Ceftazidime in the Treatment of Pediatric Patients with Severe Urinary Tract Infections Due to *Pseudomonas* spp.

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Fifteen pediatric patients with complicated urinary tract infections due to *Pseudomonas* spp. were treated for 10 to 18.5 days with ceftazidime administered intramuscularly twice daily. Urine sterilization during therapy was obtained in all patients. Three patients had relapses which were cured with a second course of ceftazidime. Minor liver damage, eosinophilia, and *Candida* superinfection developed in one patient each.

In 1983 several urinary tract infections (UTI) due to *Pseudomonas* spp. developed among children with urological disorders hospitalized in our clinic. Primary infection with this organism is uncommon (8). *Pseudomonas* spp. may easily enter the urinary tract when catheters are introduced for diagnostic or therapeutic reasons or as a consequence of inappropriate antibiotic prophylaxis (5). Most of our patients required pyelostomy, urethral splints, or suprapubic cystostomy during the postsurgical period, and they were treated with cefazolin. The bacterial isolates obtained were resistant in vitro to many beta-lactam and aminoglycoside antibiotics, and five patients failed to respond to therapy with appropriate doses of gentamicin, amikacin, or cefitoxime despite the fact that these antibiotics were initially active in vitro against the infecting organisms. It was therefore decided to undertake an open trial with ceftazidime, a new beta-lactam antibiotic with elevated anti-*Pseudomonas* activity (6, 11). Since ceftazidime is an investigational drug in Italy, informed consent was obtained from the parents of all patients.

A total of 15 patients, 5 males and 10 females, with a mean age of 3.1 years (range, 0.1 to 13 years) were treated for 16 infectious episodes. One patient received two courses of ceftazidime therapy with an interval of 2 months. Urine cultures obtained between the two courses of therapy were sterile. In 14 cases UTI developed after surgical treatment for various urological abnormalities (10 cases of grade III to IV vesicoureteral reflux, 6 of hydronephrosis, 1 of ureteropelvic junction obstruction, 1 of prune belly syndrome, 1 of hypospasia, 1 of nephrolithiasis, 1 of duplicated kidney and collecting systems). Two patients suffering from neurogenic bladders became infected while undergoing clean intermittent catheterization. A diagnosis of infection was based in each case on the presence of bacteriuria at ≥10³ CFU/ml in at least two consecutive urine samples obtained by bladder or ureteral catheterization or pyelostomy. In four patients a diagnosis of upper UTI was made in the presence of bacteriuria at ≥10³ CFU/ml in urine obtained by direct ureteral catheterization or pyelostomy (10). An erythrosedimentation rate of ≥25 mm/h or a C-reactive protein concentration in serum of ≥20 μg/ml or both were present in these patients and in 10 other patients in whom the site of infection was not diagnosed by direct methods. A fever of ≥38°C was present in five cases. In two cases none of these parameters was present.

The bacteria isolated from all of the patients were susceptible to ceftazidime when tested by the disk diffusion method. The MICs of ceftazidime and other beta-lactam and aminoglycoside antibiotics were determined by the two-fold agar dilution technique. Each plate was inoculated with a final bacterial test population of 10⁵ CFU/ml from an overnight Mueller-Hinton broth (Difco Laboratories) culture and incubated for 18 h at 37°C (12). Ceftazidime was administered intramuscularly at a mean daily dose of 95.6 mg/kg per day (range, 87.4 to 111.1) at 12-h intervals for 12 days (range, 10 to 18.5 days). One patient with chronic renal failure (glomerular filtration rate, 18 ml/min per 1.73 m²) received a single daily dose of 33 mg/kg for 13 days. Efficacy of treatment was evaluated from urine cultures performed every 2 to 3 days until sterilization was confirmed by two consecutive urine cultures. Further cultures were obtained 3 to 7 days and 3 to 4 weeks after treatment was completed. The erythrosedimentation rate and the C-reactive protein concentration in serum were determined on days 3 to 5 and at the end of treatment. Each patient was examined daily for evidence of adverse clinical effects, and in addition, liver (serum glutamic oxalacetic transaminase [SGOT], serum glutamic pyruvic transaminase, alkaline phosphatase, and total bilirubin) and renal (blood urea nitrogen, serum creatinine, and urinalysis) function tests and complete blood counts were made before and at the end of therapy.

The susceptibility of bacteria isolated to some beta-lactam and aminoglycoside antibiotics is shown in Table 1. Two of four *Pseudomonas maltophilia* isolates were resistant to all of the antibiotics tested except ceftazidime. The other two isolates were only susceptible to ceftazidime and amikacin. The activity of ceftazidime against *Pseudomonas aeruginosa* was superior to that of the other cephalosporins and aminoglycosides tested, although amikacin also showed good activity.

