Aztrenam in the Treatment of Severe Urinary Tract Infections in Pediatric Patients

FRANCA RUSCONI,1* BAROUKH M. ASSAEL,1 ANTONIO BOCCAZZI,1 ROSARIA COLOMBO,2 ROSELLA M. CROSSIGNANI,1 LAURA GARLASCHI,2 AND LAURA RANCILIO1

Department of Pediatrics 2, University of Milan,1 and Department of Microbiology, Istituti Clinici di Perfezionamento,2 Milan 20122, Italy

Received 7 October 1985/Accepted 8 May 1986

Aztrenam was administered to 30 patients, ages 0.03 to 15.4 years, with severe and in 21 cases complicated urinary tract infections caused by members of the family Enterobacteriaceae and Pseudomonas aeruginosa which were resistant to ampicillin and susceptible to the study drug in vitro. A mean dose of 47.7 mg/kg was given intramuscularly every 12 h to 26 patients. In four patients with renal insufficiency, the dose was reduced according to pharmaco-kinetic data. Permanent urine sterilization and clinical cure were achieved in 22 patients, 13 of whom had urological malformations. In two patients with P. aeruginosaa and Proteus mirabilis infections, the treatment failed. Another patient had an Escherichia coli reinfection 21 days after the end of therapy. Four patients with various urological abnormalities had gram-positive superinfections, and two patients had gram-negative superinfections during and at the end of therapy: all six had indwelling ureteric splints or pyelostomy as predisposing conditions. No adverse clinical effects were observed. Some transient and slight or moderate alterations were observed at the end of treatment: eosinophilia (nine cases), elevation of hepatic enzymes (eight cases), prolongation of prothrombin time (three cases), and neutropenia (one case). A pharmacokinetic study was performed in six patients with normal renal function and in seven patients with various degrees of renal insufficiency. The elimination half-life of the drug was inversely correlated with the glomerular filtration rate. At the dosage used, aztrenam proved effective for severe urinary tract infections caused by members of the family Enterobacteriaceae in pediatric patients.

Aztrenam is the first monobactam antibiotic to undergo clinical trials in humans. It inhibits most of the members of the family Enterobacteriaceae at concentrations of <1 μg/ml and also has significant activity against Pseudomonas aeruginosaa but exhibits little or no activity against gram-positive bacteria and anaerobes (10, 29). Aztrenam possesses a high degree of resistance to enzymatic hydrolysis by most of the common chromosomal and plasmid-mediated beta-lactamases (16). Its limited spectrum of activity therefore gives physicians the possibility of aiming treatment at specific organisms while reducing the risk of gastrointestinal disturbances by leaving the normal anaerobic and gram-positive flora undisturbed. In adults, 1 or 2 g of aztrenam given intravenously (i.v.) produces effective serum concentrations for 8 to 12 h; the drug is primarily excreted in the urine (28). Aztrenam has been evaluated in the treatment of serious gram-negative infections in adult patients (6, 8, 20, 23), whereas no data are available so far on its clinical efficacy and safety in pediatric patients.

We studied the bacteriological and clinical efficacy and safety of aztrenam in 30 pediatric patients with severe urinary tract infections (UTIs) caused by bacteria which were resistant to ampicillin and susceptible in vitro to the study drug. Because these infections often appear in patients with renal insufficiency, we also obtained pharmaco-kinetic data in 13 patients with different degrees of renal function to better define aztrenam dosage schedules in this kind of patient.

MATERIALS AND METHODS

Patients. The study population consisted of 30 patients, 16 males and 14 females, with a mean age of 4.2 years (range, 0.03 to 15.4 years). Underlying urological abnormalities (12 cases of hydronephrosis, 9 of grade III to IV vesico-ureteral reflux, 3 of uretero-pelvic junction obstruction, 2 of spastic neurogenic bladder, and 5 cases of other multiple abnormalities of the urinary tract) were present in 21 patients of whom 10 had surgical treatment for their urological abnormalities in the previous 2 weeks. One patient had renal calculi. According to the normal values for age given by Goldsmith (7), 13 patients had renal failure, mild in 6, moderate in 5, and severe in 2 (creatinine clearance, 50 to 80, 30 to 50, and <30 ml/min per 1.73 m², respectively). In patients <13 years old, glomerular filtration rate was estimated from plasma creatinine concentration and body length by using two different formulas for patients who were <1 year and >1 year old (24, 25). Seven patients had been previously treated for the same infection in another hospital with appropriate doses (one case each) of co-trimoxazole, ampicillin, cefotaxime, piperacillin, gentamicin, amikacin, and netilmicin. These antibiotics were reported to be initially active in vitro against the infecting organisms. We discontinued them after at least 6 days because of microbiological failure (bacteriuria > 10⁵ CFU/ml and the development in 6 of 7 cases of in vitro resistance to the drug as determined by Kirby-Bauer criteria). Before aztrenam treatment, seven other patients received co-trimoxazole and six received ampicillin as prophylactic antibiotics; in these cases, also, the pathogens were
TABLE 1. Microbiological results

