Pharmacokinetics of Cefamandole in Patients Undergoing Hemodialysis and Peritoneal Dialysis

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The pharmacokinetics of cefamandole nafate, a new parenteral cephalosporin derivative, were evaluated in 11 patients with chronic renal failure (creatinine clearance less than 5 ml/min), including five patients during hemodialysis, four patients during routine peritoneal dialysis, and two patients during the interdialytic period. Peak serum levels of cefamandole were comparable to those observed in patients with normal renal function. Clearance of the drug during the interdialytic period and during hemodialysis and peritoneal dialysis was minimal, with a resultant significant prolongation of serum half-life. The nondialyzability of cefamandole is in contrast with reported studies of cephalothin, where significant reduction of the serum half-life was achieved during hemodialysis but not peritoneal dialysis. The concentration of cefamandole in the peritoneal dialysate after parenteral administration was observed to be bactericidal for many gram-negative pathogens and, with the exception of Streptococcus faecalis, most gram-positive organisms found in bacterial peritonitis in patients with severe renal failure. The present data suggest that if stable bactericidal serum levels of cefamandole are to be maintained during hemodialysis and peritoneal dialysis, a parenteral loading dose must be administered followed by one-half the loading dose every half-life.

Cefamandole nafate is a new parenteral cephalosporin active against a wide variety of gram-positive and gram-negative organisms including cephalothin-resistant Enterobacter species, indole-positive Proteus species resistant to cephalothin, and particularly Haemophilus influenzae isolates (2, 9-11). In previous studies, the pharmacokinetics of cefamandole have been studied in normal volunteers, but no studies have been done in patients with chronic renal failure who are not being dialyzed or in patients undergoing hemodialysis or peritoneal dialysis. Therefore, it is the purpose of this investigation to evaluate the pharmacokinetics of this agent during the course of routine hemodialysis and peritoneal dialysis and during interdialytic periods.

MATERIALS AND METHODS

Patients. Eleven chronic dialysis patients with chronic renal failure (creatinine clearance <5 ml/min) were studied. Two chronic hemodialysis patients were studied during the interdialytic period, five patients during the course of a routine hemodialysis, and four patients during the course of a routine peritoneal dialysis. No patient was septic, nor had any received antibiotics for at least 2 weeks before the study. Informed consent was obtained from each patient.

Dialysis. (i) Peritoneal. All patients studied had indwelling Tenckhoff catheters in place. Dialysis solutions (1.5% dextrose) were prewarmed to a temperature of 37°C and instilled into the peritoneal cavity over a 10-min period. Dwell time in the peritoneal cavity was limited to 20 min. and dialysate was drained over a 30-min period. Heparin was not added to the dialysate. The overall flow rate was 2 liters/h.

(ii) Hemodialysis. Patients underwent dialysis for 6 h with a recirculating single-pass delivery system using extracorporeal Ex-23 coils. An initial loading dose of heparin, 1 mg/kg of body weight, was given followed by hourly injections of 1,000 U of heparin through the 4th hour of dialysis.

Study protocol. Control serum samples were taken from all patients just before administration of the antibiotic as well as before institution of dialysis for those patients being studied during dialysis. One gram of cefamandole nafate (supplied by Eli Lilly and Co.) was then administered intramuscularly. The time of the injection of the antibiotic was considered to be time zero. In patients studied during hemodialysis, dialysis was begun at time zero, and arterial (coil inflow) bloods were obtained from these patients at 0.5, 1, 2, 3, 4, 5, and 6 h. Concomitant venous (coil outflow) bloods were obtained at 2, 4, and 6 h. Patients who were studied while not being dialyzed had venous samples drawn at 0.5, 1, 2, 3, 4, 5, and 6 h. The patients being evaluated during peritoneal dialysis had blood drawn at 0.5 and 1 h after the injection of cefamandole, and di-
analysis was begun immediately after the 1-h sample was obtained. Thereafter, samples were obtained at the following intervals: 1.5 h after time zero (0.5 h after institution of dialysis) and 2.5, 6.5, 7.5, and 12.5 h after time zero. Aliquots of the outflow dialysate fluid were obtained from exchanges one, two, three, four, five, six, seven, and twelve at the start of the drainage period. Both serum and dialysate samples were either assayed immediately or stored for no longer than 48 h at −4°C before assay.

