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Treatment of Typhoid Fever with Ceftriaxone for 5 Days or Chloramphenicol for 14 Days: a Randomized Clinical Trial

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To compare the therapeutic efficacy of ceftriaxone given once daily for 5 days and chloramphenicol given four times daily for 14 days, a controlled trial was carried out with 59 patients who were culture positive for *Salmonella typhi*. Ceftriaxone was given to 28 patients in once-daily intravenous doses of 75 mg/kg of body weight to children and 4 g to adults for 5 days; chloramphenicol was given to 31 patients at a dosage of 60 mg/kg/day until defervescence and then at 40 mg/kg/day to complete 14 days of treatment. All *Salmonella* isolates were susceptible to both antibiotics. Clinical cures (defervescence without complications, no relapse, and no need for further treatment) occurred in 79% of the patients treated with ceftriaxone and 90% of those treated with chloramphenicol ($P = 0.37$). On the third day of treatment, blood cultures were positive for *S. typhi* for 60% of the patients in the chloramphenicol group and 0% of the ceftriaxone group ($P = 0.001$). Defervescence occurred in half the patients in both groups during the first 7 days, but on days 9 to 13 after the start of treatment, nine patients in the ceftriaxone group, compared with six patients in the chloramphenicol group, remained febrile ($P = 0.4$). The median hematocrit and total leukocyte counts at day 14 were significantly lower for the chloramphenicol group than those for the ceftriaxone group ($P = 0.01$ and $P = 0.02$, respectively). These results indicate that the effects of therapy with ceftriaxone for typhoid fever differed from those of chloramphenicol therapy in that blood cultures became negative earlier, prolonged fever persisted in some patients, and bone marrow suppression was reduced. We conclude that a short, 5-day course of ceftriaxone is a useful alternative to conventional 14-day chloramphenicol therapy in the treatment of typhoid fever.

Chloramphenicol has been the treatment of choice for typhoid fever for nearly 40 years, particularly in developing countries, where the cost of treatment is of considerable importance. However, newer antibiotics with good in vivo activity against *Salmonella typhi* are needed because of the alarming spread of R-factor-mediated chloramphenicol-resistant *S. typhi* throughout the world (3, 4, 11, 23). Recently, ceftriaxone has emerged as a satisfactory alternative to chloramphenicol (1, 2, 5, 8, 10, 12, 13, 21, 22).

Ceftriaxone has good broad-spectrum activity against gram-positive and gram-negative bacteria, including *S. typhi* (15). It has a long half-life in serum (ranging from 6.0 to 8.6 h), making it suitable for a once-daily dose regimen (16, 20). Randomized trials comparing chloramphenicol to ceftriaxone given once daily for 7 days for typhoid fever in Bangladesh (8) showed an efficacy of ceftriaxone comparable to that of chloramphenicol. The need for less expensive, shorter regimens prompted us to evaluate further the efficacy of ceftriaxone for treating typhoid fever in both children and adults; use of ceftriaxone would reduce the duration of therapy to 5 days, thereby lowering bed occupancy and hospitalization cost.

MATERIALS AND METHODS

Selection of patients. The study was conducted in the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), during 1986 and 1987. Patients who met the following criteria were eligible for enrollment: age, 6 months to 60 years; fever for >4 days; diarrhea, defined as more than three liquid stools in 24 h; and a somatic O agglutinin titer of >80 for *S. typhi*, as determined by the Widal test. Patients with such clinical presentations as blood and/or stool cultures that tested positive for *S. typhi* were included. Exclusion criteria were the presence of jaundice, gastrointestinal hemorrhage or perforation, a history of recent antibiotic therapy, and a history of known allergy to penicillin or cephalosporins. Patients were requested to remain in the hospital for 14 days for treatment. Written informed consent was obtained from adult patients and for children from their guardians. The study was approved by the Ethical Review Committee of ICDDR,B.

Sample size calculation. To allow detection of a 90% cure rate in the ceftriaxone group by day 7 of treatment, with the assumption that 60% of patients in chloramphenicol group would be cured by that time, for calculations the number of patients in each group was taken to be 30 ($\alpha = 0.05$; $\beta = 0.2$) (24).

Clinical studies. Patient histories were obtained and physical examinations were performed before the start of treatment and daily during treatment for 14 days, with results recorded daily. Rectal temperatures, pulse rates, respiratory rates, and blood pressures were recorded every 8 h throughout the treatment period. The frequency and consistency of stools were also recorded every 8 h.

