Pharmacokinetics of Cefmenoxime in Patients with Impaired Renal Function and in Those Undergoing Hemodialysis

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The pharmacokinetics of cefmenoxime were studied after a single intravenous 1.0-g dose to 24 subjects grouped according to their renal functions. Creatinine clearance was above 85, 50 to 85, 10 to 50, and below 10 ml/min per 1.73 m² in groups 1, 2, 3, and 4, respectively. Cefmenoxime obeyed two-compartment-model kinetics in all four groups. The volume of distribution based on the area under the serum concentration-time curve was renal function independent, the average value being 0.270 ± 0.075 liters/kg. The elimination-phase half-life (t1/2B(2)) was 0.82 ± 0.30 h in group 1, 1.38 ± 0.36 h in group 2, 3.32 ± 1.82 h in group 3, and 7.60 ± 1.28 h in group 4. Cumulative 24-h urinary excretion accounted for 65.5 ± 7.6% of the dose in group 1 and for 7.50 ± 3.72% in group 4. Recommendations for dosage adjustment in patients with renal insufficiency are proposed based on the data obtained in this study. The effect of hemodialysis on cefmenoxime pharmacokinetics was studied in six patients in group 4; hemodialysis shortened the average t1/2B from 7.60 ± 1.28 to 4.19 ± 1.66 h. It was estimated that in a hypothetical anephric subject with a body weight of 60 kg, 5-h hemodialysis would remove 28.2% of the drug present in the body at the start of hemodialysis.

Cefmenoxime is a new semisynthetic cephalosporin with a broad spectrum of activity against many gram-positive and gram-negative bacteria and excellent beta-lactamase stability (10, 16). Studies on subjects with normal renal function have shown that the drug is primarily eliminated unchanged in the urine (7). Renal insufficiency is, therefore, expected to prolong the elimination of cefmenoxime, and this study was conducted to examine the pharmacokinetics of this antibiotic in patients with various degrees of renal insufficiency and to determine the influence of hemodialysis on its elimination.

MATERIALS AND METHODS

Antibiotic. Cefmenoxime was supplied by Takeda Chemical Industries Ltd., Osaka, Japan.

Subjects. Twenty-four adult male and female subjects with renal function ranging from normal to anephric were studied after informed consent was obtained. Endogenous creatinine clearance (CLCR) was determined by collecting urine over 24-h period. The subjects were divided into four groups according to their renal function: group 1, CLCR of greater than 85 ml/min per 1.73 m²; group 2, CLCR of 50 to 85 ml/min per 1.73 m²; group 3, CLCR of 10 to 50 ml/min per 1.73 m²; and group 4, CLCR of less than 10 ml/min per 1.73 m². All six subjects in group 4 were receiving maintenance hemodialysis for end-stage renal failure.

Procedure. Each subject received 1.0 g of cefmenoxime dissolved in 20 ml of physiological saline intravenously over exactly 5 min. Blood samples for serum cefmenoxime levels were obtained 10, 20, and 30 min and 1, 2, 4, 6, 12, and 24 h after injection. Urine samples were collected during time intervals of 0 to 2 h, 2 to 6 h, and 6 to 24 h postdosing. Serum and urine samples were stored at −70°C until assayed.

The six hemodialysis patients in group 4 were studied on two separate occasions, i.e., during and between hemodialysis. The interdialysis period study followed the same protocol as used in other patients not receiving hemodialysis. The study during the hemodialysis session consisted of injection of cefmenoxime into the venous return of the dialyzer over 5 min at the start of dialysis followed by collection of blood samples from the blood inlet and outlet of the dialyzer for determination of the drug concentration at 30 min and 1, 2, and 4 h after injection of the drug and also at the termination of the dialysis procedure. Cefmenoxime concentration was also determined on the pooled dialysate outflow fluid. The dialyzer used was RENEL-1A 10M (Kuraray Co., Ltd., Osaka, Japan), a hollow-fiber dialyzer with a surface area of 1.0 m². Each subject was dialyzed for 5 h with a dialysate fluid flow rate of 500 ml/min and a blood flow rate of 200 ml/min.

