Evaluation of Aztreonam in Experimental Bacterial Meningitis and Cerebritis

W. MICHAEL SCHELD,1,2* JAMES P. BRODEUR,¹ JEAN C. GRATZ,¹ PAM FORESMAN,3 AND GEORGE RODEHEAVER²

Departments of Internal Medicine (Division of Infectious Diseases),¹ Plastic Surgery Research,³ and Neurosurgery,² University of Virginia School of Medicine, Charlottesville, Virginia 22908

Received 9 May 1983/Accepted 22 August 1983

Aztreonam (SQ 26,776), a new monocyclic β-lactam agent, was compared with ampicillin, ampicillin plus chloramphenicol, and gentamicin in rabbits with experimental meningitis induced by, respectively, ampicillin-susceptible Haemophilus influenzae, ampicillin-resistant H. influenzae, and Escherichia coli. Aztreonam was also compared with gentamicin in experimentally induced E. coli cerebritis in rats. Doses of the various agents were delivered that produced near-peak concentrations in serum comparable to those attained in humans on standard parenteral regimens. The percent penetration ([concentration in cerebrospinal fluid/concentration in serum] x 100) of aztreonam into purulent rabbit cerebrospinal fluid was 23% (versus 12, 27, and 21%, respectively, for ampicillin, chloramphenicol, and gentamicin). In experimental meningitis in vivo, aztreonam was more rapidly bactericidal than was ampicillin in ampicillin-susceptible H. influenzae meningitis, ampicillin or chloramphenicol in ampicillin-resistant H. influenzae meningitis, or gentamicin in E. coli meningitis. In the therapy of experimental cerebritis, the early stage of brain abscess formation, aztreonam reduced the numbers of E. coli in rat brain as rapidly as did gentamicin. Aztreonam deserves further evaluation in acute gram-negative bacterial infections of the central nervous system in both experimental animals and in humans.

Despite the introduction of new antimicrobial agents and a more thorough understanding of the pathophysiology of infections of the central nervous system, the mortality and morbidity of bacterial meningitis and of brain abscess remain high. The recent emergence of penicillin-, chloramphenicol-, and penicillin- and chloramphenicol-resistant pneumococci and ampicillin-, chloramphenicol-, and ampicillin- and chloramphenicol-resistant Haemophilus influenzae (8, 32) and the poor results with aminoglycoside therapy for gram-negative bacillary meningitis (9, 21, 22) requires the continued development of new antimicrobial agents for therapy of these infections.

Aztreonam (SQ 26,776) is a new synthetic β-lactam agent characterized as a monobactam because of its 2-oxoazetidine-1-sulfonyl acid moiety (41, 43). This agent displays high activity in vitro against aerobic gram-negative bacteria (13, 24, 25, 28, 31, 42, 45), including β-lactamase-positive H. influenzae (24) and many aminoglycoside-resistant members of the family Enterobacteriaceae (13, 28, 42, 45). Many of these organisms are important meningeal pathogens or are implicated in mixed infections of cerebral parenchyma. In addition, aztreonam appears to be promising in vivo in the treatment of rats with experimental ampicillin-resistant H. influenzae meningitis (6). The low molecular weight of aztreonam may facilitate its penetration into cerebrospinal fluid (CSF), but data in animals (or humans) are not available. For these reasons, aztreonam was deemed worthy of evaluation in experimental models of bacterial meningitis and of brain abscess.

The purposes of this study were: (i) to compare aztreonam with ampicillin, ampicillin plus chloramphenicol, and gentamicin in the therapy of rabbits in experimental meningitis induced by ampicillin-susceptible H. influenzae, ampicillin-resistant H. influenzae, and Escherichia coli, respectively, and (ii) to compare aztreonam with gentamicin in the therapy of experimental E. coli brain abscess (during the early stage of cerebritis) in rats.