Laboratory studies. Venous blood, stool, and urine samples of patients were bacteriologically cultured for *S. typhi* and other bacteria at the time of admission. Stool swabs were streaked onto MacConkey agar and salmonella-shigella agar. Stool specimens were examined microscopically for the presence of leukocytes, ova, parasites, and occult blood. Isolates of *S. typhi* were sent to the Enteric Reference

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Laboratory (Colindale, London, United Kingdom) for further confirmation. The isolated strains were tested for antimicrobial susceptibility by disk diffusion methods. Ceftriaxone disks containing 30 μg of antibiotic were used, and a clear zone >16 mm in diameter was used to indicate sensitivity. Blood cultures were repeated during the study on days 3 and 14, and stool specimens were cultured on days 5 and 14 and 1 week after the patient's discharge from the hospital. Complete blood cell counts were performed before therapy and repeated on days 5 and 14.

Treatment schedules. After the initial clinical laboratory tests, patients were assigned to one of two treatment groups by using sealed envelopes containing a numeric treatment code obtained from a table of random numbers. Chloramphenicol was given orally or intravenously in four divided doses daily for 14 days. Adults and children received chloramphenicol (Kemicetene; Farmitalia Carlo Erba, Italy) in dosages of 60 mg/kg of body weight per day until defervescence occurred (rectal temperature of <37.8°C for 48 h) and then at 40 mg/kg/day to complete the course of 14 days. Ceftriaxone (F. Hoffmann-La Roche, Basel, Switzerland) was administered intravenously over 30 min in a single daily dose for 5 days. The daily dose of ceftriaxone was 4 g for adults (>14 years old) and 75 mg/kg of body weight for children (≤14 years old).

Assessment of treatment effects. The effects of therapy were assessed both clinically and bacteriologically. Patients were considered clinically cured if they became afebrile (rectal temperature of <37.8°C for 48 h) by day 7 after the start of therapy and if no complications (including intestinal perforation, bleeding, or pneumonia) developed, no retreatment for typhoid fever was required, and no relapse was experienced after discharge. Relapse was defined as a recurrence of fever after the initial course of therapy had been completed and isolation of *S. typhi* from blood or stool samples within 2 weeks after the start of therapy. The first afebrile day was defined as the first day the patient's rectal temperature dropped to and remained at <37.8°C for at least 48 h. Diarrhea was considered to have ended when the last liquid stool was passed. Adverse reactions to the drugs were monitored daily. Patients were asked to return to the hospital 1 week after the date of discharge or any time there was a recurrence of fever for bacteriological and clinical assessment.

Statistical analysis. Bacteriological and clinical efficacy results were compared by using the nonparametric Mann-Whitney U test. The significance of the differences in proportions was tested with the chi-square test. Statistical significance was defined as $P < 0.05$.

RESULTS

Patients. Fifty-nine patients with culture-proven typhoid fever assigned to the two treatment groups had comparable clinical features of age, gender, duration of illness, and duration of fever (Table 1).

Bacteria. Most patients (88%) had bacteremic infections, but a few patients (12%) without bacteremia had positive stool cultures and showed clinical features of acute typhoid fever that were indistinguishable from those of the rest of the patients. All isolates were susceptible to ceftriaxone and chloramphenicol.

Clinical response to treatment. Clinical cures occurred in 22 patients (79%) who received ceftriaxone and in 28 patients (90%) who received chloramphenicol (Table 2) ($P = 0.37$). The six patients in the ceftriaxone group who were not cured included one patient who had a relapse after discharge, two who developed pneumonia in the hospital, one who developed a urinary tract infection, and two who remained febrile for more than 14 days after the start of treatment without an apparent cause for the fever and were given chloramphenicol. The ages of the six patients not cured with ceftriaxone were 6, 15, 16 (two patients), 20, and 30 years, indicating that clinical failure occurred in children and adults alike. The three patients in the chloramphenicol group who were not cured included one patient who had a relapse and two who had urinary tract infections.