Antibiotic assay. The cefamandole standard was supplied by Eli Lilly and Co., Indianapolis, Ind., as cefamandole lithium. The standard was dissolved in sterile distilled water just before use. The assay used in the study is based on the procedure for gentamicin determination initially described by Winters et al. (12), utilizing Bacillus globigii as the test organism, and modified in our laboratory as previously described (8). All serum and dialysate assays were done in duplicate in each plate to verify reproducibility. Each plate contained, in duplicate, cefamandole standards of 20, 10, 5, 2.5, 1.25, and 0.625 μg/ml.

Data analysis. (i) Serum and peritoneal dialysate antibiotic levels. The values for each patient and standards were determined by linear regression analysis on a Monroe 1950 statistical calculator.

(ii) Clearance. The mean peritoneal clearance of the administered antibiotic, urea, and creatinine was calculated by the equation $C = (D \times V)/S \times t$, where $C$ is the clearance in milliliters per minute; $D$ is the mean dialysate concentration (antibiotic in micrograms per milliliter, creatinine or urea in milligrams per 100 ml); $S$ is the mean serum concentration (micrograms per milliliter or milligrams per 100 ml as above); $V$ is the volume of dialysate (in milliliters); and $t$ is the time in minutes (60).

(iii) Amount of antibiotic removed. The total antibiotic removed per exchange over the 12 h of peritoneal dialysis was calculated by the equation $V \times D = A$, where $V$ is the volume of dialysate (in milliliters); $D$ is the dialysate antibiotic concentration (in micrograms per milliliter); and $A$ is the amount of antibiotic removed per exchange.

The total antibiotic extracted over the 6 h of hemodialysis was calculated by the equation $S_1 - S_2 = A$, where $S_1$ is the peak arterial serum antibiotic concentration (in micrograms per milliliter); $S_2$ is the venous serum antibiotic concentration at 6 h (in micrograms per milliliter); and $A$ is the total antibiotic extracted (in micrograms per milliliter).

(iv) Extraction ratio. The extraction ratio of the antibiotic and creatinine on the hemodialysis patients was determined at the end of the 2nd, 4th, and 6th hours and was calculated by the equation $ER = [(A - V)/(A)] \times 100$ (7), where $ER$ is the extraction ratio; $A$ is the arterial serum antibiotic concentration (in milligrams per milliliter) or arterial creatinine concentration (in milligrams per 100 ml); and $V$ is the venous serum antibiotic concentration (micrograms per milliliter) or venous creatinine concentration (in milligrams per 100 ml). Extraction ratios for antibiotic and creatinine were then compared by the formula $A(B) \times 100 = C$, where $A$ is the extraction ratio of antibiotic; $B$ is the extraction ratio of creatinine; and $C$ is the ratio of the percentage of antibiotic extracted to the percentage of creatinine extracted at each time interval measured.

(v) Half-life. The kinetics of the present study are characterized by a monoeponential decay curve. Thus, the half-life of the antibiotic was determined by the method of least squares using the slope ($m$) as calculated from the formula (6):

$$m = \frac{N\Sigma(x \log y) - (\Sigma x)(\Sigma \log y)}{N\Sigma x^2 - (\Sigma x)^2}$$

half-life = $\log 2/m$

where $x$ is the time in hours; $y$ is the concentration of antibiotic in serum; and $N$ is the number of observations.

RESULTS

Hemodialysis. In the five patients studied, the 1-h peak arterial concentration (Table 1, Fig. 1) was 27.85 μg/ml (range: 20.38 to 37.07). After 6 h of dialysis, the mean arterial concentration fell to 16.03 μg/ml (range: 11.72 to 24.84). The mean amount of antibiotic extracted over the 6-h dialysis was 13.27 μg/ml (range: 8.75 to 17.38). Extraction ratios calculated on each patient at 2, 4, and 6 h were

<p>| Table 1. Half-life and serum concentration of cefamandole in patients undergoing hemodialysis |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Serum conc (μg/ml)</th>
<th>0.5 h (arterial)</th>
<th>1 h (arterial)</th>
<th>2 h</th>
<th>3 h (arterial)</th>
<th>4 h</th>
<th>6 h</th>
<th>Half-lifea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arterial</td>
<td>Venous</td>
<td>Arterial</td>
<td>Venous</td>
<td>Arterial</td>
<td>Venous</td>
<td>Arterial</td>
</tr>
</tbody>
</table>

a See text; each half-life determined by using monoeponential decay calculated from peak serum value of each patient.

b Time postinfusion.
variable with a mean of $8.8 \pm 1.6$ standard error. Comparison of the extraction of cefamandole with the extraction of creatinine at the above times was again variable, with a mean of $24.7 \pm 8.3$ standard error. The mean half-life determined by monoexponential decay was $6.61$ h (range: 11.58 to 4.74).

