Pharmacokinetics of Cefamandole in Patients with Normal and Impaired Renal Function

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The pharmacokinetics of cefamandole, a new cephalosporin antibiotic, is presently being clinically evaluated in the treatment of bacterial infections. It has several advantages over presently available cephalosporins. From in vitro laboratory studies, cefamandole appears to be active against a significant number of gram-negative bacteria, especially indole-positive Proteus strains that are resistant to other cephalosporins (2, 6, 11). Generally, the minimum inhibitory concentration values against susceptible gram-positive organisms are lower (0.03 to 1.0 μg/ml) than those for gram-negative strains (1 to 2 μg/ml). The drug has no effect against Pseudomonas aeruginosa minimum inhibitory concentrations > 128 μg/ml. However, cefamandole seems to be inferior to cefaloridine and cefazolin in the inhibition of α-hemolytic streptococci, pneumococci, and almost all strains of β-hemolytic streptococci (6, 8, 11).

The effectiveness of this drug is based on interference with the cell wall biosynthesis. Thus, it is only effective against proliferating cells. Similar to other cephalosporins, cefamandole is resistant to many penicillin-hydrolyzing β-lactamases produced by gram-positive as well as gram-negative bacteria (11). Cefamandole appears to have less renal toxic effects than cefaloridine and cefazolin (6).

The present study was designed to evaluate the pharmacokinetics of cefamandole in patients with normal and varying degrees of renal function impairment and urinary tract infection. Other clinical pharmacokinetic studies have also recently been published (3, 7).

MATERIALS AND METHODS

Twenty-three male patients from 32 to 88 years of age (average, 66 years) on a urological ward were treated for urinary tract infections with 1.5 to 3.0 g of cefamandole intramuscularly daily for 5 to 6 days. In five patients, the drug was administered prophylactically before and after instrumentation of the urinary tract. The drug was given at 8-h intervals to all but two patients who had severely impaired renal function. Fourteen patients had normal renal function (serum creatinine ≤ 1.5 mg/100 ml), and nine patients had impaired renal function (serum creatinine ≥ 1.6 mg/100 ml). After intramuscular injection on day 1 of treatment, blood samples were drawn for bioassay at 30, 60, 90, 120, 360 and 450 min. Urine was collected after the injection from 0 to 2, 2 to 4, and 4 to 7.5 h. In thirteen patients, this regimen was repeated on the last day of treatment. In eight of these patients, 1 g of probenecid was given orally every 2 h starting 0.5 h before the last injection on the last day of treatment. In eight patients with normal renal function, approximately 20 μCi of 125Ijodohippurate and 40 μCi of 131Ijodohippurate were injected intramuscularly along with cefamandole. The same blood and urine samples used for bioassays were also used for count-
ing radioactivity in a Gamma well counter. Iothalamate is excreted by the kidneys only by glomerular filtration and iothalamate clearance therefore represents the glomerular filtration rate (1), whereas hippurate is excreted by additional tubular secretion: the hippurate clearance thus represents the effective renal plasma flow (10). These two radioactive drugs, which conveniently can be counted simultaneously, served as additional evaluation of the renal function and as a standard to which the cefamandole could be compared. Creatinine clearances were also carried out in all patients.

Bioassays for determination of plasma and urine concentrations of cefamandole were carried out by a cup plate microbiological assay method using Bacillus subtilis (Difco 0453) as test organism on Penassay seed agar (Difco B263) and streptomycin assay agar (Difco 0277). Dilution of serum samples was carried out with pooled normal human serum, and the urine samples were diluted with phosphate buffer at pH 6. All standard curves were made up by diluting the standard antibiotic powder with human serum for the serum readings and with phosphate buffer for the urine readings and were made up simultaneously with the biological samples. No differences were found between standard curves obtained by dilution with urine and dilution with buffer. When equilibration had been reached after about 1 h after injection, a linear decrease could be seen when the serum concentrations were plotted against time on semilogarithmic paper. From this part of the curve, the linear regression line for the serum concentrations against time was determined by the method of the least squares. Half-life, plasma clearance, and renal clearance were calculated by well-established methods (4, 9). The renal clearances were based on the 2- to 4-h and 4- to 7.5-h urine values, and midpoint plasma concentrations were obtained by interpolation.

