Effects of Renal Failure and Dialysis on Cefazolin Pharmacokinetics

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Serum and urinary levels of cefazolin were determined after a 500-mg parenteral dose in eight azotemic volunteers. The mean peak serum concentration was 1.5 to 5 times the levels obtained in nonazotemic patients. The serum half-life of cefazolin was increased significantly. In patients on dialysis, the mean serum half-life of cefazolin was 4.05 h during (or after) hemodialysis, and 32.1 h during (or after) peritoneal dialysis. There was a significant decrease in cefazolin removal when dialysate flow or membrane surface area of the dialyzer were decreased. It was also shown that one circuit through the dialysis unit caused measurable decrease in cefazolin concentration. These data and previously published reports suggest: (i) the maintenance dose of cefazolin can be decreased in azotemic patients; (ii) patients on hemodialysis will require an additional half dose after dialysis because of efficient removal during hemodialysis; and (iii) patients on peritoneal dialysis do not require an extra dose.

Cefazolin, a recently introduced cephalosporin antibiotic, was reported not to be nephrotoxic in recent clinical studies (2, 6, 7). However, this antibiotic produced higher serum levels in uremic than in nonazotemic patients. It was also noted that the serum half-life of cefazolin was reduced by hemodialysis, but was little affected by peritoneal dialysis (1, 3, 5). We have confirmed these results in patients with varying degrees of renal failure and in patients undergoing peritoneal and hemodialysis. We also studied the pharmacokinetics of cefazolin using standard 4-h large-surface-area (2.4 m²) hemodialysis, hemodialysis with reduced membrane surface area, and also the effects of reduced duration of dialysis.

MATERIALS AND METHODS

Eight uremic patients not on dialysis were given 500 mg of cefazolin as a single intramuscular injection. Serum and urine samples were collected before the injection and at 0.5, 1, 4, 8, 12, and 24 h after administration of the drug.

Ten patients on dialysis were divided into three groups. Four patients in Group I were given 1 g of cefazolin intravenously at the initiation of a 4-h hemodialysis by using two Cordis Dow Model no. 4 hollow fiber kidneys. Blood flow during dialysis was approximately 200 ml/min, and dialysate flow was 500 ml/min. Blood samples were collected serially from venous dialysis lines without anticoagulant, and aliquots of 20 ml were taken from the dialysate for cup-plate assay.

Three patients studied in Group II were similar to Group I, except that they received the same dose of cefazolin 2 h prior to hemodialysis.

Three patients in Group III were given 1 g of cefazolin intravenously at the beginning of a 48-h peritoneal dialysis run at a rate of 2 liters/h. Total dialysate was pooled in 6-h periods, and a representative sample was taken from each period for cup-plate assay.

Cefazolin concentrations were determined by the modified cup-plate method by using Bacillus subtilis as the test organism (8). The regression lines of the logarithms of serum concentrations of cefazolin versus time were calculated by the method of least squares to obtain the half-life in each patient, and their correlation coefficients (r) were determined.

RESULTS

Azotemic patients. Serum half-lives in patients with chronic renal failure with creatinine clearance ranging from 2 to 59 ml/min are shown in Fig. 1. The half-life is markedly prolonged in patients with severe azotemia.

The urinary concentration of cefazolin during the first 6 h after the injection varied from 62 to 580 µg/ml. Figure 2 shows the 6-h urinary recovery in four selected patients. Recovery of cefazolin in azotemic patients was lower and varied inversely with reduced renal function. Despite the reduced urinary excretion, patients with creatinine clearances between 20 to 30 ml/min had urinary concentrations of cefazolin ranging from 30 to 150 µg/ml, which exceed the minimum inhibitory concentration of most susceptible urinary pathogens.
Patients on dialysis. The results of Group I patients who were given 1 g of cefazolin intravenously at the beginning of the 4-h hemodialysis are shown in Table 1. The major reduction in concentration occurred during the 4 h of dialysis when average serum levels dropped from 61 to 35.3 µg/ml. In contrast, in the following 20 h, concentrations fell on the average of 3 µg/ml. Mean half-life was 4 h. Forty-six percent of the original dose was recovered from the dialysate. In one patient, when the dialysate flow was reduced by half, 26.12% was recovered over the same period.

After the intravenous administration of 1 g of cefazolin, 2 h prior to hemodialysis, the concentrations were similar to the first group (Table 2). Average half-life was 4.1 h. If only one Cordis hollow fiber kidney was used, reducing the dialyzing area by half (1.2 m²), the half-life was increased to 5.75 h, and only 23.8% of the drug was recovered in the dialysate.

Figure 3 illustrates the results obtained when one patient was given cefazolin intravenously and dialyzed for 4 h with two dialyzers compared to the dialysis with only one dialyzer. Only 13.5% of the cefazolin was removed by using one kidney compared to 63.6% with the two kidneys.

