Cephalexin: Absorption and Excretion as Related to Renal Function and Hemodialysis

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Cephalexin is a new semisynthetic cephalosporin C derivative, which is well absorbed from the gastrointestinal tract and excreted in high concentration in the urine. Even in patients with impaired renal function, the concentrations of cephalexin present in the urine are adequate for the treatment of most urinary tract infections produced by Escherichia coli, Klebsiella, and Proteus mirabilis. In anephric patients, single doses of 250 or 500 mg of cephalexin resulted in high, prolonged serum concentrations. Peak levels were usually observed within 1 hr. However, in two of six anephric patients, peak levels were reached after 6 and 12 hr due to delayed absorption. Hemodialysis for 6 hr reduced the serum concentration of cephalexin by 58%.

Cephalexin, 7-(D-α-amino-α-phenylacetoxy)-3-methyl-3-cephem-4-carboxylic acid, is quite similar structurally to cephaloglycin, differing only in the removal of an acetoxy group (Fig. 1). This change has resulted in almost complete absorption from the gastrointestinal tract (4, 7). In contrast, the parent cephaloglycin is poorly absorbed. Cephalexin is excreted in active form in the urine. Urine concentrations of cephalexin many fold greater than the concentrations in serum can be achieved (7). Most strains of Escherichia coli, Proteus mirabilis, and Klebsiella (all frequent urinary tract pathogens) are inhibited by the increased concentration of cephalexin in the urine (6).

The present study was undertaken to determine the urine and serum concentrations of cephalexin in patients with impaired renal function and to evaluate the efficacy of hemodialysis in lowering the concentrations in serum in the anephric patient. In addition, a number of patients with renal transplants who had urinary tract infections were studied.

MATERIALS AND METHODS

Antibiotics. Cephalexin, supplied in powdered form (Eli Lilly Co., Indianapolis, Ind.), was freshly diluted in phosphate-buffered saline (pH 7.0) and used in all assay procedures. Volunteer subjects and patients were given 250- or 500-mg doses of cephalexin in gelatin capsules.

In vitro tests. Blood obtained from patients was allowed to clot, and the serum was harvested and stored at −20 C until assayed by the cylinder cup method of Grove and Randall (2) with Sarcina lutea as the test organism. Urine samples were passed through Seitz filters and stored at −20 C until assayed by serial twofold dilution. All specimens were assayed within 2 weeks of collection.

In vivo studies. Ten clinically well volunteers ingested 250 mg of cephalexin after an overnight fast. Blood samples were drawn aseptically just prior to and 1, 2, 4, 6, and 8 hr after oral administration. In addition, all urine voided over this 8-hr period was collected.

Three patients with endogenous creatinine clearances ranging from 18 to 40 ml/min were given 250 or 500 mg of cephalexin. Appropriate timed blood and urine samples were obtained over a 24-hr period.

Serum cephalexin levels in the absence of renal excretion were measured in six anephric patients undergoing chronic hemodialysis (twin coil Kolf Kidney, usual blood flow or 150 ml/min) who were given 250 or 500 mg of cephalexin 24 hr prior to dialysis. Blood samples were obtained just prior to dialysis and hourly for 6 hr during dialysis.

Clinical drug trial in urinary tract infections. Five renal transplant patients, all of whom had chronic urinary tract infections as documented by a urine colony count of greater than 10⁵ organisms per ml, were treated with 250 mg of cephalexin four times a day for 11 to 150 days, after in vitro sensitivity tests indicated that this drug might have a beneficial effect.

RESULTS

Absorption and renal excretion of cephalexin in normal subjects. After the 10 volunteers ingested 250 mg of cephalexin, the peak concentration in serum was observed at 1 hr. The mean level at
Adsorption and excretion of cephalixin in patients with impaired renal function. Three patients with endogenous creatinine clearances ranging from 18 to 40 ml/min were given 250 or 500 mg of cephalixin after an overnight fast (Table 1). Peak serum levels were just slightly higher than those of normal controls. However, a much slower decline in the serum levels of cephalixin was observed so that at 12 hr, and in one patient (G.S.) at 24 hr, an appreciable concentration of cephalixin remained. The concentration of cephalixin in urine collected over the first 8 hr ranged from 50 to 400 µg/ml and paralleled the endogenous creatinine clearance.

Serum levels of cephalixin in the anephric patient and effect of hemodialysis. Peak serum levels in the anephric patient were seen in 1 hr after oral administration (Fig. 2). After a short, rapid fall in the 2nd hr, the serum level remained elevated over the next 12 hr. In two patients, whose serum concentration of cephalixin 2 hr after oral ingestion was 4.5 and 4.3 µg/ml, peak levels of 17 and 11 µg/ml were reached at 6 and 12 hr, respectively. This accounted for the small secondary rise in the mean concentration of cephalixin in the group as a whole seen at 6 and 12 hr.

Hemodialysis proved to be an efficient procedure in lowering the serum cephalixin concentration. The mean predialysis concentration of cephalixin in the six anephric patients was 9.6 µg/ml (range, 5.5 to 17.5 µg/ml). After 6 hr of dialysis, this had been lowered to 4.0 µg/ml (range, 3.0 to 5.2 µg/ml), a mean reduction of 58%. Although dialysis was usually carried out for 8 hr, only two
patients had serum samples obtained at this time. These showed a reduction of 60 and 62% from the predialysis levels.