The rates of defervescence in the ceftriaxone and chloramphenicol groups were similar (50 versus 51%) in the first week after the start of treatment (Fig. 1), but during the second week, on days 9 through 13, nine patients in the ceftriaxone group and six patients in the chloramphenicol group remained febrile; however, this difference was not statistically significant ($P = 0.4$). Despite the persistence of fever in patients treated with ceftriaxone, most of the patients experienced clinical improvement. The mean maximal temperature on the 10th day after the start of treatment in 15 patients who were still febrile was 38.4°C, compared

TABLE 1. Characteristics of patients culture positive for typhoid fever at the time of admission

Characteristic	Median value (range) for treatment group[a]	
	Ceftriaxone	Chloramphenicol
No. of patients treated	28	31
Age (yr)	18 (3.5–35)	18 (2–35)
No. of males/females	16/12	16/15
Duration of fever (days)	8 (3–21)	10 (4–30)
Duration of diarrhea (days)	5 (1–15)	5 (2–30)
No. of patients with positive cultures		
Blood only	15	15
Blood and stool	9	14
Stool only	4	2

TABLE 2. Clinical and bacteriologic responses to treatment

Result	No. of patients in treatment group with result	
	Ceftriaxone ($n = 28$)	Chloramphenicol ($n = 31$)
Clinical cure[a]	22	28
Relapse	1	1
Pneumonia	2	0
Urinary tract infection	1	2
Prolonged fever requiring retreatment with other antimicrobial agents	2	0
Blood cultures positive for *S. typhi* on:		
Day 3	0	20[b]
Day 14	0	0
Stool cultures positive for *S. typhi* on:		
Day 5	1	0
Day 14	1	0

[a] Defervescence (temperature of ≤37.8°C for 48 h) within 14 days after the start of treatment without complications, relapse, or need for retreatment with another antimicrobial agent.

[b] $P = 0.01$ in comparison with the results for the ceftriaxone group.

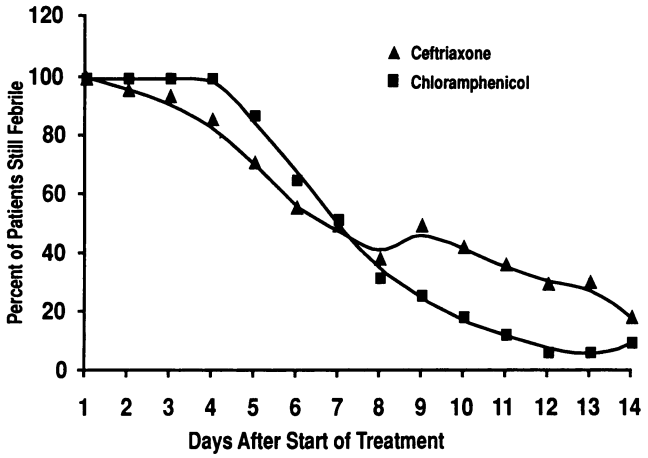

FIG. 1. Percentages of patients with fever on each day after the start of treatment with ceftriaxone or chloramphenicol. Fever was considered present on days when at least one rectal temperature reading was >37.8°C; to be considered afebrile, a patient was required to have a temperature of ≤37.8°C for 48 h. The percentages of patients treated with ceftriaxone who were still febrile on days 9 to 13 after the start of treatment were not significantly greater (P = 0.40) than those of patients treated with chloramphenicol.

with 40.2°C for the same patients at the time of admission (P < 0.05).

Bacteriologic response to treatment. At the end of the 14-day observation period, blood cultures were negative for all patients. Blood cultures obtained on the third day of treatment, however, were still positive for *S. typhi* for 20 patients receiving chloramphenicol, whereas they were negative for all patients receiving ceftriaxone (P = 0.001) (Table 2). Stool cultures were positive after the start of treatment for only two patients in the ceftriaxone group. Seventeen patients (61%) in the ceftriaxone group and 23 patients (74%) in the chloramphenicol group returned for follow-up visits a week or more after discharge. Two patients (one in each treatment group) with clinical relapses detected 1 to 2 weeks after discharge had stool cultures positive for *S. typhi*. One patient in the chloramphenicol group had a positive stool culture 1 week after discharge but had no fever.

Hematologic effects of treatment. Patients who received chloramphenicol showed a significantly lower median hematocrit (30.5%) on day 14 after the start of treatment than the patients treated with ceftriaxone (hematocrit, 34.5%) (P = 0.01) (Table 3). The median leukocyte count on day 14 was also lower for patients treated with chloramphenicol (P = 0.02), but the median platelet counts did not differ significantly between the treatment groups (P = 0.17).

The median duration of diarrhea after therapy was similar (3.0 days) in both groups. Patients treated with ceftriaxone had a median volume of stool passed on day 1 of 12.0 ml/kg of body weight, compared with 17.2 ml/kg for those treated with chloramphenicol, which was not significantly different (P = 0.7). Similarly, the cumulative stool volumes on day 3 were 38.8 versus 55 ml/kg for the ceftriaxone and chloramphenicol groups, respectively (P = 0.3). Microscopic examination of stool samples from the 59 patients revealed ova of *Ascaris lumbricoides*, alone or in association with ova of *Trichuris trichiura* and *Ankylostoma duodenale*, in 50 and 51% of patients treated with ceftriaxone and chloramphenicol, respectively. No other side effects in patients of either treatment group were noted, except that one patient in the ceftriaxone group had a skin rash which disappeared after discontinuation of the drug.

