In Vitro Susceptibility of *Brucella melitensis* to New Cephalosporins Crossing the Blood-Brain Barrier

ELIA PALENQUE,* JOAQUÍN R. OTERO, AND ANTONIO R. NORIEGA

Servicio de Microbiologia, Hospital Primero de Octubre, 28041 Madrid, Spain

Received 25 July 1985/Accepted 22 October 1985

The in vitro susceptibilities of 83 clinical isolates of *Brucella melitensis* to seven cephalosporins and a monobactam were determined. Ceftizoxime, ceftriaxone, and cefotaxime were the most effective agents tested, with MICs ranging from 0.25 to 2 μg/ml. Moxalactam, cefoperazone, cefuroxime, and ceftazidime showed MICs between 4 and 64 μg/ml, with moxalactam being the most active agent in this group. Aztreonam showed poor activity, with MICs higher than 64 μg/ml.

A few antimicrobial combinations are widely accepted for the treatment of acute brucellosis, and the disease, as well as its most frequent complications, can be adequately controlled with these drugs (11). However, these conventional therapeutic regimens have given poor results when used in the treatment of brucella meningoecephalitis (4), a severe complication of not uncommon occurrence in highly endemic areas of brucellosis. The bacteriostatic nature of the tetracyclines and the poor penetration of streptomycin into the cerebrospinal fluid may be the causes of this therapeutic failure, in view of recent evidence suggesting the requirement of bactericidal concentrations of antibiotics in the cerebrospinal fluid for the control of bacterial meningitis (10).

Cephalosporin antibiotics are not included in any of the commonly accepted regimens for the treatment of brucellosis. Hall and Manion (6) found that concentrations of cephalosporins up to 100 μg/ml were needed to inhibit 100% of their strains. However, some of the new expanded-spectrum cephalosporins have properties which are very desirable in any drug potentially useful in central nervous system infections. They are bactericidal and very active against most gram-negative bacilli, as well as the conventional pathogens of meningitis, and they achieve reasonably good penetration of the cerebrospinal fluid in the presence of infection (7). Gutiérrez Altés et al. (5) recently reported good in vitro activity of imipenem against *Brucella melitensis*, and Young (12) successfully treated a case of meningitis due to *Brucella suis* with a combination of moxalactam and rifampin. These reports encouraged us to test the activity of a number of expanded-spectrum cephalosporins and a monobactam, reported to show reasonably good penetration into the central nervous system (7).

A total of 83 *B. melitensis* strains isolated from human blood cultures were tested. The strains were identified by standard methods (1) and preserved in skim milk at −70°C. The antimicrobial agents tested were kindly supplied in pure form by their manufacturers as follows: ceftizoxime (Cepa S. A.), ceftriaxone (Roche Diagnostics, Div. Hoffman-LaRoche, Inc.), cefotaxime (Hoechst-Roussel Pharmaceuticals Inc.), moxalactam (Eli Lilly & Co.), cefoperazone (Pfizer Inc.), cefuroxime and ceftazidime (Glaxo Pharmaceuticals, Ltd.), and aztreonam (E. R. Squibb & Sons). MICs were determined by a serial twofold agar dilution method as previously described (5). Briefly, Isosensitest Agar CM47L (Oxoid Ltd.) was used as the culture medium, with dilutions of each antibiotic ranging from 0.06 to 256 μg/ml. The inoculum was prepared from an initial culture in a Trypticase soy agar slant (BBL Microbiology Systems). Each strain was subcultured in brain heart infusion broth (Difco Laboratories) for 48 h at 37°C, and then seeding suspensions were prepared by a 1/20 dilution in brain heart infusion broth for a final concentration of approximately 10⁵ CFU per spot. Plates were inoculated with a Steers replicator, and the results were read after 48 h of incubation at 37°C in air. The MIC was considered to be the lowest concentration in which growth was ≤3 isolated colonies. *Escherichia coli* ATCC 25922 was tested on each plate as a control. The MICs for this control strain were: ceftriaxone, ceftizoxime, and cefotaxime, 0.12 μg/ml; moxalactam, cefoperazone, and ceftazidime, 0.25 μg/ml; cefuroxime, 8 μg/ml; and aztreonam, 0.06 μg/ml.

The results are summarized in Table 1. The antibiotics tested fell into three distinct groups. In the first group, composed of ceftizoxime, ceftriaxone, and cefotaxime, MICs ranged from 0.25 to 2 μg/ml. Cefotaxime and ceftriaxone were the most effective agents in this group. In the second group, composed of moxalactam, cefoperazone, ceftazidime, and cefuroxime, MICs ranged from 4 to 64 μg/ml. Moxalactam was the most effective agent of the group, with MICs between 4 and 16 μg/ml. Finally, aztreonam showed poor activity, with MICs higher than 64 μg/ml.

On the basis of our own clinical observations, as well as

### TABLE 1. Comparative activities of seven cephalosporins and aztreonam against *B. melitensis*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Range</th>
<th>MIC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50%*</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.5–1</td>
<td>0.5</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.25–1</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.5–2</td>
<td>1</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>4–16</td>
<td>16</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>4–64</td>
<td>16</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>16–32</td>
<td>32</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>8–64</td>
<td>32</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>64–&gt;256</td>
<td>128</td>
</tr>
</tbody>
</table>

* Corresponding author.

* 50 and 90% MICs for 50 and 90% of strains tested, respectively.
data on brucella susceptibility (3, 5) and other opinions as to the treatment of brucella meningoencephalitis in the literature (12), we suggest that a potentially effective treatment of the severe complications of brucella meningoencephalitis includes rifampin associated with another antibiotic. The data presented here indicate that ceftriaxone and ceftizoxime could be the appropriate choices for this second drug. Both enter the cerebrospinal fluid at approximately the same rate, with mean concentrations of 8.5 µg/ml for ceftizoxime and 9.5 µg/ml for ceftriaxone (2, 8), that is, 10 to 40 times the MICs for our strains. Ceftriaxone has, the advantage of a much longer half-life than ceftizoxime, permitting a twice-daily dosage (9). This may be convenient in long-term treatments.

LITERATURE CITED