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of patients with positive urinary cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before therapy</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
</tr>
<tr>
<td>E. coli</td>
<td>16</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>3</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>2</td>
</tr>
<tr>
<td>C. freundii</td>
<td>1</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>2</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>3</td>
</tr>
<tr>
<td>E. coli plus</td>
<td>1</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>2</td>
</tr>
<tr>
<td>E. coli plus</td>
<td>1</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>2</td>
</tr>
</tbody>
</table>

*a* Staphylococcal superinfection.
b* Enterococcal superinfection.
c* P. aeruginosa superinfection.
d* K. pneumoniae superinfection.

resistant to the drug used. The remaining patients received no antibiotic treatment during the previous month.

Diagnosis of infection was based on the presence of bacteruria (>10^5 CFU/ml) in two consecutive urine samples, obtained by bladder or ureteral catheterization or pyelostomy. In nine patients, a diagnosis of upper UTI was made by direct methods (presence of bacteriuria of >10^6 CFU/ml in urine obtained by ureteral catheterization or pyelostomy [26]). Laboratory findings suggesting upper localization of the infection (erythrocyte sedimentation rate of >25 mm/1 h, C-reactive protein concentration of >20 μg/ml and a fever of >38°C) (11) were present in 10 other patients.

**In vitro susceptibility tests.** Bacteria isolated from all the patients were identified by the Minitek system (BBL Microbiology Systems, Cockeysville, Md.) and were tested before therapy was started for their susceptibility to aztreonam by the disk diffusion method (Kirby-Bauer). Subsequently, the MIC of aztreonam was evaluated and compared with that of cefotaxime, ceftriaxone, cefazidime, gentamicin, and amikacin. MICs were determined by a microdilution method in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) supplemented with CaCl_2 (50 mg/liter) and MgCl_2 (25 mg/liter) with an inoculum of 10^5 CFU/ml (5).

**Drug dosage and duration of therapy.** A mean daily dose of 47.7 mg/kg (range, 32.4 to 63.5) of aztreonam was given intramuscularly at 12-h intervals. In four patients with moderate or severe renal failure (creatinine clearance, 21.7 to 51.7 ml/min per 1.73 m²) the interval between administrations was 18 to 24 h. The mean duration of therapy was 12 days (range, 10 to 16 days). In the patients in whom serum and urine pharmacokinetics were studied, the first dose of the drug was given i.v., and blood and urine samples were collected afterwards.

**Clinical and microbiological evaluation.** The efficacy of the treatment was evaluated by urine cultures every 2 or 3 days until sterilization, by erythrocyte sedimentation and C-reactive protein serum concentrations determined on day 4 or 5 and at the end of treatment, and by the daily temperature patterns and clinical symptoms. Follow-up urine cultures were obtained 1 to 3 days, 5 to 10 days, and 20 to 30 days after treatment was completed. Each patient was examined daily for evidence of adverse clinical effects; in addition, we performed liver function tests (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, and total bilirubin), renal function tests (blood urea nitrogen, serum creatinine, and urinalysis), complete blood counts, platelet counts, prothrombin times, and partial thromboplastin times before and at the end of therapy. Any laboratory test yielding abnormal values that could possibly be attributed to the study drug was repeated until the values returned to normal.

**Pharmacokinetics.** The pharmacokinetics of aztreonam were studied in 13 patients, 5 infants (18 days to 1.1 years), and 8 children (2.6 to 15.4 years) after a dose given i.v. Six patients had normal renal function, and one patient had mild, five patients had moderate, and one patient had severe renal insufficiency. Since most of our patients were very young, only a limited number of blood samples could be obtained. The disappearance of aztreonam from the blood has been reported to follow a biexponential decay after i.v. administration in adults, with the elimination phase starting approximately 60 min after dosing (18, 28). We thus decided to focus on the terminal elimination phase to calculate the elimination half-life (t_1/2b), a useful parameter in establishing therapeutic drug regimens. Blood samples were collected in infants by capillary puncture of the heel 1, 3, 6, 9, and 12 h after drug administration and in children from an antecubital vein 1, 2, 4, 6, 8, 10, and 12 h after drug administration. The data were fitted by least-squares linear regression analysis according to the formula log (concentration) = Ae^-t/b, and the elimination half-life was given by 0.693/a. In five patients, timed urinary collections were obtained from 0 to 12 h after aztreonam administration. Serum and urine samples were kept frozen at −20°C until analysis. Aztreonam concentrations in serum were determined within 1 week by the microbiological agar diffusion method with Escherichia coli SC 12155 as a test organism and nutrient agar (Difco) as the medium. Parental informed consent was obtained before the study.

