Penetration of Aztreonam into Cerebrospinal Fluid of Patients with Bacterial Meningitis

J. MODAI,* D. VITTECOQ,1 J. M. DECAZES,1 M. WOLFF,2 and A. MEULEMANS3

Department of Infectious Diseases, Saint-Louis Hospital, 75475 Paris Cedex 10,* Intensive Care Unit, Claude Bernard Hospital, Paris,2 and Department of Biophysics, Xavier Bichat Faculty of Medicine, Paris,3 France

Received 28 May 1985/Accepted 30 October 1985

The penetration of aztreonam into the cerebrospinal fluid was determined in 16 patients with bacterial meningitis undergoing treatment with other antibiotics. Three aztreonam doses of 30 mg/kg were infused intravenously over 30 to 45 min at 8-h intervals, first between days 2 and 4 and again between days 11 and 20 after onset of the disease. Concentrations of aztreonam in serum and cerebrospinal fluid samples obtained at 60, 90, 120, or 240 min after the third aztreonam dose were measured by high-pressure liquid chromatography. The concentrations of aztreonam in cerebrospinal fluid ranged from 3.5 to 62 μg/ml, depending on the sampling time and the time elapsed since the onset of the disease. These concentrations were equal to or higher than the MICs for most of the gram-negative bacilli (including Pseudomonas aeruginosa).

Aztreonam is a new β-lactam antibiotic belonging to the group of monobactam agents. It is active against most gram-negative bacilli, including Pseudomonas aeruginosa. It penetrates the subarachnoid spaces of experimentally infected rabbits (3). Since experimental animal data cannot merely be extrapolated to humans, we carried out a study of the penetration of aztreonam into the cerebrospinal fluid (CSF) of patients with bacterial meningitis to determine whether the concentrations of aztreonam achieved in human CSF are therapeutically active against the pathogens responsible for bacterial meningitis.

(This work was presented in part at the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., October 1984.)

MATERIALS AND METHODS

A total of 16 hospitalized patients with purulent meningitis, 4 women and 12 men, were included in the study. Their mean age was 55 years (range, 26 to 83 years). Except one patient with tuberculosis meningitis, all had macroscopically purulent CSF, with leukocyte counts ranging from 140 to 13,600 cells per mm³, 17 to 96% of which were polymorphonuclear leukocytes. The protein concentrations in CSF were elevated (80 to 1,000 mg/dl), and the ratio of glucose in CSF and blood was decreased in all patients.

Eight of the patients (nos. 1, 3, 6, 8, 9, 10, 13, and 16) were undergoing treatment with ampicillin in daily doses of 10 to 16 g. Three patients (nos. 5, 14, and 15) were receiving chloramphenicol, two patients (nos. 2 and 12) were receiving cefotaxime in a daily dose of 6 g, one patient (no. 11) was treated with penicillin G, and one patient (no. 7) was receiving a daily combination of pefloxacin and amikacin (5 mg/kg). One patient (no. 4) was receiving a combination of isoniazide and rifampin for tuberculous meningitis. Each patient received three aztreonam doses of 30 mg/kg infused intravenously over 30 to 45 min at 8-h intervals, in addition to the above regimens. These doses were administered twice after acute bacterial meningitis was diagnosed, once between days 2 and 4, and again, only when ethically possible, between days 11 and 20 of treatment with the other antibiotics. The nature of the study was explained to each patient, and informed consent was obtained.

The concentrations of aztreonam in serum and CSF were measured in samples drawn 60, 90, 120, or 240 min after the end of the infusion of the third dose of aztreonam. In all cases, lumbar puncture was performed only when clinically indicated; in no case was it done purely for the purpose of this study. This explains why only 11 patients had a second sample obtained between days 11 and 20. All patients were monitored for adverse reactions.

