Hemodialysis-Associated Infections: Treatment with Cephapirin

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Large doses of cephapirin (50 mg/kg) administered during the first and last half hours of routine hemodialysis produced effective antimicrobial serum concentrations for 48 h. Repetitive administration during five successive hemodialysis sessions did not result in accumulation or accelerated metabolism of cephapirin. Ten infectious episodes in nine patients were treated in this manner with good clinical results and no toxicity.

Much of the morbidity of chronic renal failure has not been relieved by hemodialysis (HD). Infections remain among the most common causes of hospitalization and death (6). Contributing to a lengthy hospitalization may be the administration of parenteral drugs by recommended schedules (3–5). If infections can be treated by administering antibiotics only at the time of HD, the benefits will include cost reduction, the length of hospital stay, and the achievement of a full course of therapy.

Cephapirin, a semisynthetic cephalosporin for parenteral use, has been chosen to test this proposal. It is a derivative of 7-aminocephalosporanic acid and is metabolized to desacetylcephapirin, which also appears to be microbiologically active (7). The half-life of 1.0 g of cephapirin during HD is 107 min (5). There are no data regarding the dose of cephapirin that must be administered during HD to maintain sufficient antibacterial activity for the interdialysis period, usually a minimum of 42 h. We have performed single- and multiple-dose pharmacokinetic studies to establish dosage schedules and treated 10 infectious episodes to determine the feasibility of this approach.

MATERIALS AND METHODS

Single-dose pharmacokinetics. Nine patients with end-stage renal disease and no other active clinical illness whose creatinine clearances were <5 ml/min were studied on either a Travenol, Lifemed, or Milton Roy recirculating single-pass HD machine using extracorporeal EX-23 coils. A 40-mg/kg amount of cephapirin was administered by intravenous infusion over 30 min, starting 1 h before HD; arterial and venous samples were drawn at the initiation of HD, at 1, 2, and 4 h, and at the completion of HD.

Multiple-dose pharmacokinetics. Five patients received 50 mg of cephapirin per kg in 75 ml of normal saline during the first 30 min of a routine HD (predialysis dose) and then received a duplicate amount of the drug during the last 30 min of HD (postdialysis dose). Cephapirin was administered through the arterial line of the dialyzer and was drawn in by the negative pressure of the machine. Venous blood samples were obtained at the conclusion of each HD period (peak) and just before the initiation of the next session (trough). HD was conducted for 5.5 h on a schedule of three times a week; the patients were studied for five consecutive HD periods. After administration of the last dose of cephapirin, serum concentrations were assayed at 24, 48, and 72 h.

Plasma assay cephapirin. Arterial and venous blood samples were drawn in 5-ml sodium heparin vacuum tubes. Blood samples were placed immediately in an ice bath, and the plasma was separated within 30 min. All specimens were frozen until assayed. Plasma was diluted with an equal volume of acetone-phosphate buffer, pH 6.0 (50/50), and centrifuged at 2,000 rpm for 10 min to remove precipitated protein. The supernatant was further diluted if necessary in acetone buffer solution. Specimens were assayed by the agar plate bioassay method, using Staphylococcus epidermidis ATCC 29213 (2).

Tube dilution sensitivities. Clinical isolates were grown in Mueller-Hinton broth to a concentration of 10⁶ organisms, and the procedure was performed as outlined by others (1). Pure cephapirin and desacylcephapirin were supplied by Bristol Laboratories. Minimal inhibitory concentrations were read after 18 h of incubation. The minimal bactericidal concentration was defined as that concentration of antibiotic which killed >99% of the organisms in 18 h as demonstrated by subculture on antibiotic-free Mueller-Hinton plates.

RESULTS

Single-dose pharmacokinetics. Cephapirin (40 mg/kg) was administered intravenously to nine patients (Fig. 1). After equilibration for
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0.5 h, HD was started (time 0). The mean plasma concentration of cephapirin at time 0 was 216 ± 58 μg/ml. After 5.5 h, HD was concluded, and the venous concentration averaged 33 ± 10 μg/ml. Using the least-squares method, the mean half-life was 2.8 ± 0.9 h. The total volume of dialysate was collected and assayed for two patients. A 1.8-g amount of a 3.5-g dose was extracted in one patient (52%), and 1.5 g of a 2.7-g dose (50%) was recovered in the second individual.

Multiple-dose pharmacokinetics. For five consecutive HD sessions, five patients received 50 mg of cephapirin per kg over a 30-min period at the beginning and again at the end of HD. The mean peak postdialysis serum concentration was 297 ± 125 μg/ml, and the mean trough predialysis serum concentration was 5 ± 6 μg/ml. There was no evidence of drug accumulation after repetitive dosing.

Tube dilution sensitivity patterns. Cephapirin and desacetycephapirin were compared by the method of tube dilution minimal inhibitory and minimal bactericidal concentrations since the interval between doses suggested that in vivo desacetylation of cephapirin may be of clinical significance. Ten clinical isolates of Staphylococcus aureus were tested, and all cultures were sterilized by 3 μg/ml or less. No difference was noted between cephapirin and desacetycephapirin (Table 1).

Clinical studies. Nine patients with 10 episodes of infection were treated with cephapirin. A 50-mg/kg dose was administered twice during each HD session (see Materials and Meth-ods). The infectious episodes included septicemias, arteriovenous fistula bovine graft infections, arteriovenous shunt infection, cardiac pacemaker site infection, and a postoperative flank abscess (Table 2). The organism responsible for nine of the infections was S. aureus, and Escherichia coli was isolated from the other patient. The ages of the patients ranged from 14 to 76 years. The causes of end-stage renal disease included diabetes mellitus, pyelonephritis, idiopathic glomerulonephritis, and systemic lupus erythematosus.

