Randomized Comparison of Aztreonam and Chloramphenicol in Treatment of Typhoid Fever

EDUARDO GOTUZOZ,1,2 JUAN ECHEVARRÍA,1,2 CARLOS CARRILLO,1,2 JORGE SÁNCHEZ,1 PABLO GRADOS,1 CIRO MAGUIÑA,1 AND HERBERT L. DUPTON3*

Instituto de Medicina Tropical 'Alexander von Humboldt,' Universidad Peruana 'Cayetano Heredia,' and Departamento de Enfermedades Transmisibles, Hospital Nacional Cayetano Heredia, Lima, Peru, and University of Texas Medical School and School of Public Health, Houston, Texas 77030

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Patients with clinical typhoid fever plus a blood, bone marrow, or bile culture positive for Salmonella typhi or Salmonella paratyphi were included in an open clinical trial to compare the efficacy of aztreonam (6 g/day [2 g intravenously every 8 h]) given for 10 days with that of chloramphenicol (50 mg/kg of body weight per day [intravenously or orally]) administered for 14 days. A total of 44 patients, 22 in each group, were included in the study, and both groups were comparable in terms of baseline parameters. All patients randomized to receive chloramphenicol completed the 14 days of treatment, while two patients randomized to receive aztreonam developed an intestinal hemorrhage, and a third patient elected to withdraw from the trial. Defervescence occurred more quickly in the subjects receiving chloramphenicol than in those receiving aztreonam ($P < 0.05$). All patients in the chloramphenicol group were clinically cured during therapy, while four patients (21%) in the group receiving aztreonam were declared clinical treatment failures. None of the 19 patients receiving aztreonam, compared with 7 of 22 (32%) patients receiving chloramphenicol, had a positive blood culture after 24 h of therapy ($P < 0.05$). Adverse experiences were unusual and mild. In the study, aztreonam was less effective than chloramphenicol with regard to clinical effectiveness and time of defervesence but was more effective in the elimination of the infecting Salmonella organisms from the bloodstream.

In excess of 12.5 million cases of typhoid fever occur annually throughout the world (5). The expected mortality rate without therapy of 15 to 30% (3, 13) can be reduced to very low levels with antimicrobial therapy. The conventional drug of choice worldwide has been chloramphenicol because of its excellent bioavailability by the oral route, its low cost, and its clinical efficacy (11, 17, 19). Unfortunately, therapy with chloramphenicol has little effect on the recurrence of disease relapse or chronic intestinal carriage of Salmonella typhi posttherapy (9, 10). Because of the drug’s low cost, these limitations had been accepted by many public health officials and clinicians in the developing world until drug resistance began to occur. In some areas of the world, resistance of S. typhi to each of the three standard antityphoid drugs (chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole) has become common (1, 8).

Between 2 and 4% of patients with typhoid fever become chronic intestinal carriers of S. typhi for more than 1 year (10). Typhoid carriers are important to the epidemiology of this infection, in which humans represent the exclusive reservoir of the organism. New chemotherapeutic drugs are needed that would be more predictably effective in areas where resistance is reported and that, hopefully, would decrease the occurrence of posttreatment typhoid relapses and chronic intestinal carriage of the organism.

Because of its in vitro and in vivo activity against bacterial enteropathogens (8), aztreonam was examined as an antityphoid drug in clinical studies with patients with typhoid fever. In two preliminary uncontrolled clinical trials, the drug appeared to be effective for the therapy of typhoid disease (7, 18). The present study was carried out to examine its comparative therapeutic efficacy in a clinical trial employing chloramphenicol as standard therapy.

MATERIALS AND METHODS

Patients 14 years of age or older with clinical typhoid fever (temperature higher than 38.3°C, systemic toxicity, headache, anorexia, diarrhea, constipation, or presence of rose spots) and a positive bone marrow, bile (obtained by Entero-Test), or blood culture were admitted to Hospital Nacional Cayetano Heredia in Lima, Peru, and were entered into the trial. Exclusion criteria included the following: complicated typhoid fever (bowel perforation, gastrointestinal bleeding, endocarditis, meningitis, ceptiviral meningitis, or meningococcal meningitis), hyperosmolar dehydration, beta-lactam antimicrobial agents, and receipt of antityphoid antimicrobial agents, including ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, or a fluoroquinolone or broad-spectrum cephalosporin. Lactating or pregnant females were also excluded. Patients meeting the enrollment criteria were randomized to receive aztreonam (2 g intravenously every 8 h) or chloramphenicol (50 mg/kg of body weight per day in four divided doses, with a maximum daily dose of 3 g/day intravenously or orally). The durations of therapy were 10 days for the aztreonam group and 14 days for the chloramphenicol group. Patients were kept in the hospital for the duration of the trial. Immediately before initiation of therapy, blood, stool, bile (through an Entero-Test small bowel study), and bone marrow samples were obtained for culturing S. typhi. During therapy, blood cultures were obtained on days 1, 2, 3, and 4 and 1 h before the first dose of the following day of treatment (5 to 10 ml of blood was placed in 30 ml of culture broth), and stools were cultured on days 1, 2, 3, 4, and 5. After the end of treatment,
blood cultures were obtained from outpatients on days 1, 2, 7, and 14 posttreatment, and stools were cultured on days 1, 2, 7, and 21 posttherapy. Patients then returned for clinical assessment 8 weeks after completing therapy.

