Aztrenon Treatment of Gram-Negative Septicemia

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Seventy-five aztreonam treatment courses in 74 patients with gram-negative septicemia resulted in 56 clinical cures (75%), 12 partial clinical cures (16%), and 7 clinical failures (9%). Eradication of the original pathogen from the blood was obtained in all patients but two, who had relapses 1 and 4 days, respectively, after treatment. In nine patients (12%) a superinfection was reported. Significant adverse reactions were limited to one transient urticarial rash. Aztrenon may prove to be an effective alternative for the treatment of gram-negative septicemia, but superinfections should be carefully monitored.

Gram-negative septicemia remains a serious condition, especially in patients with underlying disease and impaired host defenses. New molecules such as the monobactams could be an alternative to combination treatment, including aminoglycosides, which are associated with a high risk of toxicity in these patients who are often exposed to other risks of nephro- or ototoxicity. Aztrenon is the first monobactam to be investigated clinically (7, 8). Its activity is only directed against gram-negative aerobic organisms and is comparable to that of broad-spectrum cephalosporins on members of the family Enterobacteriaceae and Pseudomonas aeruginosa (3–5, 10). We present here the results of an open clinical study of aztreonam therapy in 79 patients with bacteriologically proven septicemia due to gram-negative rods.

A total of 44 patients were hospitalized in the Akademisch Ziekenhuis, Vrije Universiteit Brussel, and 35 were hospitalized in the Algemeen Ziekenhuis Sint Jan, Bruges. The study protocol was approved by the ethical committees of both hospitals, and all patients gave informed consent. Criteria for exclusion were negative pretreatment blood cultures, a history of hypersensitivity to beta-lactam antibiotics, pregnancy or lactation, a neutrophil count lower than 1,000/mm3, and antibiotic treatment within the previous 72 h (except when the causative organism proved to be resistant to the antibiotic used). Four patients were not assessed because of death unrelated to the infection between days 3 and 5 of aztreonam treatment. An additional patient was not evaluable because aztreonam therapy had to be stopped after the first injection because of a side effect (see below).

The 74 evaluable patients included in this study comprised 40 men and 34 women from 16 to 88 years of age (mean, 65.3 years). One patient was treated for two successive episodes of septicemia. Three patients were in frank shock and three were hypotensive before treatment was started. Many patients were severely debilitated by underlying conditions, with the most frequent being malignant disease (15 patients), diabetes mellitus (12 patients), neurological disorders (11 patients), corticosteroid therapy (5 patients), and major trauma (4 patients). In 15 patients treatment was started within 2 weeks of some surgical procedure. Aztrenon was administered intravenously as a 30-min infusion in 66 of the 75 treatment courses and by intramuscular injection in the remaining 9. The standard dosage regimen used was 2 g every 12 h in Brussels and 1 g every 8 h in Bruges. Two grams every 8 h was administered to three severely ill patients. In seven patients with severe renal insufficiency, the dose was cut by half, and in two patients on maintenance hemodialysis the dosage was 0.25 g every 8 h, supplemented after each dialysis by 0.25 g. The duration of treatment ranged from 5 to 18 days (mean, 9.5 days), and the total dose administered was from 8.25 to 72 g (mean, 31.7 g).

In only three patients was another antibiotic administered concomitantly: clindamycin in two patients and fluoroxyacin in one patient.

In Table 1 are listed the 82 aerobic gram-negative rods isolated from the blood. Table 2 lists the overall clinical and microbiological results of the treatments. A total of 75 treatment courses in 74 patients resulted in 56 (75%) clinical cures (complete resolution of signs and symptoms of infection), 12 (16%) partial clinical cures (substantial or temporary improvement in signs and symptoms without complete resolution), and 7 (9%) clinical failures (persistence or progression in signs and symptoms of infection). Details on clinical failure are shown in Table 3. Two patients in this group fully responded to treatment after the addition of an aminoglycoside, possibly pointing to a synergistic effect between aminoglycosides and aztreonam, as reported by others (9). Eradication of the original pathogen from the blood during therapy was obtained in all cases, but a relapse occurred in two patients (3%) 1 and 4 days, respectively, after completion of treatment. In two patients rated as having been clinically cured, the original pathogen persisted asymptomatically at the primary site of infection: the urinary tract in one and a duodenal fistula in the other.

We observed nine superinfections (septicemia with an organism that was different from the original isolate), corresponding to 12% of the treatment courses, leading to death in three patients. Superinfections occurred during aztreonam therapy (days 2 to 11) in eight patients and on day 4 posttreatment in one patient. Gram-positive organisms were found in six patients (two Streptococcus faecalis, two Staphylococcus epidermidis, one Staphylococcus aureus, one Streptococcus pneumoniae, and one Bacillus brevis), Candida albicans was found in one patient, and both C. albicans and S. faecalis were found in one patient; the sole

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Acinetobacter antitratus 3 1 0.25-1 1 1 0 0 1 3
Enterobacter \[4^a\]
Proteus mirabilis