The samples were frozen at −80°C and stored until assayed, and the concentrations of aztreonam in serum and CSF were determined by high-pressure liquid chromatography. No degradation of the drug was observed over a 3-month storage period. Isopropyl alcohol (2.5 ml) was added to 0.5 ml of a standard or unknown sample in a polypropylene tube, and this preparation was then mixed for 15 min. The tubes were centrifuged for 10 min at 2,000 × g at 4°C. The supernatant (2 ml) was extracted with 25 ml of a mixture of chloroform (100 ml) and isoamyl alcohol (4 ml), mixed for 15 min on a rotator-mixer, and centrifuged for 10 min at 2,000 × g at 4°C. The supernatant (0.06 ml) was mixed with an equal volume of ammonium acetate (0.04 M, pH 6), and 0.1 ml of this mixture was injected into the chromatograph. This solution is stable for up to 1 day. The chromatographic separation procedure was a reverse-phase system with the mobile phase consisting of acetoniq-water (17:83, vol/vol) and 0.05 M tetrabutylammonium in phosphate buffer at pH 2.5. The column was a µ-Bondapack C18 (Waters Associates, Milford, Mass.), the flow rate was 2 ml/min, and detection was at 280 nm. The retention time of aztreonam was 6.5 min. The sensitivity of the method was 0.1 μg/ml for plasma and CSF. The reproducibility and recovery errors were less than 8%.

The blood and CSF levels of aztreonam as well as the percentages of penetration of the drug into the CSF were analysed by using a one-way analysis of variance. Whenever an overall difference at the 5% level was detected, the method of least significant difference was used to determine...
TABLE 1. Comparison of aztreonam concentrations in CSF and serum

<table>
<thead>
<tr>
<th>Patient no. (age [yr], sex)</th>
<th>Etiological agent</th>
<th>Aztreonam concs (µg/ml) from samples collected on:</th>
<th>Days 2 to 4</th>
<th>Days 11 to 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CSF</td>
<td>Serum</td>
<td>CSF/serum (%)</td>
</tr>
<tr>
<td>1 (53, F)</td>
<td>Neisseria meningitidis</td>
<td>8</td>
<td>72</td>
<td>11.1</td>
</tr>
<tr>
<td>2 (26, F)</td>
<td>N. meningitidis</td>
<td>3.5</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>3 (48, M)</td>
<td>N. meningitidis</td>
<td>52</td>
<td>120</td>
<td>43.3</td>
</tr>
<tr>
<td>4 (38, M)</td>
<td>Mycobacterium tuberculosis</td>
<td>10</td>
<td>90</td>
<td>11.1</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>18.37</td>
<td>81.5</td>
<td>18.4</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>22.58</td>
<td>31.9</td>
<td>16.7</td>
</tr>
<tr>
<td>5 (48, M)</td>
<td>Bacteroides sp.</td>
<td>6</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>6 (39, M)</td>
<td>Streptococcus pneumoniae</td>
<td>5</td>
<td>80</td>
<td>6.3</td>
</tr>
<tr>
<td>7 (73, M)</td>
<td>Acinetobacter sp.</td>
<td>13</td>
<td>75</td>
<td>17.3</td>
</tr>
<tr>
<td>8 (64, M)</td>
<td>S. pneumoniae</td>
<td>4.5</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>7.1</td>
<td>57.5</td>
<td>14.2</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>4</td>
<td>25.3</td>
<td>8</td>
</tr>
<tr>
<td>9 (75, F)</td>
<td>S. pneumoniae</td>
<td>62</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10 (40, M)</td>
<td>Aseptic</td>
<td>26</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11 (35, M)</td>
<td>S. pneumoniae</td>
<td>7.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>12 (83, F)</td>
<td>Escherichia coli</td>
<td>16</td>
<td>105</td>
<td>15</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>27.8</td>
<td>88</td>
<td>9.5</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>24</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>13 (56, M)</td>
<td>Listeria monocytogenes</td>
<td>22</td>
<td>13</td>
<td>169</td>
</tr>
<tr>
<td>14 (56, M)</td>
<td>Bacteroides sp.</td>
<td>8</td>
<td>28</td>
<td>28.6</td>
</tr>
<tr>
<td>15 (77, M)</td>
<td>S. pneumoniae</td>
<td>39</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>16 (65, M)</td>
<td>S. pneumoniae</td>
<td>7</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>19</td>
<td>20</td>
<td>98.8</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>15</td>
<td>10.6</td>
<td>99.2</td>
</tr>
</tbody>
</table>

* Sampling times, patients 1 to 4, 60 min; patients 5 to 8, 90 min; patients 9 to 12, 120 min, patients 13 to 16, 240 min. F, Female; M, male.

a ND, Not determined.
b Ventricular concentration of aztreonam.

possible differences at the 5% level among sampling times or between the two time periods.