Peritoneal dialysis. In the four patients studied, the observed mean peak serum concentration was 25.4 $\mu$g/ml (range: 19.5 to 33.96) 1.5 h after the intramuscular injection. The level fell to 8.71 $\mu$g/ml (range: 6.85 to 12.26) (Table 2, Fig. 2) 12.5 h after the injection (11.5 h after dialysis was begun). The mean peritoneal dialysate concentration (Table 3) was 5.79 $\mu$g/ml (range: 4.01 to 8.52). The mean quantity of antibiotic removed per exchange over the 12 h was 11.56 mg/h (range: 8.02 to 17.04). Total mean amount of drug removed was 139.2 mg, or 3.9% of the initial 1-g dose.

The mean clearance of cefamandole per exchange and the mean over 12 h are listed in Table 3. The mean was 10.22 ml/min, with a range of 8.25 to 11.64. The mean half-life (Table 2) calculated by monoexponential decay was 7.15 h (range: 5.68 to 8.67).

Chronic renal patients: interdialytic period. In the two patients studied, the mean peak serum concentration was 24.63 $\mu$g/ml 1 h after intramuscular injection of 1 g of cefamandole. Six hours after injection, the mean serum concentration was 20.21 $\mu$g/ml. The half-life of cefamandole in patient 1, calculated from antibiotic concentrations at 1, 2, 3, 4, 5, and 6 h, was 8.4 h. The half-life in patient 2, similarly calculated, was 9.24 h. The mean half-life was 8.84 h.

**DISCUSSION**

In an earlier study of the pharmacokinetics of cefamandole in patients with normal renal

![Graph](http://aac.asm.org/)
function (creatinine, 0.8 to 1.7 mg/100 ml; creatinine clearances, 31 to 123 ml/min), Shemonsky et al. (11) observed that doses of 6 to 11 mg/kg (comparable to a dose of 500 mg) given by intramuscular injection resulted in a mean peak serum concentration of 13.7 ± 3 μg/ml at 1.5 h and ≤1.0 μg/ml at 6 h. In the same study, with doses in the 11- to 17-mg/kg range (approximating the 1-g intramuscular dose used in the present study), the mean peak serum concentrations were observed to be 31.0 ± 17.8 μg/ml at 0.5 h and 1.7 ± 0.7 μg/ml 6 h after cefamandole administration. The calculated half-life in their study ranged from 49 to 129 min. In a similar study in normal volunteers given a 1-g intramuscular injection, the mean peak serum concentration was 21 μg/ml (3). In the same study (3), a 1-g intravenous dose of cefamandole given to normal volunteers resulted in a \( t_{1/2} \) of 0.5 h. These workers (3) observed that cefamandole was 74% bound to serum protein and had a volume of distribution of 12.8 liters/1.73 m\(^3\). The data observed in the present study, which were obtained from two patients with chronic renal failure who were studied during the interdiastolic period, indicated a mean peak serum concentration of 24.63 μg/ml at 1 h after the injection of 1 g of cefamandole and were comparable to the results observed in normal patients (3, 11). However, the 6-h mean serum concentration in our patients was 20.21 μg/ml, and the calculated \( t_{1/2} \) was 8.8 h. The striking contrast in serum levels in patients with chronic renal failure as compared with patients with normal renal function reflects the significant clearance of cefamandole by renal mechanisms.

The four patients in the present report who were studied on peritoneal dialysis again demonstrated peak serum levels comparable to those of normals, with a mean of 25.4 μg/ml. The 12.5-h postinjection mean level of 8.71 μg/ml suggests that cefamandole is not effectively removed by peritoneal dialysis. This statement is supported by our observations that approximately 130 mg of cefamandole, or 13% of the initial 1-g dose, was found in the dialysate over the 12-h period of dialysis. The present study also indicates that the mean half-life of cefamandole is prolonged in patients undergoing peritoneal dialysis, i.e., 7.5 h as compared with 30 min in patients with normal renal function.