Assay. Cefmenoxime concentrations in serum, urine, and dialysate fluid were determined by the cylinder-plate technique with Escherichia coli NIHJ JC-2 as the test organism grown in DST agar medium, pH 7.4 (Oxoid Ltd., London, England) (5). Standards for serum samples were prepared in Monitrol I (American Hospital Supply Co.), while urine and dialysate standards were made with 0.1 M phosphate buffer, pH 7.4. A concentration of cefmenoxime as low as 0.1 μg/ml could be measured by this method. The within-day coefficients of variation were 3.3 and 2.3% for the low and high assay extremes, respectively, whereas the between-day coefficients of variation were 7.8 and 9.0%, respectively.

Pharmacokinetic analysis. The serum cefmenoxime levels after intravenous administration were described in terms of a two-compartment open model, and the individual serum level profiles were fitted to a biexponential function of the form: \( C = A \times e^{-\alpha t} + B \times e^{-\beta t} \), in which \( C \) is the concentration of antibiotic in serum at time \( t \) postdosing; \( \alpha \) and \( \beta \) are the rate constants governing the distribution and elimination phases of drug loss from serum, respectively; and \( A \) and \( B \) are the intercepts of slopes \( \alpha \) and \( \beta \) with the ordinate. Pharmacokinetic analysis was performed with a nonlinear least-squares program developed by Yamaoka et al. (17), with the reciprocal square concentrations as the weights. AUC (area under the concentration-time curve) and \( V_{area} \) (volume of distribution by the area method) were calculated by the equations \( AUC = (A/\alpha) + (B/\beta) \) and \( V_{area} = \text{dose}/(\beta \times \text{AUC}) \), respectively. The micro-rate constant (\( k_{el} \)) and the central volume of distribution (\( V_c \)) were calcu-
lateral by conventional methods. The serum clearance of the drug (CL$_S$) was calculated by the formula $\text{CL}_S = \text{dose}/\text{AUC}$. The renal clearance (CL$_R$) was obtained by the equation $\text{CL}_R = \text{U}_{0-24}/\text{AUC}_{0-24}$, where $\text{U}_{0-24}$ is the amount of cefmenoxime excreted in the urine during 0 to 24 h, and AUC$_{0-24}$ is the AUC during the same interval. The nonrenal clearance of cefmenoxime (CL$_{NR}$) was calculated by $\text{CL}_s = \text{CL}_R - \text{CL}_S$. The pharmacokinetic parameters in patients receiving hemodialysis were calculated by simultaneously fitting the time-concentration data obtained during dialysis and between dialysis to two separate equations of the two-compartment open model for inter- and intradialysis periods (17).

**Statistics.** Interaction between the kinetic parameter and the level of renal function was tested by analysis of variance on data obtained for groups 1, 2, 3, and 4, and the difference between groups was tested by a multiple range test (Student-Neuman-Kuels test) (13).

### TABLE 1. Mean cefmenoxime levels in serum after a 1.0-g intravenous dose for four groups of patients with different renal functions

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yrs)</th>
<th>Wt (kg)</th>
<th>Cmax (mg/l)</th>
<th>t$_{1/2}$ (h)</th>
<th>AUC$_{0-24}$ (mg.h/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.5 (12.5)</td>
<td>65.1 (10.6)</td>
<td>102.5 (14.8)</td>
<td>30.8 (9.9)</td>
<td>95.4 (11.0)</td>
</tr>
<tr>
<td>2</td>
<td>35.8 (15.7)</td>
<td>59.4 (13.8)</td>
<td>97.5 (7.9)</td>
<td>28.7 (6.7)</td>
<td>85.3 (11.5)</td>
</tr>
<tr>
<td>3</td>
<td>54.0 (17.5)</td>
<td>55.5 (6.7)</td>
<td>72.1 (11.6)</td>
<td>26.7 (4.3)</td>
<td>77.9 (7.7)</td>
</tr>
<tr>
<td>4</td>
<td>62.0 (8.1)</td>
<td>55.7 (7.8)</td>
<td>51.2 (16.4)</td>
<td>24.7 (5.6)</td>
<td>88.8 (10.1)</td>
</tr>
</tbody>
</table>

All data are shown as mean (standard deviation). Data for cefmenoxime levels in serum for group 4 were obtained during the intermediate period.