**RESULTS**

**In vitro susceptibility.** The pathogens isolated were E. coli (19 cases), Klebsiella pneumoniae (4 cases), Enterobacter spp. (2 cases), Proteus mirabilis (2 cases), Citrobacter freundii (1 case), and P. aeruginosa (5 cases). They were all susceptible (inhibition zone, ≥22 mm) to aztreonam when tested by the disk diffusion method. When MICs were tested, one Enterobacter cloacae and three P. aeruginosa strains were actually resistant (MIC = 32 μg/ml) and intermediately resistant (MIC = 16 μg/ml), respectively, to aztreonam. The mean geometric MIC for aztreonam against the other members of Enterobacteriaceae was 0.11 μg/ml (range, <0.03 to 0.25), whereas MICs against the other two P. aeruginosa strains were 2 and 8 μg/ml. The MICs of the other beta-lactam antibiotics tested (ceftazidime, ceftriaxone, and ceftizoxime) were similar to that of aztreonam. Aztreonam was also active against three strains (two E. coli and one Enterobacter agglomerans) resistant to gentamicin.

**Microbiological and clinical outcome.** Urine sterilization from the initial infecting strain was obtained by day 3 or 4 of therapy in 26 of 30 patients (Table 1). Urine was sterile only by day 6 of therapy in four cases, three infected with P. aeruginosa. In one of these three, in which the P. aeruginosa strain had intermediate susceptibility to aztreonam in vitro, urine sterilization was only transient; a bacterial count of 10^9 CFU/ml was again found after 7 days of therapy, and the drug was therefore withdrawn. This patient had grade IV vesico-ureteral reflux and had been previously treated with amikacin for the same infection. After aztreonam failure, she was successfully treated with ceftazidime. In the other two
patients, *P. aeruginosa* isolates were susceptible to aztreonam in vitro (MIC = 2 and 8 µg/ml). The first, with a mixed infection, had been previously treated surgically for intrabladder ureteral stricture and vaginal atresia but still had incomplete urinary voiding. This could possibly have contributed to a slow sterilization of both *P. aeruginosa* and *E. coli* bacteriuria. The second patient was oliguric and developed *P. aeruginosa* UTI because of a permanent bladder catheter. He had no urological abnormality. The renal insufficiency was resolved before aztreonam treatment. A relapse occurred within 1 week in one patient with renal calculi who was infected with a strain of *P. mirabilis*. Another patient had a reinfection 21 days after the end of therapy with an *E. coli* strain which had an in vitro susceptibility different from that of the initial infecting strain. Three patients experienced enterococcal superinfections and one patient experienced staphylococcal superinfection while being treated with aztreonam; penicillin V and dicloxacillin, respectively, were administered concurrently. Two other patients were reinfected within 1 week with strains of *K. pneumoniae* and *P. aeruginosa* that were resistant in vitro to the drug. They were successfully treated with cefotaxime and ceftazidime, respectively.

All the patients with superinfections had indwelling ureteric splints catheters or pyelostomy. Defervescence, clinical improvement, and normalization of erythrocyte sedimentation rate and of C-reactive protein serum concentrations were rapidly obtained in all patients with permanent urine sterilization. In three of six cases, superinfection was symptomatic and in five of six cases, there was a rise in erythrocyte sedimentation rate and C-reactive protein serum concentrations.

Safety. No adverse clinical effects were observed. Nine patients presented eosinophilia (>250 mm<sup>3</sup>). Slight or moderate (1.5 to 3 times the upper limit of normal) elevation of serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase or lactic dehydrogenase occurred in six patients. Two other patients had a moderate elevation of alkaline phosphatase. Slight prolongation of prothrombin time was observed in three patients. One patient had neutropenia (957 neutrophils per mm<sup>3</sup>). All these abnormalities returned to the normal range within 2 weeks.

