC were two and eight times higher than the data previously reported for healthy volunteers, respectively. The pharmacokinetic data suggest that 100 mg of oral cefdinir once a day would result in a sufficient concentration in plasma in hemodialysis patients, but this remains to be confirmed by multiple-dose studies.

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 \( C_{\text{max}} \) and the area under the concentration-time curve (AUC) after a single oral dose of 50 to 200 mg of cefdinir. \( C_{\text{max}} \), time to \( C_{\text{max}} \) (\( T_{\text{max}} \)), 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 Shirito 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 hollowfiber cartridges with a 1.5-, 1.8-, or 2.0-m2 cuprammonium rayon membrane. Flow rates were maintained at 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 drug administration. In the test with dialysis, hemodialysis was started 8 h after drug administration, since the median \( T_{\text{max}} \) 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 BioClinical 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 ceftefoxime 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 (100 mg) (GL Science, Tokyo, Japan) for 30 s and preconditioned with methanol (0.2 ml), followed by distilled water (1.0 ml). The column was washed by eluting with 0.01 N HCl (2 ml) followed by distilled water (1.0 ml). Cefdinir was eluted from the column with 0.2 M Na2HPO4 (1.0 ml). The eluent was collected in a tube, and aliquots (50 μl) were applied to HPLC. An LC-6AD high-performance liquid chromatograph (Shimazu, Kyoto, Japan) equipped with a spectrophotometric detector, SPD-10AV (Shimazu), was used. The column, 25 cm long and 4.6 mm in inner diameter, was packed with TSKgel ODS-80TM (Tosoh, Japan). The chromatograph was equipped with a flow rate of 1.2 ml/min, and the effluent was monitored at 280 nm. The detection limit for cefdinir was 0.05 μg/ml, and the coefficients of variation on samples of 0.05, 0.10, 1.00, and 5.005 μg of cefdinir per ml were 13.12, 13.84, 2.13, and 4.77%, respectively. The coefficients of day-to-day variation on samples of 0.10, 1.00, and 5.005 μg/ml were 9.64, 2.27, and 4.75%, respectively. Day-to-day precision was 1.03 to 6.27%.

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TABLE 1. Pharmacokinetic parameters of cefdinir after a single oral 100-mg dose in the test without hemodialysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Dry wt (kg)</th>
<th>C max (μg/ml)</th>
<th>T max (h)</th>
<th>t 1/2 (h)</th>
<th>AUC 0–t (μg · h/ml)</th>
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<tbody>
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<td>58</td>
<td>54.7</td>
<td>55.0</td>
<td>1.72</td>
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<td>15.81</td>
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<td>18.21</td>
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<tr>
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<td>16.92</td>
<td>62.94</td>
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<td>6</td>
<td>18.53</td>
<td>76.41</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>53.3</td>
<td>53.2</td>
<td>3.19</td>
<td>8</td>
<td>16.66</td>
<td>91.70</td>
</tr>
</tbody>
</table>

Mean (SD) 2.36 (0.53) 9.00 (2.45) 16.95 (1.20) 69.05 (14.84)

Pharmacokinetic analysis. Pharmacokinetic parameters were calculated by a model-independent method. C max and T 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. 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 (fd) by hemodialysis was calculated by the equation fd = [1 − t 1/2 (HD)] × [1 − exp(−0.693t 1/2 (HD))] / 100, where t 1/2 (HD) is t 1/2 in the test with hemodialysis and t 1/2 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 cefdinir was 75.7 (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.

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 max of cefdinir was 2.36 ± 0.53 μg/ml and the mean T max was 9.00 ± 2.45 h, with a median T max of 8 h. The mean AUC 0–t 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 max of cefdinir was 2.03 ± 0.54 μg/ml. No significant difference was observed in the mean C 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 dialysis and t 1/2 in the test without dialysis. Mean AUC 0–t 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).

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 max, T max, t 1/2, and AUC 0–t 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 max and AUC would be increased and t 1/2 prolonged in patients with renal dysfunction. In this study, the mean C 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 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 max and AUC of ceftodime 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 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 CL of creatinine and urea nitrogen, respectively. The hemodialysis CL of cefdinir by hemodialysis was 61%. The fractional removal of cefdinir 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 this 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.

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.

### REFERENCES


### 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 (m²)</th>
<th>$C_{\text{mean}}$ (µg/ml)</th>
<th>$t_{1/2}$ (h)</th>
<th>$t_{1/2}(\text{HD})$ (h)</th>
<th>AUC$_{0-\infty}$ (µg · h/ml)</th>
<th>fd$^a$</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>
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<td>1.9</td>
<td>1.99</td>
<td>13.95</td>
<td>2.31</td>
<td>24.52</td>
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</tr>
<tr>
<td>3</td>
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<td>2.0</td>
<td>1.18</td>
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<td>2.02</td>
<td>14.09</td>
<td>0.70</td>
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<tr>
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<td>13.26</td>
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<tr>
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<tr>
<td>6</td>
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<td>2.78</td>
<td>16.56</td>
<td>2.18</td>
<td>43.78</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Mean (SD) 2.03 (0.54) 15.59 (2.42) 2.76 (1.01) 30.18 (12.03) 0.61 (0.11)

$^a$ 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.

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>CL (ml/min)</th>
<th>Cefdinir</th>
<th>Creatinine</th>
<th>Blood urea nitrogen</th>
<th>CL$<em>{\text{cef}}$/CL$</em>{\text{cre}}$</th>
<th>CL$<em>{\text{cre}}$/CL$</em>{\text{RUN}}$</th>
<th>CL$<em>{\text{cre}}$/CL$</em>{\text{RUN}}$</th>
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<td>1</td>
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<td>99.9</td>
<td>122.5</td>
<td>0.71</td>
<td>0.58</td>
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</table>

Mean (SD) 75.7 (7.9) 105.0 (6.2) 128.6 (5.8) 0.72 (0.07) 0.59 (0.06)

$^a$ CL$_{\text{cef}}$, cefdinir hemodialysis clearance; CL$_{\text{cre}}$, creatinine hemodialysis clearance; CL$_{\text{RUN}}$, blood urea nitrogen hemodialysis clearance.