A prompt bacteriological response to ceftazidime was obtained in 10 patients, whereas in 6 other patients the fall in bacterial count was slower (Fig. 1). In 13 cases, permanent urine sterilization was obtained. In three of the six patients who responded more slowly, UTI recurred within 1 week. These patients were three infants (aged 7, 9.5 and 10.5 months) who underwent bilateral ureteral transplantation for vesicoureteral reflux (degree IV according to Smellie et al. [9]) 10 to 12 days earlier. Indwelling ureteral catheters were used after surgery to avoid possible obstruction by circumventing the effect of edema at the orifice. In each case catheters were withdrawn before ceftazidime therapy. The bacteria (*Pseudomonas maltophilia*) causing the relapse showed the same in vitro susceptibility as the
The urine samples of patients treated with Pseudomonas spp. were analyzed to determine the geometric mean of MICs (µg/ml) for different drugs. As shown in Table 1, Ceftazidime, Cefotaxime, and Tobramycin had lower MICs for P. aeruginosa and P. maltophilia compared to other drugs. Piperacillin, Amikacin, and Nettimicin had higher MICs for these bacteria.

**Table 1: Comparative activity of different antibiotics against Pseudomonas spp. a isolated from infants and children with UTI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>P. aeruginosa</th>
<th>P. maltophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>1.6 (1–4)b</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>20.1 (8–64)</td>
<td>38.05 (16–64)</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>9.33 (4–64)</td>
<td>&gt;64b</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>9.33 (4–64)</td>
<td>&gt;64b</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2.72 (1–64)</td>
<td>&gt;64b</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1.71 (0.5–64)</td>
<td>&gt;64b</td>
</tr>
<tr>
<td>Amikacin</td>
<td>2.72 (2–8)</td>
<td>19.02 (8–64)</td>
</tr>
<tr>
<td>Nettimicin</td>
<td>5.44 (2–64)</td>
<td>&gt;64b</td>
</tr>
</tbody>
</table>

a P. aeruginosa, 12 isolates; P. maltophilia, 4 isolates.
b Numbers in parentheses represent ranges.
c MIC found for all isolates.

Initial infecting strains. For these three patients, MICs were 2, 4, and 2 µg/ml for ceftazidime, 8, 8, and 64 µg/ml for amikacin, and ≥64 µg/ml for the other antibiotics tested; therapy with ceftazidime was reinstituted for 10 more days. The urine samples were sterile within 3 days (two cases) and 6 days (one case), and definite cure was obtained.

When initially elevated, the erythrocytesedimentation rate and the C-reactive protein concentration returned to within the normal range by the end of therapy in all patients. Elevation of serum enzymes (SGOT, serum glutamic pyruvic transaminase, and alkaline phosphatase) was noticed in three patients. Two patients displayed slight elevation of a single enzyme (SGOT in one case and alkaline phosphatase in the other) which returned to normal values within 2 weeks. Both SGOT and serum glutamic pyruvic transaminase were raised in one patient (1.5 months old) from 35 IU/liter to 91 IU/liter and from 14 IU/liter to 61 IU/liter, respectively, and decreased slightly 2 weeks later. After treatment with ceftazidime, this patient was treated with nitrofurantoin (2.2 mg/kg per day) for 1 month. At day 36 after treatment had been stopped, this patient developed mild anicteric hepatitis. Serological tests for hepatitis A and B were normal. The patient had received a blood transfusion 40 days before, and a diagnosis of non-A non-B infectious hepatitis was suggested.

Drug-induced hepatitis (due to either ceftazidime or nitrofurantoin) could not, however, be ruled out. Elevation of eosinophils (from 156 to 702/mm³) was seen in one patient during ceftazidime treatment. During the last 2 days of therapy, one patient developed moderate anaphylaxis. *Candida albicans* was isolated from his feces and urine.

The microbiological and clinical results obtained in this trial confirm the good activity of ceftazidime against *Pseudomonas* spp., including aminoglycoside-resistant isolates (2, 7). One-third of our patients had already been treated with other antibiotics which failed to sterilize urine and induced bacterial resistance. The response to ceftazidime therapy was quite slow in 6 of 16 patients, and a relapse occurred in 3 patients despite the fact that the bacteria remained susceptible to the drug in vitro. In five of the six patients who responded more slowly, at least one of the following factors was associated with a delayed response to ceftazidime: (i) the upper localization of the infection in the urinary tract and (ii) the presence of *Pseudomonas maltophilia* as an infecting agent. More prolonged treatment or higher dosages of ceftazidime might be warranted under these conditions. In fact, prolongation of the therapy with the same drug allowed definite remission. Ceftazidime was well tolerated. The only patient who developed *Candida* enteritis and cystitis was seriously ill and had already been treated with other antibiotics. A transient elevation of SGOT after therapy with beta-lactam antibiotics has been reported in several studies both in adult and pediatric patients and has been related to muscle damage at the injection site (1, 4). In our experience with patients with cystic fibrosis, ceftazidime, even at high dosages, never raised these enzymes when administered intravenously (7). The elevation of alkaline phosphatase or serum glutamic pyruvic transaminase in two cases should be considered indicative of minor liver damage, probably induced from the study drug. The relation between hepatitis and the use of ceftazidime in one case was not proven.

In conclusion, this study confirms previous results (2, 3, 7) on the possible use of ceftazidime as an alternative to aminoglycosides in the treatment of multiresistant *Pseudomonas* infections. We think, however, that further data are needed concerning the safety of this and other new beta-lactam antibiotics for use in the small, seriously ill infant.

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**LITERATURE CITED**

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