**Pharmacokinetics.** The calculated $t_{1/2}$ values in the 60-min to 12-h interval after drug administration correlated inversely with renal function, with progressive prolongation of aztreonam elimination from 1 h in subjects with normal renal function to 3 h in patients with creatinine clearance <30 ml/min per 1.73 m<sup>2</sup> (Fig. 1). Regression analysis of the two variables yielded the following equation: $y = 0.004 x + 169.056$; ($y$ = serum concentrations in µg/ml; $x$ = time in hours) with a linear correlation coefficient ($r$) of 0.8.

Serum concentrations above the mean geometric MICs for *Enterobacteriaceae* isolates (0.11 µg/ml) were maintained up to the eighth hour in all patients, but MICs for *P. aeruginosa* isolates (9.2 µg/ml) were only exceeded for 2 h. Ten to twelve h after administration, mean urinary aztreonam levels (38 µg/ml) were 350 times higher than the mean MICs for members of *Enterobacteriaceae* but were only 4 times higher than mean MICs for *P. aeruginosa* strains (Fig. 2).

**DISCUSSION**

The choice of an effective and safe antibiotic is often a major problem in patients with recurrent UTIs and severe urological abnormalities, in whom infections are mostly sustained by multiresistant bacteria (15, 31). Aminoglycosides were used previously as first-choice antibiotics in such patients (31). However, hospital-acquired pathogens are sometimes resistant to these antibiotics (17, 19). Furthermore, the concomitant presence of renal failure in patients with severe urological abnormalities often makes it difficult to use this kind of drug. In the last 2 years we successfully treated such infections with new beta-lactam agents (ceftizoxime and ceftazidime) (21, 22). We have also shown

The microbiological and clinical results obtained in this study confirm our previous in vitro data. This is particularly interesting when it is considered that 7 of the 30 patients had already been treated with other antibiotics which failed to sterilize urine and that most patients were severely ill. A relapse occurred during the follow-up period in one child with renal calculus. However, the rate of failures and of relapses expected in this kind of patient is very high (14). The results obtained in patients with UTIs sustained by P. aeruginosa were less satisfactory. This was possibly due to the low dosages used. In adult patients with P. aeruginosa UTIs, failures or relapses were commonly seen when aztreonam was given at a dose of 2 g or less per day (9). Calculating the doses administered to our patients by body surface area instead of by kilogram of body weight, all children with P. aeruginosa UTI were given a dose <2 g/1.73 m². The reason that higher concentrations might be needed in P. aeruginosa infections deserves consideration. Eng et al. (2) recently demonstrated a large inoculum effect and a poor bactericidal activity for aztreonam as well as for other beta-lactam antibiotics against P. aeruginosa. Since most infected urine contain bacteria at a higher density than 10⁵ CFU/ml, it may be hypothesized that even if antibiotic concentrations in the urine are high they may in some cases be insufficient to inhibit bacterial multiplication or kill the bacteria.

Aztreonam pharmacokinetic data in pediatric patients with normal renal function were recently reported by Stutman et al. (27). In patients 1 month to 12 years old, the serum elimination half-life was similar to that found in adult patients (1.7 h) (28). In our children with normal renal function, the drug disappeared from the serum faster (t₁/₂β = 1.1 h). We have no explanation for such discrepancies, but it should be noted that t₁/₂β for most beta-lactams has been found to be shorter in pediatric than in adult populations (13, 22, 30). As expected, and as previously seen in adults (3, 18), the t₁/₂β value for aztreonam was increased in patients with renal impairment. In patients with moderate or severe renal failure, aztreonam concentrations in serum were still detectable 18 to 36 h after administration. Based on these data, the dose interval should be lengthened in these patients. Aztreonam was well tolerated. Hematologic and biochemical side effects in our patients were similar to those described in adult patients treated with the drug (8, 20, 23) and in pediatric patients treated with other new beta-lactam antibiotics (1, 4, 12, 21, 22). Thus, it seems reasonably safe to use aztreonam also in severely ill patients and in patients with renal failure.

The percentage of superinfections (8, 20, 23) we found during and at the end of aztreonam treatment was also similar to that reported in comparable clinical trials in adults. Superinfections, mostly by gram-positive bacteria, were almost exclusively restricted to immunocompromised patients or to those with predisposing conditions (8, 23).

In conclusion, these data suggest a significant clinical potential for aztreonam in the treatment of severe UTIs caused by multiresistant members of Enterobacteriaceae in pediatric populations. In patients with predisposing conditions, however, superinfections with resistant bacteria should be carefully monitored.

ACKNOWLEDGMENT

This work was supported in part by a grant from Squibb S.p.a.-Italia.

LITERATURE CITED

18. Mihindu, J. C. L., W. M. Scheld, N. D. Bolton, D. A. Spyker,