MATERIALS AND METHODS

Test organisms. The ampicillin-susceptible H. influenzae strain used was a clinical isolate from the CSF of a patient at the University of Virginia, as described previously (35, 36). The ampicillin-resistant H. influenzae type b (Wylie) strain was kindly provided by J. Nelson, Dallas, and the K1-positive E. coli (C94) was a gift from G. McCracken, Dallas. Both were CSF
isolates. This strain of E. coli (C94) was used in studies of experimental meningitis, but another E. coli strain (ATCC 25922) was used in the experimental cerebritis studies. The minimal bactericidal concentrations (MBCs) of aztreonam and ampicillin for the ampicillin-susceptible H. influenzae isolate were 0.06 and 0.5 μg/ml, respectively. Corresponding MBCs of aztreonam, ampicillin, and chloramphenicol for the ampicillin-resistant strain (Wylie) were 0.06, 16, and 1 μg/ml, respectively. Both E. coli isolates used in the models of experimental meningitis and cerebritis had identical tetracyclines as follows: aztreonam, 0.125 μg/ml; gentamicin, 0.5 μg/ml. All MBCs were determined against 5 × 10^3 CFU by microbiodepletion techniques (Dynatech Laboratories, Inc., Alexandria, VA) in Mueller-Hinton broth.

Preparation of inocula for meningitis model. The procedures have been described in detail previously (35–37). The final inocula (in CFU; final volume, 0.25 to 0.3 ml) were as follows: E. coli, ca 10^5–5; H. influenzae, 10^5–5.

Induction of meningitis. New Zealand white rabbits (2 to 3 kg each) were prepared, with minor modifications, as described previously (10, 37). A total of 126 rabbits were inoculated; 11 died before the end of the experimental period and were not included in the analysis. After the administration of pentobarbital (30 mg/kg intravenously) anesthesia, a dental acrylic helmet was attached to the skull of the animal to facilitate rigid immobilization within a stereotaxic frame. A Quincke spinal needle (25 gauge by ca. 9 cm) was introducedatraumatically into the cisterna magna by a geared electrode introducer. These needles were used for initial bacterial inoculation and later for sampling of CSF during the course of treatment. After the withdrawal of 0.5 ml of normal CSF, inoculation was accomplished by direct injection into the cisterna magna. The animals were returned to their cages. The time between inoculation and initiation of treatment was 6 h in animals infected with H. influenzae and 18 h when E. coli was used. All animals developed meningitis as manifested by fever (>40°C), neurological signs, CSF pleocytosis (>95% polymorphonuclear leukocytes), and CSF bacterial concentrations of log_{10} 4.0 to >8.0 CFU/ml. All untreated control animals in each group died within 4 days of inoculation.

Induction of cerebritis. The techniques have been described in detail previously (23, 44). Briefly, adult, female, 250- to 300-g Sprague-Dawley rats (Hilltop Laboratory Animals, Inc., Scottsdale, Pa.) were anesthetized by intraperitoneal injection of pentobarbital (38 mg/kg) and placed in a stereotactic head holder. The skull was exposed, and a 2-mm burr hole was placed just posterior to the coronal suture and 4 mm lateral to the midline. After the dura was pierced, a 25-gauge needle connected to a 10-μl syringe was lowered stereotaxically over a 10-min period for a distance of 2 mm into the white matter. The inoculum (mean ± standard deviation log_{10} 6.31 ± 0.26 E. coli organisms in a volume of 1.0 μl) was then slowly injected over 50 min. Ten minutes later, the needle was slowly withdrawn. The calvarial defect was closed with bone wax, and the skin was closed in a single layer. This technique results in experimental brain abscess in 100% of rats that survive the procedure (surgical mortality is <3%); early deaths due to meningitis have not been observed (23, 44).

Treatment regimens and assessment of therapeutic results with experimental meningitis. The dosages of drugs (in milligrams per kilogram per hour) were as follows: ampicillin sodium (Omnipen-N; Wyeth), 30; chloramphenicol sodium succinate (Chloromycetin; Parke-Davis), 30; gentamicin sulfate (Garamycin; Schering-Plough), 2.5; aztreonam sodium, 10. Aztreonam was compared to the standard regimen(s) (as above) in each of the three models. In addition, at least eight untreated animals were included in each group. Antibiotics were administered with a constant intravenous infusion pump (Sage model 352) via a catheter in the femoral vein. An initial loading dose consisting of 20% of the total 8-h dose was administered intravenously immediately before the start of the infusion. Serial blood (3-ml) and CSF (0.25-ml) samples were obtained from an indwelling femoral arterial catheter and spinal needle, respectively, before treatment and after 4 and 8 h of therapy. Quantitative CSF bacterial titers were obtained by standard serial dilutions in tryptic soy agar pour plates (E. coli) or by inoculation on the surface of chocolate agar with IsoVitalX (BBL Microbiology Systems, Cockeysville, Md.) added (H. influenzae). The remaining CSF and serum samples were kept at −70°C until antibiotic assays were performed (within 2 weeks). This period of storage did not affect the assay results.