The trial was a two-center study which was to include a total of 134 patients. A randomization table (randomization of 1:1) was provided by the sponsor. Investigators were not able to see the assignments for treatment prior to enrollment of the subjects. The study was stopped at both sites when each found an inordinate number of failures in the aztreonam group. The sample size for the study was statistically adequate on the basis of the expected clinical cure rates of 100% for chloramphenicol and between 75 and 80% for aztreonam. With an overall statistical significance limit set at $P = 0.05$ (two sided) and a power of 80%, the numbers of subjects necessary to detect the differences are between 15 and 20 in each group.

To be included in bacteriologic analysis, patients needed to have had at least two blood cultures performed during therapy and immediately posttherapy. The age, sex, weight, height, duration (days) of fever, and clinical severity of the illness as determined by the admitting physician were assessed and compared between groups. The clinical parameters compared between groups were hours until defervescence, clinical cure (defervescence and resolution of preenrollment symptoms), clinical failure (continued fever after 10 days of therapy), and typhoid relapse (defined as clinical symptoms of typhoid fever with isolation of \textit{S. typhi} or \textit{Salmonella paratyphi} in blood within 8 weeks after completing treatment). Bacteriologic response was defined as negative blood cultures during therapy, and microbiologic relapse was defined as patients who had a bacteriologic response but who had reappearance of the \textit{S. typhi} in posttherapy blood samples. Convalescent carriage was defined as reappearance of \textit{S. typhi} in posttherapy stool samples within the first 8 weeks after completion of therapy but having negative cultures without further therapy by 3 months. Patients were removed from the study if they had blood cultures positive for the infecting organism after 5 days of therapy or if they experienced a severe, adverse event during therapy.

To monitor for potential adverse drug effects, a complete blood count and serum chemistry tests (including serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, alkaline phosphatase, creatinine, fasting blood glucose, total protein, albumin, sodium, and potassium) were performed pretreatment, on day 7, on the last day of therapy, and at the 7th day posttreatment follow-up. Antimicrobial susceptibility testing with the \textit{Salmonella} isolates was performed with agar dilution to determine MICs (14).

Serum samples were drawn at admission for antityphoid agglutinins (O and H), and a titer of anti-O agglutinin of $\geq 1:80$ was considered to be positive.

Analysis of variance for continuous variables and chi-square and Mantel-Haenszel tests for discrete variables were used in the analyses, employing the SPSS/PC+ program.

The study was reviewed and approved by the Ethical Institutional Review Board of the Universidad Peruana 'Cayetano Heredia.' All patients included in the study gave written consent.

**RESULTS**

A total of 52 patients were enrolled in the trial. Eight patients were later removed from the study, because five patients had negative baseline cultures, and three patients elected not to enter the trial. A total of 44 patients, 22 in each group, with culture-proven typhoid fever were enrolled in the trial and served as the basis of this study. Three subjects randomized to the aztreonam group were removed from the clinical efficacy analysis because they failed to complete the required therapy. One of the subjects withdrew voluntarily from the study on day 4, and two were removed from the trial (one on day 1 and the other on day 4 of therapy) because they developed gastrointestinal bleeding. These subjects were removed from the efficacy analysis.

The groups (aztreonam versus chloramphenicol, respectively) were comparable at enrollment in terms of mean age (25.3 versus 21.9 years), mean body weight (52.3 versus 52.7 kg), mean body height (156.4 versus 157.9 cm), complaints of malaise (82 versus 68%), headache (68 versus 77%), diarrhea (32 versus 45%), abdominal pain or cramps (36 versus 41%), presence of fever (100% for both groups), hepatomegaly (86 versus 95%), splenomegaly (13 versus 4%), and the presence of rose spots (23 versus 32%). Twelve subjects (55%) randomized to receive aztreonam were females, while 15 (68%) of the chloramphenicol-treated subjects were females. The clinical severity of the patients as judged by the admitting physician differed slightly: 16 (73%) of the aztreonam-treated patients were felt to have mild illness, and 6 (27%) were felt to have moderate illness; 11 (50%) of the chloramphenicol-treated patients were judged to have mild illness, and 11 (50%) were judged to have moderate illness.