Escherichia coli 44 3 0.03 -2 24 21 12 4 1 3
Klebsiella pneumoniae 14 2 0.03 -2 14 14 1 1 1 0 0
Serratia marcescens 6 2 0.25-1 0.125-4 6 6 6 6 0 0 5
Proteus mirabilis \[4^a\]
Enterobacter cloacae 3 1 0.25-1 1 1 1 0 0 0

Enterobacter agglomerans 1 0.06 1 1 1 0 0 0 0
Salmonella typhimurium 1 1 0.06 0 0 0 0 0 0
Pseudomonas aeruginosa 1 64 1 1 1 1 1 1 1 1

Pseudomonas fluorescens 1 1 128 1 1 1 1 1 1 1 1
Pseudomonas maltophilia 1 1 16 1 1 1 1 1 1 1 1

Total 82 56 50 31 21 8 15
Percent 68 61 38 26 10 18

\[^a\] Abbreviations Amp, ampicillin; Car, carbenicillin; Cfz, cefazolin; Cmn, cefamandole; Ctx, cefotaxime; Gen, gentamicin.

\[^b\] In one case S. faecalis and B. fragilis were also isolated.

TABLE 2. Clinical and microbiological outcome of 75 episodes of septicemia in 74 patients

<table>
<thead>
<tr>
<th>Origin</th>
<th>No. with the following clinical outcome:</th>
<th>No. with the following microbiological outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure</td>
<td>Partial cure</td>
</tr>
<tr>
<td>Urinary</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Catheter-related</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>56</td>
</tr>
<tr>
<td>Percent</td>
<td>68</td>
<td>61</td>
</tr>
</tbody>
</table>

\[^a\] Two separate episodes of septicemia occurred in one patient.

superinfection with a gram-negative rod (a susceptible Escherichia coli with a different serotype from the first isolate) occurred in a patient with septicemia of abdominal origin. The focus of the superinfection was detected in four cases: a central venous catheter in three patients and the urinary tract in one patient. In addition, S. faecalis was isolated from the urine of three patients during aztreonam therapy, leading to a symptomatic urinary tract infection in one patient with

TABLE 3. Details of clinical failures

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Underlying disease</th>
<th>Source of septicemia</th>
<th>Organism</th>
<th>Duration of therapy (days)</th>
<th>Further course of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>19</td>
<td>Traumatic tetraplegia</td>
<td>Urinary</td>
<td>E. coli</td>
<td>14</td>
<td>On day 8, septicemia with C. albicans; patient died after 3 weeks of amphotericin B therapy</td>
</tr>
<tr>
<td>M</td>
<td>45</td>
<td>Surgery for pancreatic carcinoma</td>
<td>Gastrointestinal</td>
<td>E. coli</td>
<td>11</td>
<td>Very severe abdominal pathology; patient died on day 11 of aztreonam therapy</td>
</tr>
<tr>
<td>M</td>
<td>73</td>
<td>Polytrauma; lung contusion</td>
<td>Pulmonary</td>
<td>E. coli</td>
<td>9</td>
<td>Relapse of septicemia 1 day after interruption of aztreonam therapy (stopped because was not effective); other antibiotics also failed; patient died 12 days later</td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>Diabetes</td>
<td>Urinary</td>
<td>E. coli</td>
<td>7</td>
<td>Cured with cefuroxime</td>
</tr>
<tr>
<td>F</td>
<td>24</td>
<td>Diabetic coma, aspiration pneumonia</td>
<td>Pulmonary</td>
<td>K. pneumoniae</td>
<td>6</td>
<td>Not improved after addition of gentamicin; cured with cefuroxime-gentamicin</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>Surgery for hypospasias</td>
<td>Orchiepididymis</td>
<td>P. aeruginosa</td>
<td>11</td>
<td>Cured after addition of amikacin on day 4</td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>Biliary surgery</td>
<td>Urinary</td>
<td>S. marcescens</td>
<td>10</td>
<td>Cured after addition of amikacin on day 7</td>
</tr>
</tbody>
</table>
a bladder catheter. No gram-negative organisms resistant to aztreonam were found during the study period.

A clinically significant adverse reaction was seen in only one patient, the patient developed a generalized transient urticarial rash 30 min after the first 2-g intravenous dose of aztreonam, necessitating discontinuation of the therapy. In all other patients clinical tolerance was excellent. Four patients showed unexplained transient elevations of transaminases, exceeding two to three times their basal levels, without clinical impact. Although nine patients had abnormal liver function tests at the start of aztreonam treatment, no further progression was observed. Local tolerance was excellent; only two patients had phlebitis at the site of intravenous infusion.

We conclude from the results of this study that aztreonam, at a dosage of 1 g every 8 h or 2 g every 12 h, is an effective and safe antibiotic for the treatment of gram-negative septicemia. However, the lack of activity of aztreonam against gram-positive organisms requires some caution; if the possibility of mixed infection exists, it would be prudent to start concomitant treatment with an additional antibiotic. The superinfection or colonization with gram-positive organisms, especially *S. faecalis*, has also been reported by others during aztreonam treatment (1, 2, 6) and should be carefully monitored.

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**LITERATURE CITED**