Treatment regimens and assessment of therapeutic results with experimental cerebritis. All drug regimens were begun 24 h after intracerebral inoculation during the early stage of cerebritis and continued for 4 days. Each drug was administered subcutaneously every 6 h in the following dosages (in milligrams per kilogram): gentamicin, 3; aztreonam, 100. An untreated control group was also included. Concentrations of antibiotic in serum were determined at frequent intervals at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 6 h after drug injection. Kinetic analysis after the first, fifth, and ninth dosages revealed no accumulation of either agent in serum under these conditions (data not shown). Animals were sacrificed 12 h after the last dose. The brain was removed, and the injected hemisphere was separated in toto, weighed, and homogenized in a Polytron grinder (Brickmann Instruments, Inc., Westbury, N.Y.). The numbers of bacteria in 10-fold serial dilutions of the homogenate were determined in tryptic soy agar pour plates. The results were expressed as mean ± standard deviation log_{10} CFU of E. coli per injected hemisphere.

Antibiotic assays. All levels were determined by agar well diffusion techniques. Ampicillin concentrations were determined against a Bacillus subtilis spore suspension (Difco Laboratories, Detroit, Mich.), 0.9 ml per 1,000 ml of antibiotic medium no. 11 (Difco). Gentamicin concentrations were assayed with a multi-drug-resistant strain of Staphylococcus epidermidis (ATCC 27626), as described previously (1). Chloramphenicol bioassays employed a marine bacterium (Beneckea natriegens) in 1.5% salt agar (3). The aztreonam assay utilized E. coli (SC 12155; kindly provided by the Squibb Institute for Medical Research) added to antibiotic medium no. 1 (Difco) at a 0.2% inoculum. All standards and specimens were tested in triplicate. All assays displayed good reproducibility (±10%) and had low limits of detectability (<0.3 μg/ml).

Statistical procedures used in data analysis. The
percent penetration of drug into CSF is defined by the formula: percent penetration = (concentration in CSF)/(concentration in serum) × 100. Statistical analysis for changes in CSF bacterial concentrations in experimental meningitis or for log10 recovered E. coli per injected hemisphere in experimental brain abscess was done on unpaired data by Student’s t test. The percentage of CSF samples rendered sterile after 8 h of therapy was compared between experimental meningitis groups by Fisher’s exact test. In addition, covariance and regression line analysis were performed to assess differences between drugs in each model.

RESULTS

Penetration of antibiotics into CSF with experimental meningitis. The antibiotic concentrations attained and the percentage of the antibiotic concentration in serum found in the CSF are shown in Table 1. In each case, steady-state levels in serum and CSF were achieved within 1 h of intravenous infusion, and levels in serum closely approximated those found in humans during standard parenteral therapy. The mean ampicillin concentration in serum was 37.4 μg/ml. The mean level in CSF was 4.7 μg/ml, and the percent penetration, defined as the concentration in CSF divided by the concentration in serum and multiplied by 100, was 12.6, in close agreement with results in other models of bacterial meningitis. The mean chloramphenicol concentration in serum was 29.1 μg/ml, close to peak levels attained clinically. The overall percent concentration of chloramphenicol in CSF was 26.5% of that found in serum, very close to values cited for this drug in humans. The gentamicin levels in serum were high (e.g., >10 μg/ml), and the mean percent of the serum concentration in CSF (21.3) (Table 1) was identical to results obtained previously in experimental meningitis. The mean steady-state aztreonam level in serum was 32 μg/ml, similar to that attained in humans 30 to 60 min after the administration of 500 to 1,000 mg of aztreonam (39, 40). The mean concentration in CSF, expressed as a percentage of simultaneous drug concentrations in serum into purulent CSF, approached 23, quite high for a β-lactam antibiotic (Table 1). The mean concentration of antibiotic in CSF (Table 1) exceeded the MBC for the test strain by at least eightfold for all agents, excepting ampicillin, in experimental meningitis caused by ampicillin-resistant H. influenzae. The concentrations of ampicillin in CSF were undetectable by our bioassay in these animals, presumably reflecting in vivo hydrolysis of the drug by β-lactamase within the subarachnoid space, and were far below the MBC of 16 μg/ml for the test strain.