**FIG. 1.** Mean concentrations of cefmenoxime in serum of patients with normal renal function and with renal dysfunction. (Data for group 4 subjects were obtained during interdialysis period.)

**FIG. 2.** Mean cefmenoxime levels in serum after a 1.0-g intravenous injection in six patients with end-stage renal failure. Data were obtained during a period of nondialysis and during hemodialysis.
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TABLE 2. Mean urinary concentration and cumulative urinary recovery of cefmenoxime after a 1.0-g intravenous dose in patients grouped according to renal functions

<table>
<thead>
<tr>
<th>Group</th>
<th>Urinary concn (µg/ml)</th>
<th>Urinary recovery (% dose administered)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-2 h</td>
<td>2-6 h</td>
</tr>
<tr>
<td>1</td>
<td>4,590 (3,070)</td>
<td>420 (317)</td>
</tr>
<tr>
<td>2</td>
<td>7,440 (7,450)</td>
<td>806 (751)</td>
</tr>
<tr>
<td>3</td>
<td>2,520 (2,740)</td>
<td>471 (469)</td>
</tr>
<tr>
<td>4</td>
<td>271 (214)</td>
<td>212 (178)</td>
</tr>
</tbody>
</table>

* Data are given as mean (standard deviation).

RESULTS

Table 1 presents the characteristics of the subjects as well as the mean and range for each group of serum levels of cefmenoxime at each sampling interval. The mean drug levels in serum for each group are also depicted in Fig. 1. The subjects in groups 1 and 2 were significantly older than those of group 3 or group 4, but the body weights and heights were similar among the four groups. The biexponential decay of cefmenoxime concentrations in the serum was evident in each case, and the peak cefmenoxime concentration in serum was reached at 10 min in all subjects. The mean peak concentration in serum was 93.8 ± 18.3 µg/ml in group 1, 98.9 ± 17.9 µg/ml in group 2, 108 ± 13 µg/ml in group 3, and was 130 ± 31 µg/ml in group 4.

A summary of the data for mean urinary concentrations and mean cumulative urinary recovery of cefmenoxime is shown in Table 2. The mean urinary recovery during 24 h amounted to 65.5% of the dose in group 1 and decreased progressively with reduced renal function to 7.50% of the dose in four patients in group 4 who were anuric.

The values for the pharmacokinetic parameters are summarized in Table 3. The V̄ area and V̄ c did not differ significantly among the four groups, and the average V̄ area for all the subjects was 0.270 ± 0.075 liters/kg. Meanwhile, β, the half-life at the β phase (t1/2β), k12, and AUC, as well as CLs, were renal function dependent. The t1/2β was 0.82 ± 0.30 h in group 1, 1.38 ± 0.36 h in group 2, 3.32 ± 1.82 h in group 3, and 7.60 ± 1.28 h in group 4. Both renal and serum clearances of cefmenoxime (CLR and CLs) decreased according to the severity of renal dysfunction, but the nonrenal clearance (CLRNR) remained renal function independent.

The mean concentrations of cefmenoxime in serum after 1.0-g intravenous doses in six patients in group 4 observed during hemodialysis are depicted in Fig. 2, together with the serum concentration-time curve obtained during interdialysis periods. The mean pharmacokinetic parameters of cefmenoxime calculated from the concentration-time data obtained during and between hemodialysis are summarized in Table 4. Hemodialysis shortened the average t1/2β from 7.60 ± 1.28 to 4.19 ± 1.66 h; the average serum clearance of cefmenoxime was 19.6 ± 5.2 ml/min between dialysis and 40.0 ± 15.4 ml/min during dialysis. The amount of cefmenoxime recovered in the pooled dialysate outlet fluid during 5 h of hemodialysis was 397 ± 128 mg.