RESULTS

The concentrations of aztreonam in serum and CSF are shown in Table 1. Concentrations of aztreonam in both CSF and serum at each of the sampling periods varied from patient to patient. The CSF levels determined at 60, 90, 120, and 240 min after completion of the third infusion of aztreonam ranged from 3.5 to 52, 4.5 to 13, and 7 to 39 µg/ml, respectively. When mean serum levels were compared, no significant differences were found between the first and second administration periods. However, the serum levels of aztreonam achieved at 240 min were significantly different (P = 0.01) from those obtained at 60, 90, and 120 min. The CSF concentrations of aztreonam determined between days 2 and 4, when the meninges were the most inflamed, were not significantly higher than those observed between days 12 and 20, at the time when the meningitis had responded to treatment.

No adverse reaction was noted. Because aztreonam was administered only intermittently, no attempt was made to evaluate its contribution to the control of the disease.

DISCUSSION

The decrease in the serum levels of aztreonam observed at 240 min after the end of the third intravenous infusion is not surprising. As far as the CSF was concerned, no significant differences in aztreonam levels could be observed at 60, 90, 120, or 240 min after the end of the third infusion; thus it was impossible to determine the time required to obtain steady-state conditions. In the patients in whom the coefficient of correlation (−0.44) between the serum concentrations of aztreonam and its percentage of penetration into the CSF was calculated, the percentage of penetration into the CSF appeared to be inversely proportional to the serum concentration with a risk of error of about 15% (Fig. 1). However, their calculation could be performed for only a small number of patients (data available for 11 patients at the time of first sampling, from days 2 to 4), and there was an excessive

![FIG. 1. Aztreonam in CSF and serum (days 2 through 4).](http://aac.asm.org/Downloaded from http://aac.asm.org)
scattering in extreme values, so it is difficult to consider this
determination reliable.

In a study of 25 patients with noninflamed meninges and 9
patients with inflamed meninges, a single 2-g dose of aztreonam, administered intravenously over 5 min, resulted in
mean concentrations in the CSF at 1 and 4 h of 0.5 and 1.0
µg/ml, respectively. In the latter
group of patients with inflamed meninges, the concentrations
were approximately fourfold higher at 1.98 and 3.22 µg/ml,
respectively. After 4 h, despite being greatly exceeded by
serum levels of the drug, no further increase in CSF concen-
tration was observed.

After the intravenous infusion, over 5 min, of a single 2-g
dose, CSF levels of aztreonam were determined in 11
patients with meningitis (R. Greenman, S. Arcey, G.
Dickinson, J. Mokhbat, L. Sabbath, and L. Friedhoff, Pro-
gram Abstr. 23rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 410, 1983). In patients with viral meningitis (n = 4), the mean aztreonam concentration was 1.28
µg/ml (range, 0.76 to 1.77 µg/ml). In the remaining patients,
with bacterial (n = 5), fungal (n = 1), and carcinomatous (n
= 1) meningitis, higher levels were achieved (mean, 7.2
µg/ml; range, 2.54 to 16.1 µg/ml).

Single intravenous doses (30 mg/kg) were administered to
29 children aged from 2 days to 11 years. The concentration
of aztreonam in CSF was measured for six patients. In five
patients who received aztreonam 24 to 72 h after acute
bacterial meningitis was diagnosed, the CSF concentrations
of aztreonam ranged between 2.1 and 20.8 µg/ml, with a
mean CSF/serum concentration ratio of 17.3%. A patient
studied at the completion of a 14-day course of therapy for
pneumococcal meningitis had a CSF/serum concentration
ratio of 3.1% (4).

The concentrations of aztreonam in CSFs of all patients in
this study were higher than the MICs for most gram-negative
bacilli, with the exception of Acinetobacter spp. (2). Be-
cause of its good penetrability when the meninges are
inflamed, aztreonam might be considered in cases of bacte-
rial meningitis when the susceptibility of the pathogen indi-
cates its usefulness. However, in view of the various MICs
of different organisms and the interindividual differences
in the diffusion of aztreonam in the CSF, monitoring of the
activity of the drug is essential. The therapeutic use of this
antibiotic should be preceded by the determination of its
CSF concentration and then by a comparison between the
CSF level and the MIC for the causative organism and if
possible by the determination of the bactericidal activity in
the CSF.

ACKNOWLEDGMENT
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