Rate of bacterial killing in vivo with experimental meningitis. The results of therapy are shown in Table 2. The numbers of organisms in CSF before therapy were not significantly different among experimental groups in any of the infections. In each case, organism numbers in the CSF of the untreated controls declined slightly during the 8 h of observation (Table 2), although all animals died within 4 days.

Azcetronam was more rapidly bactericidal than was the comparison agent(s) in each model of experimental meningitis (Table 2). In some infections (ampicillin-susceptible H. influenzae [Table 2]), aztreonam was more rapidly bactericidal than the comparison drug during the first 4 h but was not statistically different after the full 8-h treatment interval, whereas in other infections (e.g., E. coli meningitis), the opposite pattern was seen. In experimental ampicillin-resistant H. influenzae meningitis, aztreonam was more rapidly bactericidal than was ampicillin or chloramphenicol at both time periods (Table 2).

Sterilization of the CSF was analyzed for each treatment regimen in all three models after 8 h of therapy (Table 2), and differences were assessed by Fisher’s exact test analysis (P values are indicated). By this method of analysis, aztreonam and ampicillin produced equivalent results in experimental meningitis caused by ampicillin-susceptible H. influenzae. In contrast, ampicillin and chloramphenicol failed to sterilize the CSF after 8 h in 19 animals with experimental meningitis caused by ampicillin-resistant H. influenzae versus 13 cures in 15 animals treated with aztreonam (P < 0.001; Table 2). Similar results were observed in the model of E. coli meningitis (Table 2).

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of animals</th>
<th>Mean ± SD concn (μg/ml) in:</th>
<th>Mean ± SD % penetrationa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Serum</td>
<td>CSF</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>17</td>
<td>37.4 ± 12.1</td>
<td>4.7 ± 2.0</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>18</td>
<td>29.1 ± 7.0</td>
<td>7.7 ± 1.6</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>14</td>
<td>10.8 ± 4.2</td>
<td>2.3 ± 1.5</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>43</td>
<td>31.7 ± 5.4</td>
<td>7.2 ± 1.9</td>
</tr>
</tbody>
</table>

a % Penetration = (CSF/serum) × 100.
TABLE 2. Results of therapy in experimental meningitis

<table>
<thead>
<tr>
<th>Infecting organism</th>
<th>Drug</th>
<th>MBC (µg/ml)</th>
<th>Bacteriological response in CSF (mean ± SD)</th>
<th>No. rabbit cultures sterile/total no. treated after 8 h of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean CFU/ml at:</td>
<td>4 h CFU/ml after therapy for:</td>
</tr>
</tbody>
</table>
|                   |        |             | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 h | 0 h | 4 h | 8 s
treonam reduced the concentration of *E. coli* to 5.03 ± 0.18 logs (*P* = 0.07 versus the reduction by gentamicin), but none of the injected hemispheres was sterile after this short (4-day) course.

**DISCUSSION**

This study compared aztreonam with frequently used antibiotics in the therapy of three types of experimental bacterial meningitis in rabbits and in experimental *E. coli cerebritis* in rats. Aztreonam was compared with ampicillin, ampicillin and chloramphenicol, and gentamicin in experimental meningitis induced in rabbits by the intracerebral inoculation of ampicillin-resistant *H. influenzae*, ampicillin-resistant *H. influenzae*, and *E. coli*, respectively. Aztreonam was very active against common gram-negative meningeal pathogens in vitro. The dosages of all antibiotics were chosen to produce concentrations in serum in vivo in both animal species closely approximating those found in humans during standard parenteral regimens. Aztreonam was more active than the comparison agent in all models of experimental meningitis tested. The concentration of aztreonam into purulent CSF was 23% of that in serum, high for a β-lactam antibiotic. Only moxalactam is present in comparable proportions in this experimental model (27, 33, 34).