By the enrollment criteria, each of the patients had a positive isolate of \textit{S. typhi} or \textit{S. paratyphi} by blood, bone marrow, or bile (Entero-Test) culture. The biologic fluid with the highest yield was bone marrow aspirate, with bile and blood cultures being positive with about equal frequencies (Table 1). A significantly lower frequency of occurrence of positive blood culture was seen in the patients randomized to receive chloramphenicol than in those randomized to receive aztreonam ($P < 0.05$). Of the \textit{Salmonella} organisms isolated from the patients, 17 in both groups (77%) were \textit{S. typhi} and 5 (23%) were \textit{S. paratyphi}. All \textit{Salmonella} isolates were found to be susceptible to aztreonam (MIC for 90% of the strains, 0.25 $\mu g/ml$) and chloramphenicol (MIC for 90% of the strains, 8 $\mu g/ml$). Typhoid O agglutinins were detected in 71 and 77% of the patients randomized to receive aztreonam and chloramphenicol, respectively.

All patients randomized to receive chloramphenicol completed the 14 days of treatment, while two who received aztreonam developed intestinal hemorrhages (one on day 1 and the second on day 4 of therapy), and a third patient elected

### Table 1. Baseline microbiologic and serologic findings from comparison of aztreonam and chloramphenicol typhoid fever therapy

<table>
<thead>
<tr>
<th>Test</th>
<th>Aztreonam group</th>
<th>Chloramphenicol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>19/22 (86%)</td>
<td>12/22 (54%)</td>
</tr>
<tr>
<td>Bone marrow culture</td>
<td>22/22 (100%)</td>
<td>21/22 (95%)</td>
</tr>
<tr>
<td>Bile (Entero-Test) culture</td>
<td>11/16 (69%)</td>
<td>12/21 (57%)</td>
</tr>
<tr>
<td>Stool culture</td>
<td>7/22 (32%)</td>
<td>8/21 (36%)</td>
</tr>
<tr>
<td>Typhoid agglutination (O agglutinin $&gt; 1/80$)</td>
<td>15/21 (71%)</td>
<td>17/22 (77%)</td>
</tr>
</tbody>
</table>

$^a$ $P < 0.05$.

$^b$ $P$, not significant.
TABLE 2. Distribution of febrile patients by day of treatmenta

<table>
<thead>
<tr>
<th>Treatment day</th>
<th>Aztreonam group</th>
<th>Chloramphenicol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/22 (100)</td>
<td>22/22 (100)</td>
</tr>
<tr>
<td>2</td>
<td>21/21 (100)</td>
<td>20/22 (91)</td>
</tr>
<tr>
<td>3</td>
<td>20/21 (95)</td>
<td>18/22 (82)</td>
</tr>
<tr>
<td>4</td>
<td>18/19 (95)</td>
<td>14/22 (64)</td>
</tr>
<tr>
<td>5</td>
<td>15/19 (79)</td>
<td>10/22 (45)</td>
</tr>
<tr>
<td>6</td>
<td>12/19 (63)</td>
<td>4/22 (18)</td>
</tr>
<tr>
<td>7</td>
<td>11/19 (58)</td>
<td>2/22 (9)</td>
</tr>
<tr>
<td>8</td>
<td>8/19 (42)</td>
<td>0/22 (0)a</td>
</tr>
<tr>
<td>9</td>
<td>4/19 (21)</td>
<td>0/22 (0)</td>
</tr>
</tbody>
</table>

a Temperatures were taken each 6 h during therapy. Fever was defined as an oral temperature of ≥37.5°C. To be considered afebrile, the patient had to have a temperature of ≤37.5°C and be without fever thereafter during treatment.  

* P < 0.001.

TABLE 3. Clinical responses with aztreonam and chloramphenicol typhoid fever therapy

<table>
<thead>
<tr>
<th>Patient's status</th>
<th>No. with status/no. treated (%) in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aztreonam group</td>
</tr>
<tr>
<td>Completed therapy</td>
<td>19/22 (86)⁵</td>
</tr>
<tr>
<td>Was cured</td>
<td>15/22 (68)⁵</td>
</tr>
<tr>
<td>Was clinical failure</td>
<td>7/22 (32)⁵</td>
</tr>
<tr>
<td>Failed to complete trial</td>
<td>3/22 (14)</td>
</tr>
<tr>
<td>Had typhoid relapse</td>
<td>0/19 (0)</td>
</tr>
</tbody>
</table>

⁵ P, not significant.

