Effect of Hemodialysis and Renal Failure on Serum and Urine Concentrations of Cephapirin Sodium

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Six patients undergoing chronic hemodialysis and 10 patients with chronic renal insufficiency hospitalized for nondialytic therapy received 1.0 g of cephapirin sodium by the intravenous route. The concentrations of cephapirin in arterial and venous plasma, dialysate, venous blood, and urine were measured during the ensuing 6 hr. The serum half-life of cephapirin was 105 to 108 min for the dialyzed patients and 95.9 min for the nondialyzed patients. Dialysis removed 22.8% of the administered dose. Nondialyzed patients excreted 19.5% of the administered dose in the urine. The concentration of cephapirin in the urine of all nondialyzed patients exceeded 50 μg/ml. The recovery of cephapirin in the urine of all nondialyzed patients for 6 hr after injection was from 34 to 770 mg (mean 195 mg). To maintain a concentration of cephapirin in the blood and urine which exceeds the minimal inhibitory concentration for most gram-positive and gram-negative microorganisms, nondialyzed patients should receive 15 to 18 mg of cephapirin per kg every 12 hr. Dialyzed patients should receive the same dose just prior to dialysis and every 12 hr thereafter.

Cephapirin, 7-(pyrid-4-yl thiaoacetamido) cephalosporanate, is a new semisynthetic derivative of 7-aminoscephalosporanic acid effective in vitro against gram-positive and gram-negative microorganisms. Concentrations of cephapirin necessary to inhibit Diplococcus pneumoniae, Mycobacterium tuberculosis (H37Rv), and Enterobacter sp. in vivo are less than those of cephalothin (3). The amount of cephapirin bound to human serum proteins is less than that of cephalothin similarly bound (3). Seventeen children responded "satisfactorily" to cephapirin treatment of pneumonia, lung abscess, and urinary-tract and soft-tissue infections (4).

This report describes the clearance of cephapirin from the blood during hemodialysis and the urinary excretion of intravenously administered cephapirin during nondialytic treatment of azotemia.

MATERIALS AND METHODS

Patient population. Of the 16 azotemic patients who participated in the study, 10 were hospitalized for nondialytic therapy of chronic renal failure and 6 were undergoing extracorporeal hemodialysis two times weekly in anticipation of renal transplantation. The mean serum creatinine of the dialyzed patients was 13.1 mg/100 ml; that of the nondialyzed patients was 6.6 mg/100 ml. Hemodialysis lasted 6 hr and was performed by use of a twin-coil Travenol RSP dialyzer with a Visking UF 145 membrane. Each patient received 1.0 g of cephapirin sodium intravenously over a period of 5 min. From the six patients who underwent dialysis, venous blood, arterial blood, and dialysate were obtained 0.5, 1, 2, 3, 4, 6, 7, 8, 9, and 48 hr after cephapirin was injected. Venous blood and urine were obtained from the 10 nondialyzed patients 0.5, 1, 2, 4, and 6 hr after the injection of 1.0 g of cephapirin sodium.

Cephapirin concentration. Serum or plasma was diluted with an equal volume of acetone-buffer (50% acetone-50% pH 6.0 phosphate buffer, v/v) and centrifuged at 2,000 rev/min for 10 min to remove precipitated protein. Urine samples were diluted with pH 6.0 phosphate buffer. Serum and urine were assayed immediately by the agar plate bioassay method (5). Sarcina lutea (ATCC 9341) was incubated at 32 C for 18 hr, and was diluted so that a 10% suspension produced 20% light transmission at 580 nm. This suspension was the inoculum for all assays. The diameter of the inhibition zone surrounding each unknown sample was measured, and the cephapirin concentration was determined by comparison with a standard curve relating reference cephapirin concentrations (0.1 to 0.5 μg/ml) to zone of inhibition produced by the reference concentration. Reference concentrations of cephapirin were included with each assay of experimental serum, plasma, or urine.
RESULTS