The results of these experiments may suggest a role for aztreonam in the therapy of bacterial meningitis or parenchymal infections of the human brain. Ampicillin-resistant strains of *H. influenzae* are now relatively prevalent in diverse geographic areas (8). Although chloramphenicol is bactericidal against these isolates (29) and is generally used, problems of toxicity, especially in young infants, still remain. Cefamandole may be active in vitro against some of these strains, but its MICs may exceed 128 μg/ml (4) and failures in the treatment of *H. influenzae* meningitis have been reported (38). Cefoperazone is very active against these isolates in vitro (2, 46) and against experimental meningitis in vivo (33, 36), but an inoculum effect (e.g., increase in the MIC from <2 to >64 μg/ml against 10 of 19 strains at an inoculum of 10^7 CFU [46]) is observed with this agent against β-lactamase-positive *H. influenzae* in vitro. This effect has not yet been observed with aztreonam. This observation is of potential clinical importance since concentrations of *H. influenzae* exceeding 10^7 CFU/ml of CSF are often found in vivo in human cases (14). Cefotaxime and moxalactam are also active against ampicillin-resistant *H. influenzae* in vitro.

Despite the direct injection of aminoglycosides into CSF, the morbidity and mortality associated with gram-negative enteric bacillary meningitis remain high (21, 22). Chloramphenicol is bacteriostatic against these bacteria (29) and has not generally been effective in treating this type of meningitis (9). In the present study, aztreonam was much more rapidly bactericidal than was gentamicin in treating experimental *E. coli* meningitis in rabbits. Similar results were documented in experimental *E. coli* meningitis treated with mezlocillin (35), cefoperazone (36), and moxalactam, ceftriaxone, and cefotaxime when compared with netilmicin (33, 34). These agents, especially moxalactam, for which most data are currently available, appear to be a major advance in the therapy of gram-negative bacillary meningitis (20, 26, 30). Similar results may be obtained with aztreonam, as suggested by this study, but will require prospective, controlled clinical trials. Since aztreonam is not active against gram-positive meningeal pathogens, such as *Streptococcus pneumoniae* or *Streptococcus agalactiae*, this agent should not be used in purulent meningitis of unknown etiology. This disadvantage may not be associated with broader-spectrum agents, such as ceftriaxone.

Although dependent on precise location within the brain parenchyma, most brain abscesses are characterized as mixed infections often involving microaerophilic streptococci, anaerobic bacilli, and members of the family *Enterobacteriaceae* (7, 11, 15, 18). Although the precise pathogenic role of each organism in these mixed infections is unknown, prompt recognition and treatment with antibiotics of the early cerebritis stage preceding abscess may prevent abscess formation and permit early cure (12, 15, 17). Studies of antibiotic concentrations in cerebral parenchyma or abscess cavities during parenteral therapy in humans are limited and somewhat contradictory (5, 12, 19); however, aminoglycosides are rarely detectable at the site of infection in brain abscesses (12). This finding suggests that newer β-lactam agents with in vitro activity against members of the family *Enterobacteriaceae* may prove useful in this disease.

The results of this study with experimental *E. coli cerebritis* are highly preliminary and difficult to interpret since the pathogenic role of members of the family *Enterobacteriaceae* in mixed brain abscess is unclear. Nevertheless, aztreonam was as rapidly bactericidal as gentamicin in this model with slightly (although not statistically significant) greater reductions in brain *E. coli* concentrations after 4 days of therapy. Aztreonam did not sterilize the brain after this treatment interval, in contrast to the effect of penicillin G in experimental *Staphylococcus aureus cerebritis* (16). However, these preliminary, encouraging observations with aztreonam support more investigation of this agent.
in experimental brain abscess in rats, including the treatment of established encapsulated brain abscess and the effect of longer courses of treatment.

Aztreonam deserves further evaluation in acute gram-negative bacterial infections of the central nervous system in both experimental animals and in humans.

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LITERATURE CITED