We determined protein binding in 30 serum samples from patients with normal and varying degrees of impaired renal function using equilibration dialysis for 36 h. After 36 h, antibiotic concentrations inside and outside the dialyzing cellophane bag were measured by the bioassay method, and protein binding was calculated (5).

Determinations of hemoglobin, leukocytes, serum creatinine, serum glutamic oxalacetic transaminase, alkaline phosphates, and serum bilirubin were carried out before drug treatment and after the study to determine whether cefamandole had toxic effects on the hematopoetic system, the liver, or the kidneys.

RESULTS AND DISCUSSION

Figures 1 and 2 show the serum levels of cefamandole after intramuscular injection of 0.5 and 1 g on day 1 of treatment. Cefamandole levels were higher in patients with impaired renal function during the first 6 h after injection, although the differences between these data and those obtained in normals were not statistically significant. This may be due to the small number of patients in this group. After 450 min, the patients with normal function had no measurable serum levels. After administration of 1 g of cefamandole, however, we found a statistically significant difference in serum levels between patients with normal and impaired renal function. The dosage intervals in two patients with severely impaired renal function and receiving 1 g of cefamandole were increased to 12 h, and we did not find accumula-
tion of the drug in any patient after multiple injections. There was no significant difference in serum levels in the two groups of patients 60 min after intramuscular injection of 1 g on the first and the last day of treatment (21 ± 4 versus 18 ± 3 µg/ml and 62 ± 10 versus 52 ± 22 µg/ml, respectively, in patients with normal and impaired renal function). Our dosage regimen for all patients, therefore, appeared to be correct since no accumulation of cefamandole occurred. Table 1 shows urinary excretion of cefamandole after 0.5 and 1 g on day 1 of treatment in patients with normal and impaired renal function. The excretion over a period of 7.5 h was significantly lowered in patients with impaired renal function.

Table 2 shows that the renal clearances of cefamandole significantly exceeded the creatinine clearances in patients with normal as well as impaired renal function. The ratios are significantly different from 1, suggesting active tubular secretion of cefamandole. Table 2 also shows the excretion and renal handling of cefamandole and iothalamate after intramuscular injection. The plasma and renal clearances for cefamandole were significantly higher in patients with normal renal function than in patients with impaired renal function. In all cases, the values for iothalamate were lower than those for the antibiotic. The ratios between the plasma and renal clearances for cefamandole and iothalamate are significantly different from 1 (Student's t-test).

### Table 1. Urinary excretion of cefamandole after intramuscular injection

<table>
<thead>
<tr>
<th>Dosage (g)</th>
<th>Patient group</th>
<th>Time (h)</th>
<th>% Excretion (range)</th>
<th>Conc range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Normal renal function</td>
<td>0-4</td>
<td>61 ± 13 (34-93)</td>
<td>450-2,950</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-7.5</td>
<td>10 ± 2.5 (6-17)</td>
<td>110-520</td>
</tr>
<tr>
<td>0.5</td>
<td>Impaired renal function</td>
<td>0-4</td>
<td>29 ± 5.9 (10-42)</td>
<td>430-3,110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-7.5</td>
<td>22 ± 2.5 (12-27)</td>
<td>470-1,220</td>
</tr>
<tr>
<td>1.0</td>
<td>Normal renal function</td>
<td>0-4</td>
<td>47 ± 7.6 (15-97)</td>
<td>600-5,150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-7.5</td>
<td>18 ± 2.7 (4-29)</td>
<td>270-1,470</td>
</tr>
<tr>
<td>1.0</td>
<td>Impaired renal function</td>
<td>0-4</td>
<td>27 ± 9.3 (9-41)</td>
<td>390-3,450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-7.5</td>
<td>13 ± 3.7 (8-20)</td>
<td>480-1,660</td>
</tr>
</tbody>
</table>

*Mean ± standard error.*
mandole and iothalamate were never significantly different from 1, indicating that both drugs are excreted exclusively by the kidneys. By comparing the renal clearances of cefamandole and iothalamate, we obtained an indicator of the renal handling of the antibiotic. The fact that the ratio of the renal clearances of cefamandole and iothalamate was significantly higher than 1 indicates that cefamandole, in addition to being excreted by glomerular filtration, is also secreted by the renal tubules. This is strongly supported by the inhibiting effect of the probenecid administration.