Dialyzed patients. The mean serum half-time (T₁/₂) in venous plasma was 108 min (98 to 118 min). The T₁/₂ in arterial plasma was 105 min. Inspection of Fig. 1 and 2 shows that throughout dialysis a concentration of cephapirin was maintained which exceeded the minimal inhibiting concentration (MIC) for group A streptococci, D. pneumoniae, penicillin-susceptible and penicillin-

resistant Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Salmonella and Shigella spp., and Proteus mirabilis. The concentrations of cephapirin attained in the last 2 hr of dialysis would fail to inhibit 25% of indole-positive strains of Proteus sp. and Enterobacter sp. (3). For at least 3 hr after dialysis was terminated, cephapirin concentrations exceeded the MIC for gram-positive and gram-negative microorganisms except for 25 to 50% of indole-positive strains of Proteus sp. and Enterobacter sp. mentioned previously.

The mean dose of cephapirin was 18 mg/kg (13 to 21 mg/kg). The mean cumulative removal of the 1.0 g administered was 228 mg (194 to 252 mg), during the 6-hr dialysis period. Removal of cephapirin from the plasma by the dialyzer can be expressed as the dialysance of the antibiotic by

\[ (A - V) \times F/(A - D) \]

where \( A \) is the arterial plasma concentration of cephapirin (µg/ml), \( V \) is the venous plasma concentration of cephapirin (µg/ml), \( D \) is the dialysate concentration of cephapirin (µg/ml), and \( F \) is the blood flow through the dialyzer (ml/min).

The mean dialysance of cephapirin was 24 ml/min (14 to 38 ml/min) at a mean blood flow of 190 ml/min (175 to 210 ml/min). This value can be compared with the mean creatinine dialysance of 100 ml/min (75 to 123 ml/min). At 48 hr after the intravenous injection of cephapirin, immedi-

![Fig. 1. Relationship of cephapirin concentration in arterial plasma to time elapsed after the start of hemodialysis. Each patient received 1.0 g of cephapirin sodium by the intravenous route. In this figure, \( y = -7.8 + 15.25x \). Brackets indicate two standard deviations from the mean value.](image1)

![Fig. 2. Relationship of cephapirin sodium concentration in venous plasma to time elapsed after the start of hemodialysis. Each patient received 1.0 g of cephapirin sodium by the intravenous route. The lower curve represents venous plasma cephapirin concentrations after dialysis was terminated. For the upper curve, \( y = -7.9 + 14.97x \). (compare with Fig. 1). Brackets indicate two standard deviations from the mean.](image2)
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were
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venous or arterial plasma of dialyzed patients
(P > 0.05). Figure 3 shows the relationship of
T1/2 in venous blood serum to serum creatinine
at the beginning of the study period. Over a range
of serum creatinine from 1.5 to 11.5, the T1/2 value
increased only 40 min (90 to 130 min). The
regression curve in Fig. 3 can be used to predict
T1/2 when the serum creatinine is known, assuming
that dosage and serum concentration are as
found on an average in this report. During the 6 hr
after injection of cephalothin sodium, concentra-
tions of the antibiotics were maintained at
levels exceeding the MIC for most gram-positive
and gram-negative organisms with the exception
of some strains of indole-positive Proteus sp. and
Enterobacter sp. The decline of serum cephalothin
concentrations with elapsed time after injection is
shown in Fig. 4. Curves indicating the cephalothin
concentrations from sera of individual patients
with the lowest and highest creatinine values display
the prolongation of T1/2 as the serum creati-
nine value rises. The mean creatinine clearance
during the 6-hr study period was 12.6 ml/min
(2 to 60 ml/min). No correlation was observed
when creatinine clearance was compared with serum T1/2 (R = -0.57; t = -1.97; P > 0.05).
The mean ratio of creatinine clearance to serum
T1/2 was 24.1 (7.3 to 50).