TABLE 3. Hematologic characteristics of patients at time of admission and after start of treatment

Parameter and time	Median value (range) for treatment group		P value
	Ceftriaxone (n = 28)	Chloramphenicol (n = 31)	
Hematocrit, %			
Admission	36.5 (26–46)	37.0 (15–49)	0.79
Day 5	36.0 (25–46)	34.0 (17–49)	0.63
Day 14	34.5 (24–44)	30.5 (16–48)	0.01
Leukocytes, $10^3/mm^3$			
Admission	7.7 (3.5–13.6)	7.2 (3.0–21.6)	0.52
Day 5	8.2 (4.5–16.6)	7.6 (5.0–19.4)	0.92
Day 14	8.5 (5.9–13.2)	7.6 (3.8–10.8)	0.02
Platelets, $10^3/mm^3$			
Admission	156 (80–305)	135 (60–265)	0.46
Day 5	170 (85–280)	155 (90–275)	0.17
Day 14	198 (105–400)	175 (80–270)	0.17

DISCUSSION

The results of this treatment trial confirm those of other studies which used ceftriaxone in cases of acute typhoid fever (1, 2, 5, 8, 10, 12, 13, 21, 22); i.e., this antibiotic achieved satisfactory clinical and bacteriologic responses. Adults and children responded equally well to ceftriaxone treatment in our study, confirming the findings of Meloni et al. (12) and Farid et al. (5) that children can be effectively treated with ceftriaxone. The treatment for 5 days with daily injections of ceftriaxone used in this trial showed results comparable to those of treatment for 7 days (8), confirming the results of Auvergnat et al. (1) and Moosa and Rubidge (13), who used ceftriaxone for 5 days. Further studies by Lasserre et al. (10) and Chi-kin et al. (2) have shown that even shorter courses of ceftriaxone (2 to 3 days) may be adequate for the treatment of typhoid fever.

Patients treated with ceftriaxone, on the other hand, were more likely to remain febrile for a week or more after the start of treatment than patients treated with chloramphenicol. The proportion of patients having prolonged fever (lasting ≥10 days) was 32% for patients treated with ceftriaxone, compared with 23% reported by Islam et al. (8) for patients with typhoid fever who were treated with ceftriaxone for 7 days. The reasons for prolonged fever in some cases were superinfections leading to pneumonia or urinary tract infection. In other cases, the causes of prolonged fever could not be determined. It is unlikely that inadequate levels of antibiotic in the blood occurred during treatment, because concentrations of ceftriaxone in blood were measured by Islam et al. (8) in patients with typhoid fever 24 h after intravenous doses and were well above the MICs for *Salmonella* spp. (5). Most of the patients, despite the persistence of fever, improved clinically, and their maximal daily temperatures declined.

One disadvantage of giving chloramphenicol for the treatment of typhoid is that it causes suppression of the bone marrow. In this study, patients treated with chloramphenicol showed significantly lower hematocrits at the end of treatment than patients treated with ceftriaxone. The median leukocyte count was also significantly lower in patients treated with chloramphenicol. These findings were similar to

those of a previous study by Islam et al. (8), which showed lower mean counts of leukocytes and platelets after treatment of typhoid fever.

Another disadvantage of chloramphenicol treatment of typhoid fever is a high rate of relapse after treatment. In a recent outbreak of typhoid fever in Israel, 36% of the patients treated with chloramphenicol experienced relapses (7). Only one patient (3%) in each treatment group of our study was observed to have had a relapse, but this could be an underestimation of the true relapse rate, because the rate of return visits following hospital discharge was not 100%. In the study of Robertson et al. in Egypt (17), relapses occurred in 8% of typhoid patients treated with chloramphenicol versus 0% of patients treated with ampicillin, indicating that perhaps beta-lactam antibiotics are more effective in preventing relapses. Other studies using beta-lactams in typhoid fever treatment that show trends of lower relapse rates were reported by Saunders (19) for ampicillin, Morelli et al. (14) for cefoperazone, and Farid et al. (6) for aztreonam.

Ceftriaxone for treating typhoid fever will be useful for patients in whom a shorter course of injectable-drug therapy is preferable. Additionally, ceftriaxone will have a role in treating infections resistant to other antibiotics (3, 4, 9, 11, 18, 23).

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