Table 3 shows that cefamandole and hippurate clearances were significantly lowered after probenecid administration. In addition, although the ratio of cefamandole to iothalamate renal clearances without probenecid was significantly higher than 1, the ratio decreased to 1.1 after probenecid treatment.

Since cefamandole is excreted almost exclusively by the kidneys, the dosage must be adjusted according to renal function. Figure 3 shows the correlation between serum creatinine and half-life of cefamandole after intramuscular injection in 22 patients. The half-life of the drug (Y) at a certain serum creatinine (X) can be calculated simply from the formula for the correlation of X and Y, which is Y = 0.85 + 0.91X. For clinical purposes it can be simplified to Y = 1 + X. Since the drug should be given about every third half-life, the dosage interval would be 3 × (1 + X). This means that for a patient with a creatinine of 1 mg/100 ml (or less) the dosage interval should be 3 × 2 = 6 h, the individual dose being 1 g. For a patient with a serum creatinine of, for example, 3 mg/100 ml, the dosage interval should be 3 × 4 = 12 h. If one wants to avoid the wide variations of serum levels following such a dosage regimen, this may be done by giving one-third of the usual dosage every half-life. In both groups of patients we gave 0.5 as well as 1 g of cefamandole with a dosage interval of 8 h, except in two patients with severely impaired renal function, who received an injection every 12 h. The dosage regimen of 0.5 g of cefamandole every 8 h appears to be too low for patients with normal renal function, since we found very low serum concentrations after 6 and 8 h after the intramuscular administration. Therefore, we recommend a dose of 1 g every 6 h in patients with normal renal function and adjustment of the dosage according to the renal function in patients with renal failure (Fig. 3).

In 8 patients we found that cefamandole had a protein binding in serum of 32 ± 11% (mean ± standard error) (range, 17 to 58%). There was no significant difference in this respect between patients with normal and impaired renal function. In addition, the protein binding did not depend on the concentration of antibiotic (between 5 and 40 µg/ml).

We did not find toxic effects of cefamandole on the hematopoietic system, liver, or kidneys based on the tests evaluated.

**Table 3. Clearance of cefamandole, hippurate, and iothalamate in eight patients with normal renal function before and after administration of probenecid**

<table>
<thead>
<tr>
<th>Time</th>
<th>Cefamandole renal clearance (ml/min/1.72 m²)</th>
<th>Iothalamate renal clearance (ml/min/1.72 m²)</th>
<th>Ratio: cefamandole/iothalamate renal clearance</th>
<th>Hippurate renal clearance (ml/min/1.72 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before probenecid</td>
<td>302 ± 60</td>
<td>89 ± 14</td>
<td>3.4 ± 0.6b</td>
<td>308 ± 44</td>
</tr>
<tr>
<td></td>
<td>(77–527)</td>
<td>(35–154)</td>
<td>(2.2–7.1)</td>
<td>(166–467)</td>
</tr>
<tr>
<td>After probenecid</td>
<td>80 ± 14</td>
<td>71 ± 8</td>
<td>1.1 ± 0.1</td>
<td>202 ± 22</td>
</tr>
<tr>
<td></td>
<td>(26–157)</td>
<td>(33–102)</td>
<td>(0.8–1.6)</td>
<td>(132–296)</td>
</tr>
</tbody>
</table>

* Mean ± standard error (range).

* Value significantly different from 1 (Student's t test).
LITERATURE CITED