**TABLE 2. Results of group II patients given 1 g of cefazolin administered intravenously 2 h prior to 4-h hemodialysis**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Serum level (µg/ml)</th>
<th>Half-life (h)</th>
<th>Dialysate</th>
<th>% Recovered</th>
<th>Vol (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>6 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>80</td>
<td>20</td>
<td>4.25</td>
<td>47.19</td>
<td>121</td>
</tr>
<tr>
<td>Case 3</td>
<td>44</td>
<td>28.5</td>
<td>4.0</td>
<td>63.6</td>
<td>112</td>
</tr>
<tr>
<td>Avg</td>
<td>62.0</td>
<td>24.2</td>
<td>4.1</td>
<td>55.4</td>
<td>116</td>
</tr>
<tr>
<td>Standard deviations</td>
<td>±25.4</td>
<td>±6.0</td>
<td>±0.2</td>
<td>±11.6</td>
<td></td>
</tr>
<tr>
<td>Case 2a</td>
<td>160</td>
<td>43</td>
<td>5.75</td>
<td>23.75</td>
<td>108</td>
</tr>
</tbody>
</table>

* Only one Cordis Dow kidney used.

**FIG. 1. Cefazolin serum half-lives in six azotemic patients.**

**FIG. 2. Six-hour urinary recovery of cefazolin in four selected azotemic patients with creatinine clearances ranging from 20 to 60 ml/min.**

**TABLE 1. Results of group I patients given 1 g of cefazolin intravenously at the beginning of 4-h dialysis**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Serum level (µg/ml)</th>
<th>Half-life (h)</th>
<th>Dialysate</th>
<th>% Recovered</th>
<th>Vol (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>4 h</td>
<td>24 h</td>
<td>4.5</td>
<td>38.28</td>
<td>113</td>
</tr>
<tr>
<td>Case 1</td>
<td>57</td>
<td>33</td>
<td>31</td>
<td>45.12</td>
<td>98</td>
</tr>
<tr>
<td>Case 2</td>
<td>56</td>
<td>36</td>
<td>33</td>
<td>54.88</td>
<td>112</td>
</tr>
<tr>
<td>Case 3</td>
<td>70</td>
<td>37</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg</td>
<td>61</td>
<td>35.3</td>
<td>32.3</td>
<td>40.0</td>
<td>46.1</td>
</tr>
<tr>
<td>Standard deviations</td>
<td>±7.8</td>
<td>±2.1</td>
<td>±1.1</td>
<td>±0.9</td>
<td>±1.3</td>
</tr>
<tr>
<td>Case 4a</td>
<td>60</td>
<td>27</td>
<td>22</td>
<td>26.12</td>
<td>52.25a</td>
</tr>
</tbody>
</table>

* Dialysis flow was reduced to half of normal rate.
The dialyzer and This cefazolin at the initial levels decreased 3.

The patients through the dialysis neal studied pathogenic substrates with molecular square dialysis and the dialyzer. Alteration of the so-called "middle" molecules, alteration little of erythromycin concentration of 8, during removal 4

FIG. 3. Differences in cefazolin levels when using one Cordis Dow no. 4 kidney versus two Cordis Dow no. 4 kidneys after 1 g of cefazolin given intravenously.

Figure 4 illustrates the difference in the arterial and venous cefazolin serum concentrations studied in one patient. With one circuit through the dialysis unit, 47.2% of cefazolin was cleared by the dialyzer.

Results of Group III patients are shown in Table 3. These patients were given 1 g of cefazolin at the beginning of a 30-h peritoneal dialysis and the serum levels were assayed at 1, 15, and 30 h after the injection. Average concentration levels decreased at a fairly even rate with values of 70.5 μg/ml at 1 h to 37 μg/ml at 30 h. The serum half-life was 32.1 h. Only 19.3% of the initial dose was recovered in the dialysate.

DISCUSSION

The results of the present study suggest that the maintenance dose of cefazolin can be decreased in azotemia due to its increased half-life in patients with decreased renal function. Patients on hemodialysis will require an additional half dose after dialysis, since 46% of the drug is removed during 4 h of dialysis. Those on peritoneal dialysis do not require an extra dose, since little alteration in half-life is noted during dialysis. This data is in conformity with two previous studies (1, 4). The total urinary recovery of cefazolin in patients with moderate azotemia is well above the minimum inhibitory concentration of common susceptible urinary pathogens such as Escherichia coli, Klebsiella sp., and Proteus mirabilis.

The kinetics of the drug during dialysis may be altered by either reducing the surface area of the dialyzer or by reducing the dialysis time. This effect can be explained on the basis of the square meter hour hypothesis of Scribner and Maher (9), which states that the dialysis of substances with molecular weights ranging from 350 to 2,000, the so-called "middle" molecules, is related to the period of time of dialysis and/or to the membrane surface area. Cefazolin, with a molecular weight of approximately 500, falls into this category. Such substances achieve greatest removal with the usual dialysis membranes, either by increasing the time of dialysis or by increasing the membrane surface area on the dialyzer. On the other hand, removal of middle molecules is little affected by blood flow rate as are small molecules, such as creatinine and urea. The use of only three serum samples to describe the pharmacokinetics in the patients undergoing peritoneal dialysis is probably inadequate, but the results are similar to previously reported studies. The reason for the difference in recovery rate in patients undergoing hemodialysis and peritoneal dialysis (46%
with the former, and 20% with the latter) is not known and may represent alternate pathways of excretion. The results were obtained in this study after a single injection and may not apply to patients on continuous therapy with cefazolin.

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LITERATURE CITED