All patients with proven septicemias were febrile and had an initial leukocyte count of >12,000/mm³. The patients with soft-tissue or blood access infections were afebrile and did not have leukocytosis. Staphylococcal septicemias were treated for 4 weeks, and soft-tissue infections were treated for a minimum of 2 weeks. Patients were dialyzed four times a week during the period of critical illness; otherwise, the routine HD schedule of three times weekly for 5.5 h was followed. At the conclusion of therapy, all patients were considered cured by both clinical and bacteriological standards.

One patient was rehospitalized with staphylococcal septicemia and an obviously infected bovine graft site 3 months after the initial episode. In addition to retreatment with cephapirin, the bovine graft was removed. Bacteriophage typing patterns were identical for both staphylococci, suggesting that the second infection was due to the original organism protected by the foreign graft.

Plasma concentrations of cephapirin were assayed periodically during the course of treatment. The peak concentration of cephapirin ranged from 185 to 400 μg/ml. Trough concentrations were still highly therapeutic after 2 days in all but one patient (μ = 19 μg/ml), and cephapirin was still present after 3 days (μ = 5.6 μg/ml).

Cephapirin was well tolerated. One patient complained of transient itching, which was obviated by slowing the rate of infusion, and one patient complained of nausea. Skin rashes, arthralgias, or fever were not encountered. Two patients developed a positive Coombs' test, but in neither did further anemia or granulocytopenia occur. One patient (R.D.C.) mani-

Table 1. Quantitative tube dilution sensitivity patterns of S. aureus isolated from 10 patients to cephapirin and desacetycephapirin*  

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC (μg/ml)</th>
<th>MBC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephapirin</td>
<td>0.74 ± 0.47</td>
<td>1.52 ± 1.19</td>
</tr>
<tr>
<td>Desacetycephapirin</td>
<td>0.55 ± 0.38</td>
<td>1.60 ± 1.16</td>
</tr>
</tbody>
</table>

* MIC, Minimal inhibitory concentration; MBC, minimal bactericidal concentration.
fested abnormal liver function tests (serum glutamic oxalacetic transaminase = 650 IU). Three weeks before the study, the patient experienced a cardiac arrest and was resuscitated with DC countershock. At the time of the elevated transaminase values, the patient was in a state of fluid overload. Cephapirin therapy was continued and the abnormality was resolved. Subsequently, this patient has been retreated with cephapirin without evidence of hepatic toxicity.

**DISCUSSION**

This study tests cephapirin in a constant dose-constant interval setting for the treatment of infections in patients on HD. Nine patients with 10 infectious episodes, including four patients with septicemia, were treated with cephapirin (50 mg/kg) administered during the initial and final 30 min of a 5.5-h HD session. All infectious episodes responded favorably. In addition, patients were freed from intravenous tubing and repeated intramuscular injections. After patients experienced a clinical recovery, they were discharged from the hospital, and therapy was completed in an outpatient or home setting. To achieve effective antimicrobial activity during the interdialysis period, the amount of cephapirin administered produced peak serum concentrations of over 300 μg/ml. Serum sickness (8) or hemolytic anemia (9), the two complications associated with high-dose–long-duration cephalosporin therapy were not encountered.

The data suggest that staphylococcal infections can be treated by this method without concern as to whether the drug is in its parent or desacetylated form.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**


**TABLE 2. Clinical parameters of 10 infectious episodes treated with cephapirin (50 mg/kg) at the beginning and again at the conclusion of HD**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology of renal disease</th>
<th>Site of infection</th>
<th>Pathogen</th>
<th>Cephapirin, pre/post-HD (g)</th>
<th>No. of sessions</th>
<th>Total dose (g)</th>
<th>Clinical outcome</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.F.</td>
<td>Pyelonephritis</td>
<td>Blood</td>
<td><em>E. coli</em></td>
<td>2.3</td>
<td>14</td>
<td>64.4</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>R.K.</td>
<td>Glomerulonephritis</td>
<td>Lymphangitis</td>
<td><em>S. aureus</em></td>
<td>3.2</td>
<td>6</td>
<td>38.4</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>R.K., no. 2</td>
<td>Glomerulonephritis</td>
<td>Fistula</td>
<td><em>S. aureus</em></td>
<td>3.2</td>
<td>6</td>
<td>35.0</td>
<td>Cure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>I.M.</td>
<td>Diabetes mellitus</td>
<td>Blood</td>
<td><em>S. aureus</em></td>
<td>2.5</td>
<td>19</td>
<td>93.0</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>S.M.</td>
<td>Diabetes mellitus</td>
<td>Shunt</td>
<td><em>S. aureus</em></td>
<td>3.2</td>
<td>9</td>
<td>54.0</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>M.R.</td>
<td>Diabetes mellitus</td>
<td>Fistula</td>
<td><em>S. aureus</em></td>
<td>3.2</td>
<td>10</td>
<td>54.0</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>R.D.C.</td>
<td>Systemic lupus erythematosus</td>
<td>Blood</td>
<td><em>S. aureus</em></td>
<td>2.25</td>
<td>20</td>
<td>90.0</td>
<td>Cure</td>
<td>-&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>K.Y.W.</td>
<td>Diabetes mellitus</td>
<td>Pacemaker site</td>
<td><em>S. aureus</em></td>
<td>2.25</td>
<td>7</td>
<td>30.0</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>A.Mc.</td>
<td>Pyelonephritis</td>
<td>Blood</td>
<td><em>S. aureus</em></td>
<td>3.2</td>
<td>15</td>
<td>96.0</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>V.C.</td>
<td>Pyelonephritis</td>
<td>Fistula</td>
<td><em>S. aureus</em></td>
<td>0.75</td>
<td>18</td>
<td>46.0</td>
<td>Cure</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup> See text.