⁶ Denominator includes the three patients that were dropped from analysis.

⁷ P < 0.01 by Fisher's exact test.

⁸ Two patients were removed from the trial because of the occurrence of gastrointestinal hemorrhage on day 1 for one patient and on day 4 for the second, and one patient requested (on day 4) to be removed from the trial for unknown reasons.

to withdraw from the trial without explanation on day 4. Each of these three patients was withdrawn from the trial and excluded from the efficacy analysis. Defervescence occurred more quickly in the subjects receiving chloramphenicol than in those receiving aztreonam. The average time from initiation of therapy until defervescence was 6.6 ± 3.58 days in the aztreonam group, with the corresponding time in the chloramphenicol group being 4.5 ± 2.3 days (P < 0.03). By analysis of variance, adjusting for sex, day of treatment, and culture positivity, there was a statistical difference between the durations of fever between the two treatment groups (P < 0.001). The number of febrile patients was greater on each day of therapy in the aztreonam group than in the chloramphenicol group (Table 2). This difference was significant beginning with the fifth day of treatment. The difference in the persistence of fever in the groups was highly significant (P < 0.001). No patient in the chloramphenicol group was febrile after the eighth day, while 8 of 19 (42%) patients in the aztreonam group remained febrile on the ninth day of therapy. Four patients of the aztreonam group (21%) remained with fever through 10 days of therapy, when the study drug was changed to chloramphenicol.

Twenty-two of 22 (100%) patients receiving chloramphenicol were clinically cured, while 7 patients (32%) were declared treatment failures in the group receiving aztreonam (Table 3). One patient in the chloramphenicol group developed a bacteriologic and clinical relapse during the 8-week follow-up. Patients receiving aztreonam appeared to have more rapid elimination of organisms from blood than those in the chloramphenicol group. None of the 19 patients completing a course of aztreonam, compared with 7 of 22 patients receiving chloramphenicol, had a positive blood culture after 24 h of therapy (Table 4) (P < 0.01). The same difference, although less obvious, was seen for days 2 through 4 of therapy. Relapses did not occur in the aztreonam group. Stool cultures became negative more slowly than the blood cultures. At the end of treatment, (days 1 and 2 posttreatment), 2 of 15 (13%) patients who completed their treatment in the aztreonam group and 1 of 22 (5%) patients of the chloramphenicol group had a stool culture positive for Salmonella infection. One patient in each group had a stool culture positive for Salmonella infection at the seventh day of follow-up, and one patient in the chloramphenicol group was positive at the 14-day follow-up.

Adverse experiences in either group were unusual and mild. The reactions encountered in the aztreonam versus chloramphenicol groups, respectively, were as follows: paresthesia, 3 of 19 (16%) versus 0 of 22; acne, 0 of 19 versus 2 of 22 (9%); arthralgia, 0 of 19 versus 1 of 22 (5%); leukopenia, 4 of 19 (21%) versus 6 of 22 (27%); increased serum glutamic oxaloacetic transaminase, 4 of 19 (21%) versus 0 of 22; and increased alkaline phosphatase, 2 of 19 (10%) versus 0 of 22. No important changes or significant differences between treatment groups in hematocrit or hemoglobin values were seen during therapy.

DISCUSSION

During the last 20 years, reports of the occurrence of chloramphenicol-resistant S. typhi have occurred in virtually all parts of the world (1, 5, 6, 8). In a number of the reports, multiresistant typhoid strains have been identified against which none of the standard antityphoid drugs (including ampicillin and trimethoprim-sulfamethoxazole) were active. This and the ineffectiveness of standard therapy (chloramphenicol)

<table>
<thead>
<tr>
<th>Test</th>
<th>No. positive/no. treated (%) in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aztreonam group</td>
</tr>
<tr>
<td>Blood culture</td>
<td></td>
</tr>
<tr>
<td>Day of treatment</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>3</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>4</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>Day posttreatment</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>7</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>21</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>Stool culture</td>
<td></td>
</tr>
<tr>
<td>Day of treatment</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1/19 (5)</td>
</tr>
<tr>
<td>2</td>
<td>7/19 (37)</td>
</tr>
<tr>
<td>3</td>
<td>4/19 (21)</td>
</tr>
<tr>
<td>4</td>
<td>2/19 (11)</td>
</tr>
<tr>
<td>5</td>
<td>1/19 (5)</td>
</tr>
<tr>
<td>Day posttreatment</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2/15 (13)</td>
</tr>
<tr>
<td>7</td>
<td>1/15 (7)</td>
</tr>
<tr>
<td>21</td>
<td>0/15 (0)</td>
</tr>
</tbody>
</table>