Clinical trial of cephalexin in patients with chronic urinary tract infections. All five patients studied had a functioning renal transplant and were receiving corticosteroids and azathioprine at the time of antibiotic therapy. In addition, most had relapsed or had not responded to previous antibiotic regimens. Cephalexin (250 mg, four times a day) was administered for 11 to 150 days (Table 2). Two of the five patients received a second course of cephalexin therapy. In only two of the five patients was the urine sterile 1 month after initial therapy was discontinued. The urine of a third patient (P.M.) was sterile 1 month after a second course of cephalexin was extended for 150 days. Failure to eradicate the original organism, relapse with the same organism, or superinfection were encountered after the first course of cephalexin therapy in three of the five patients.

**DISCUSSION**

Cephalexin is a new semisynthetic cephalosporin derivative with an antibacterial spectrum similar to cephalothin and cephaloridine (4, 6). Given by mouth, cephalexin was found to be absorbed well by healthy volunteers. Kind and coworkers (4) noted that the serum level of cephalexin after oral administration was similar to that achieved by cephaloridine and greater than that of cephalothin, when the latter two drugs were given intramuscularly in equal dosage.

Cephalexin is excreted well into the urine, with 81% of the oral dose recovered in 8 hr in normal subjects. Even in patients with creatinine clearances in the range of 18 to 40 ml/min, urine concentrations of cephalexin were in excess of the inhibitory concentrations reported for most strains of *E. coli*, *Klebsiella*, and *Proteus mirabilis*, recognized as frequent urinary tract pathogens (6).

In patients with diminished renal function, peak levels are not much higher than those reached in normal subjects; however, serum levels remain elevated with significant amounts present after a single oral dose at 12 and 24 hr. Similar results were reported by Kunin and Finkelberg, who also noted a modest cumulative effect after 8 days of cephalexin therapy (5).

In the anephric patient, peak serum levels of cephalexin were reached in 1 hr, followed by a short, rapid fall and then by a more gradual decline over the next 22 hr. A similar biphasic decay curve has been previously reported in a severely uremic patient with a creatinine clearance of 2.5 ml/min (5). It would appear that in the anephric patient one or possibly more extra renal pathways are available for the excretion or metabolism of cephalexin.

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**Table 1. Concentration of cephalexin in serum and urine after a single oral dose in patients with impaired renal function**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Creatinine clearance (ml/min)</th>
<th>Amt of cephalexin given (mg)</th>
<th>Conc in serum (µg/ml) at hr after administration</th>
<th>Conc in urine (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>C.V.</td>
<td>48</td>
<td>M</td>
<td>24</td>
<td>250</td>
<td>10.6</td>
<td>8.2</td>
</tr>
<tr>
<td>G.S.</td>
<td>21</td>
<td>M</td>
<td>18</td>
<td>250</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>R.N.</td>
<td>30</td>
<td>M</td>
<td>40</td>
<td>500</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

* Urine was collected for the first 8 hr.

**Table 2. Urinary tract infections treated with cephalexin**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Creatinine clearance (ml/min)</th>
<th>Urine culture (10³)</th>
<th>Duration of therapy (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.S.</td>
<td>27</td>
<td>M</td>
<td>100</td>
<td>Enterobacter</td>
<td>14</td>
<td>Superinfection by <em>Klebsiella</em></td>
</tr>
<tr>
<td>P.M.</td>
<td>33</td>
<td>F</td>
<td>18</td>
<td>Escherichia coli</td>
<td>18</td>
<td>Relapse, <em>E. coli</em></td>
</tr>
<tr>
<td>O.B.</td>
<td>61</td>
<td>F</td>
<td>58</td>
<td><em>E. coli</em></td>
<td>150</td>
<td>Negative culture 1 month post-therapy</td>
</tr>
<tr>
<td>C.V.</td>
<td>48</td>
<td>M</td>
<td>23</td>
<td><em>Klebsiella</em></td>
<td>14</td>
<td>Negative culture 1 month post-therapy</td>
</tr>
<tr>
<td>N.R.</td>
<td>30</td>
<td>M</td>
<td>40</td>
<td>Enterobacter</td>
<td>72</td>
<td>Failure to eradicate organism</td>
</tr>
</tbody>
</table>

* A 250-mg dose, four times daily.
Hemodialysis proved to be efficient in lowering the serum concentration of cephalaxin. Dialysis on the twin-coil Kolff kidney for 6 hr lowered the mean serum concentration 58%. This is similar to the results published by other workers (3).

In only two of five renal transplant patients with chronic urinary tract infections was the urine sterile 1 month after discontinuing cephalaxin therapy. Superinfection with another organism, relapse, or persistence of the same organism were all observed. Similar results in the treatment of urinary tract infections have been previously reported (1, 6). The drug was well tolerated by all patients, and no renal toxicity was noted.

Cephalexin appears to be a useful addition to the antibiotics currently available. It is absorbed well from the gastrointestinal tract and rapidly excreted by the kidneys. The resulting high urine concentrations of the drug, even in the patients with impaired renal function, are adequate for the treatment of many common urinary tract pathogens. So far, serious nephrotoxicity has not been reported.

ACKNOWLEDGMENTS

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LITERATURE CITED