Despite the presence of renal failure, cephalothin
was excreted at a concentration exceeding 50 µg/ml
in the urine of all of the 10 patients. The mean
concentration was 495 µg/ml (60 to 1,140 µg/ml)
in urine collected during the 6-hr period. During
the 6 hr after injection of 1.0 g of cephalothin, the
mean total excretion was 195 mg (34 to 770 mg;

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>T1/2 (min)</th>
<th>Serum creatinine (mg/100 ml)</th>
<th>Urine concn (µg/ml)</th>
<th>Total excretion (mg/6 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>1.2</td>
<td>1,140</td>
<td>770</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>1.7</td>
<td>1,200</td>
<td>360</td>
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<td>3</td>
<td>57</td>
<td>4.5</td>
<td>85</td>
<td>42</td>
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<tr>
<td>4</td>
<td>90</td>
<td>7.6</td>
<td>280</td>
<td>56</td>
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<tr>
<td>5</td>
<td>90</td>
<td>1.8</td>
<td>650</td>
<td>143</td>
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<tr>
<td>6</td>
<td>100</td>
<td>3.3</td>
<td>650</td>
<td>208</td>
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<td>126</td>
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<td>8</td>
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<td>162</td>
<td>22.4</td>
<td>60</td>
<td>34</td>
</tr>
</tbody>
</table>
Table 1). Simple correlation coefficients were calculated comparing all combinations of $T_{1/2}$, serum creatinine, creatinine clearance, urine concentration of cephapirin, and the total amount of cephapirin excreted in the urine for 6 hr after injection. Three significant correlations emerged: $T_{1/2}$ and serum creatinine ($R = 0.81$); creatinine clearance and urine concentrations of cephapirin ($R = 0.82$); urine concentration of cephapirin and the total amount of cephapirin excreted during the study period ($R = 0.92$).

**DISCUSSION**

Previous reports of urinary excretion of cephapirin sodium by patients with normal renal function indicated that 53 to 69% of the antibiotic is excreted within 4 and 8 hr, respectively (4; B. Cavana, personal communication), at dose levels comparable to that employed in this study. Excretion of 19.5% of the administered dose within 6 hr by the 10 azotemic nondialyzed patients reported here represents a decrease in excretory capacity for a single dose of the antibiotic. Excretion of chronically administered cephapirin, such as would be encountered during actual therapy, might permit accumulation of cephapirin to undesirably high levels (1). This study did not investigate that possibility. The concentration of cephapirin attained in the urine, even during renal failure, exceeded the MIC for most gram-positive and gram-negative bacteria except for *Serratia marcescens*, *Pseudomonas aeruginosa*, and * Proteus morganii* (3). These findings point out a potentially useful application of this new cephalosporanic acid derivative in the treatment of urinary-tract infections complicated by renal insufficiency.

The technique employed for assay measured antibacterial activity resulting from the excretion of both cephapirin and desacetylcephapirin, which itself was not independently assayed. Approximately 41% of the excreted antibiotic is desacetylcephapirin, which is $0.54 \pm 0.03$ as potent as the parent compound against the assay organism, *S. lutea* (B. Cabana personal communication). A similar situation is known to obtain with cephalothin and desacetylcephalothin (10). The antibiotic concentration in the urine therefore may actually overestimate the antibacterial activity present in the urine. Future studies of the urinary excretion of cephapirin should include assay of desacetylcephapirin to resolve this question (6).

The serum creatinine was most closely correlated with the serum $T_{1/2}$ of cephapirin, and can be used to predict the serum $T_{1/2}$ in nondialyzed patients (Fig. 3). The serum creatinine determination is available essentially to all physicians attending patients with renal insufficiency and provides a reliable method for estimating $T_{1/2}$ (2, 8).


Cephapirin, like cephalothin and cephaloridine (7, 9), is removed from the blood by hemodialysis. Extrapolation of the free antibiotic concentration curve in blood after dialysis (Fig. 2) indicates that a dose of 15 to 18 mg of cephapirin per kg just before dialysis would result in concentrations below the MIC for some gram-negative bacteria 12 hr after injection of the drug. Within 48 hr, no antibiotic was present in the blood. These data indicate that 15 to 18 mg of cephapirin sodium per kg should be given just prior to dialysis and every 12 hr thereafter if free antibiotic concentrations in plasma exceeding 10 $\mu$g/ml are to be maintained.

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**LITERATURE CITED**