* P < 0.01.
in preventing intestinal carriage of *S. typhi* or typhoid relapse make the search for effective antityphoid drugs essential. Among the new drugs being examined are those with in vitro activity against *S. typhi* and *S. paratyphi*, including broad-spectrum cephalosporins, the new fluorquinolones, and aztreonam (2, 6, 12, 15). Two recent reports suggested that aztreonam might be of value in the treatment of typhoid fever (7, 18). One of these studies was with children treated in a randomized clinical trial in Mexico City (18), and the second was an open trial with adults treated in Egypt (7). In the study in Mexico, 36 children received either aztreonam or chloramphenicol. Clinical cure was seen in 18 of 18 patients randomized to aztreonam. These children were given 150 mg/kg/day, suggesting that perhaps a higher dose of aztreonam might be more effective. In the study carried out in Egypt, only four patients were treated with aztreonam (same dose as in the present trial) after undergoing an initial trial with chloramphenicol. One of the strains was resistant to chloramphenicol in the Egypt study.

The present study was a controlled randomized trial comparing aztreonam with chloramphenicol. The study confirmed the value of bone marrow aspirate cultures in establishing the diagnosis of typhoid fever. Among 44 patients with invasive disease due to chloramphenicol-susceptible typhoid *Salmonella* organisms, bone marrow cultures were positive in 43 of 44 (98%) patients, blood cultures were positive in 31 of 44 (70%) patients, bile cultures by the string test (Enterob-Test) were positive in 23 of 37 (62%) patients, and stool cultures were positive in 15 of 43 (35%) patients. Despite a high degree of susceptibility of all strains to aztreonam (MIC for 90% of the strains, 0.25 μg/ml), there was a prolonged period of fever in the aztreonam-treated patients, with an average of 2 days longer than was seen in the chloramphenicol-treated subjects; in addition, the percentage of febrile patients through treatment was higher in the aztreonam group than in the chloramphenicol group. Four of 19 (21%) patients receiving aztreonam, versus none of 22 receiving chloramphenicol, remained febrile for 10 days of therapy and were declared treatment failures (P = 0.04). Two patients in the aztreonam group were excluded because of intestinal bleeding. If the three patients prematurely dropped from the study after being randomized to receive aztreonam are included in the analysis, the rate of failure for aztreonam increases to 7 of 22 (32%) (P < 0.01).

Aztreonam appeared to have a more rapid effect on elimination of the infecting *Salmonella* organisms from the bloodstream than chloramphenicol did. In 100% of the patients receiving aztreonam, the infecting *S. typhi* organisms were eradicated from blood cultures during the first day of treatment. This is in contrast to a culture positivity rate for day 1 blood cultures of 32% for the chloramphenicol-treated patients (P < 0.01). This may have been even more important, considering the higher rate of pretreatment blood culture positivity in the aztreonam group than in the chloramphenicol group (86 versus 54%, respectively; P < 0.05). Interestingly, the four patients declared treatment failures, with fever persisting throughout the 10 days of aztreonam treatment, had consistently negative blood cultures.

Comparing the present study with previous clinical trials carried out at this institution, the rate of cure for aztreonam was lower than that seen for standard therapy, but the bacteriologic response to aztreonam was superior. One possible explanation for the findings of the various studies is that aztreonam is able to clear *Salmonella* organisms from the blood of bacteremic patients, but it is less effective in eradication of the organism from the intracellular location characteristic of the later stages of typhoid infection. We speculate that aztreonam may not have adequately penetrated and concentrated within the intracellular tissues serving as the habitat of the infecting *Salmonella*.

Recent studies indicate that aztreonam shows a high degree of in vitro activity against enteric bacterial pathogens (8, 16). The drug has been shown, furthermore, to be effective in the treatment of bacterial enterocolitis of U.S. travelers to Mexico when given orally (4). Further studies to examine the effect of aztreonam on other forms of bacterial enteric infection are indicated. Considering its rapid clearance from the bloodstream of patients with typhoid fever, it is suggested that the value of the drug in treating nontyphoidal *Salmonella* infections, such as *Salmonella enteritidis* gastroenteritis, with or without bacteremia, and extraintestinal infection, including central nervous system infection in young infants and systemic salmonellosis in patients infected with the human immunodeficiency virus, be determined.

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