Similarly, in our patients undergoing hemodialysis, the mean peak serum concentration of cefamandole was observed to be 27.85 μg/ml. Thus, mean peak serum concentrations of the antibiotic, after intramuscular injection of 1 g, appear comparable regardless of renal status. In contrast to the rapid excretion of cefamandole over 6 h in patients with normal renal function, however, the patients undergoing hemodialysis had an observed mean serum concentration of 16.05 μg/ml at 6 h. The calculated half-life was 6.61 h, similar to the value obtained for the peritoneal dialysis study group.

The pharmacokinetics of cefamandole in renal failure and dialysis differ in certain aspects from previous data derived from cephalothin studies in patients with renal failure. Kabins and Cohen (4) studied 12 azotemic patients (creatinine clearance <5 ml/min) given 1 g of cephalothin intravenously and observed that the peak serum concentrations 15 to 30 min postinjection ranged from 32 to 64 μg/ml. At 6 h, serum cephalothin values in the azotemic patients were in the range of 16 μg/ml as compared with undetectable levels in patients with creatinine clearances greater than 30 ml/min per 1.73 m\(^2\). The half-life of cephalothin in these azotemic patients was increased over the normal \( t_{1/2} \) of 0.5 h and was biphasic, i.e., 2.8 h over the first 8 h and 12 ± 4 h over 8 to 24 h and 24 to 48 h, respectively, reflecting the different urine excretion rates of cephalothin and its metabolite o-desacetyl cephalothin (4). An initial half-life value for cephalothin of 2.9 h has also been reported by Kunin and Atuk in patients with renal failure (5).

Yamasaku et al. (13) also studied cephalosporins, but not cefamandole, in patients with renal failure undergoing dialysis and found that the half-life for cephalothin was prolonged in uremic patients. These workers observed cephalothin half-life values of 4.6 h over the first 9 h and 15.9 h over the subsequent 72 h. However, half-life values were reduced to 2.3 h by hemodialysis on a coil dialyzer and to 2.6 h on the Kii dialyzer. Cephalothin did not appear to be removed by peritoneal dialysis since the average half-life in six patients in this study was 5.1 h. Thus, both cephalothin and cefamandole have prolonged half-lives in patients with severe chronic renal insufficiency, and neither cephalothin nor cefamandole is effectively removed by peritoneal dialysis, whereas cephalothin, but not cefamandole, is significantly removed from the serum during hemodialysis.

We have no obvious explanation for the nondialyzability of cefamandole, or for the difference between the dialyzability of cefamandole and cephalothin during hemodialysis. Both cephalothin and cefamandole are similarly protein bound (70 and 74%, respectively) and
have similar half-lives (30 and 34 min, respectively) as well as similar volumes of distribution (18.5 and 12.8 liters/1.73 m², respectively) and molecular weights (418 and 512, respectively) (3).

Even though cefamandole is not significantly removed from the serum during hemodialysis or peritoneal dialysis, our observations indicate that the concentration of cefamandole in the peritoneal dialysis fluid ranged from 8.52 µg/ml at 1 h to 4.02 µg/ml at 12 h, with a mean of 5.79 µg/ml. On the basis of these data, it appears that intramuscular cefamandole alone, without similar intraperitoneal instillation, should give sufficiently elevated peritoneal levels to be bactericidal for many gram-negative pathogens and, except for *Streptococcus faecalis*, most gram-positive organisms found in bacterial peritonitis (11).

Since the results of the present study indicate that the clearance of cefamandole during hemodialysis and peritoneal dialysis is minimal and that the half-life is significantly prolonged (greater than six times) in patients undergoing dialysis, the following dose recommendations can be calculated according to the formula 
\[(P/k)(Vd) \times 25 \times 10^{-3} \text{ mg/ml (11) and Vd is volume of distribution of the drug (12.8 liters/1.73 m²) (3) \times 7.45 liters/m².}\]

Substituting values, one gets the following: dosage (in milligrams per square meter) = \(25 \times 10^{-3}\) mg/ml \((7.45 \times 10^3\) ml/m²) = 186 mg/m². Therefore, patients with severe renal failure, regardless of whether they are undergoing hemodialysis or peritoneal dialysis, should receive a loading dose of cefamandole based on the above calculation, followed by one-half this loading dose every half-life (7.5 h during peritoneal dialysis and 6.6 h during hemodialysis). This method of administration has been shown to provide more stable drug levels (1).

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LITERATURE CITED