DISCUSSION

This study demonstrated that the pharmacokinetics of cefmenoxime are similar to those of other cephalosporins in that after intravenous administration, the circulating blood levels may be described by a biexponential function. The average V̄ area in the present study was 0.270 ± 0.075 liters/kg. The apparent volume of distribution of cefmenoxime after a 1.0-g intravenous bolus injection in healthy subjects has been reported to average 21.9 liters or 0.308 liters/kg by Fortillan et al. (4) and 0.39 ± 0.11 liters/kg by Gambertoglio et al. (6). The average t1/2β in group 1 subjects was 0.820 ± 0.30 h, and the value is comparable to those reported previously for individuals with normal renal function (7), although a somewhat longer t1/2β has been reported by others for healthy subjects (4, 6, 12, 14). Thus, the t1/2β of cefmenoxime after intravenous dosing in subjects with normal renal function is comparable to that of cefotax-
ime (0.9 to 1.2 h), but is shorter than those of other cephalosporins (1, 8). The mean $t_{1/2b}$ increased with a decrease in renal function (Table 3), and this is similar to the case with other cephalosporins with the notable exceptions of ceftriaxone, cefoperazone, and cefepiramide (1, 11).

In patients with reduced renal function, the widely recommended modification of the dose schedule is to prolong the dosage interval, multiplying it by $\beta_d/\beta_r$, $\beta_d$, and $\beta_r$ being the elimination rate constants in normal subjects and in those with renal failure, respectively (2, 3). A significant positive correlation existed between $\beta$ and CLCR ($r = 0.891, p < 0.01$), and $\beta$ of cefmenoxime may be predicted by the equation: $\beta = 0.00837 \times \text{CLCR} \ (\text{ml/min per 1.73 m}^2) + 0.0469 \ (\text{Fig. 3})$. Thus, assuming that the standard individual dose schedule of cefmenoxime in subjects with normal renal function is 1.0 g intravenously every 6 h, the same standard individual dose may be given every 8 h for those with a CLCR of 60 ml/min per 1.73 m$^2$, every 12 h for those with CLCR of 50 ml/min per 1.73 m$^2$, and every 24 h for those with CLCR of 20 ml/min per 1.73 m$^2$. Application of the same rule to those patients with severe renal failure would be rather inappropriate since it is expected to produce a drug level in serum that is too low over a prolonged time. It is suggested instead that 1.0 g be administered every 24 h to those with a CLCR of 10 ml/min per 1.73 m$^2$ and that 0.75 g be administered every 24 h to functionally anephric subjects.

The average hemodialysis clearance (CLHD) of cefmenoxime can be calculated either as the difference between the serum clearances of the drug during and between hemodialysis in the same patient or alternatively by the equation $\text{CLHD} = X/\text{AUC}_{0-\infty}$, where $X$ is the total amount of the drug recovered in the pooled dialysate outflow fluid, $t$ is the duration of dialysis, and AUC$_{0-\infty}$ is the AUC from time zero to $t$. CLHD as calculated by the former method averaged 20.4 ± 12.8 ml/min (Table 4) and was 24.6 ± 8.7 ml/min by the latter method.

The proportion of the body pool of drug removed by a given period of hemodialysis ($f$) is calculated by the equation: $f = ([\text{CLHD}]/[\text{CLCR} + \text{CLf}]) \times (1 - \exp \left[-(\text{CLHD} + \text{CLf})t/\text{Vf}\right])$, where CLHD is the hemodialysis clearance of the drug, CLf, is the intrinsic body clearance of the drug, and $t$ is the duration of hemodialysis (9, 15). In a hypothetical anephric patient with a body weight of 60 kg, the V$_{area}$ is expected to be 16.2 liters (i.e., 0.270 liters/kg) and $\beta$ is 0.0469/h (Fig. 3). The intrinsic body clearance of cefmenoxime (CLf) in this patient is: CLf = V$_{area} \times \beta = 12.7$ ml/min. Assuming that the hemodialysis clearance of cefmenoxime is 20.4 ml/min (Table 4), $f$ is calculated to be 0.282 when the duration of the dialysis is 5 h. Thus, a standard 5-h hemodialysis is expected to remove 28.2% of the amount of the drug present in the body at the start of dialysis. Theoretically, at least, this amount of the drug should be supplemented at the end of hemodialysis, although whether such a maneuver is necessary should be decided on clinical grounds in individual cases.

### LITERATURE CITED


