Comparative efficacy of ceftriaxone and ampicillin for treatment of severe shigellosis in children

I. Varsano, MD, T. Eidlitz-Marcus, MD, M. Nussinovitch, MD, and I. Elian, PhD

From the Department of Pediatrics and Microbiology, Tel Aviv University School of Medicine, Hasharon Hospital, Petah Tiqva, Israel

In a prospective randomized open study, ceftriaxone, 50 mg/kg per day, was compared with ampicillin, 100 mg/kg per day, both given for a period of 5 days, for the treatment of 40 children whose mean (±SD) age was 4.5 ± 3.2 years and who had severe dysentery caused by Shigella organisms. Twenty patients were treated with ceftriaxone and 20 with ampicillin. Both drugs were initially given intravenously for a period of 1 to 2 days and were continued intramuscularly, in the case of ceftriaxone, or orally, in the patients receiving ampicillin. All Shigella organisms isolated were susceptible to ceftriaxone; 28% were resistant to ampicillin. The diarrhea persisted for a mean (±SD) period of 2.5 ± 1.0 days in the ceftriaxone-treated patients versus 6.8 ± 6.3 days in the ampicillin-treated patients (p <0.005). At the end of the 5 days of therapy, stool cultures for Shigella organisms were negative in 12 (60%) of the 20 patients from the ampicillin group and in all the children (100%) from the ceftriaxone group (p <0.001). Bacteriologic relapses were observed in eight (40%) of the patients treated with ampicillin but in none of the children treated with ceftriaxone (p <0.001). In instances of clinical or bacteriologic failure in the ampicillin group, retreatment was instituted in most of the cases with ceftriaxone; persistent clearing of the Shigella organisms from the stool was finally achieved after a mean (±SD) period of 11.75 ± 9.4 days after therapy was started, as compared with 1.85 ± 0.6 days in the ceftriaxone-treated patients (p <0.001). We conclude that in children with severe shigellosis, treatment with ceftriaxone for 5 days is effective and better than use of ampicillin for clinical cure and eradication of the Shigella organisms from the stool. (J PEDIATR 1991;118:627-32)

It is generally accepted that effective antimicrobial therapy for shigellosis, especially in the pediatric population, shortens the duration of illness, achieves a rapid bacteriologic cure, and in patients from less developed countries would have a significant positive impact on growth and nutritional status of the affected children.1-4 Multiple resistance to the commonly used antibiotics for treatment of shigellosis, that is, ampicillin, trimethoprim-sulfamethoxazole, and tetracycline, has been reported from many countries,1,5-8 and resistance to nalidixic acid has been similarly encountered.9,10 Fluoroquinolones, although effective for treatment of shigellosis, are currently contraindicated for use in children.11 Ceftriaxone, a third-generation cephalosporin, has been shown to be highly active against the Shigella strains tested (minimum inhibitory concentration 0.016 to 0.2 μg/ml)12,13 Studies of more than 500 Shigella organism isolates from Europe, America, Southern and Eastern Asia, and Bangladesh12-22 reveal that all but two strains, both from Turkey,19,20 were susceptible to ceftriaxone. An important advantage of this cephalosporin is its long serum
half-life of 4½ to 9 hours, which allows once-daily administration. This study compares the outcome of severe shigellosis in children treated with a single daily dose of ceftriaxone with that after treatment with ampicillin, both drugs having been given over a 5-day period.

METHODS

Study design. Children aged 6 months to 16 years with severe dysentery requiring hospital admission to the Hasharon Hospital Department of Pediatrics, Petah Tiqwa, Israel, during the period from June 1988 through September 1989, were included in the study.

Severe clinical dysentery was defined as two or more diarrheal stools during the 24 hours preceding the admission, together with two or more of the following: macroscopic blood in the stools, temperature ≥ 38.5°C, leukocyte band forms >15%. Patients who received any antibiotic therapy during the previous 2 days were excluded. After stool cultures were obtained, the patients were assigned at random to receive ampicillin or ceftriaxone for a period of 5 days by using a standard randomized numbers table and block size of 16. If no Shigella organism was isolated, the trial therapy was stopped and the patient excluded from the study.

Ceftriaxone was administered in single daily doses of 50 mg/kg, maximum 1.5 gm, and ampicillin 100 mg/kg per day divided into four equal doses. During the first 24 hours and occasionally longer as indicated by the severity of the disease and need for rehydration, the drugs were administered intravenously and continued intramuscularly in the case of ceftriaxone or orally in the patients receiving ampicillin. The type of therapy administered was known to the physician involved but was unknown to the personnel performing the bacteriologic studies.

Clinical failure was arbitrarily defined as the persistence of toxic reactions for more than 48 hours after initiation of the treatment, that is, ongoing temperature of > 38.5°C, tenesmus, and profuse diarrhea. Continuation of the diarrhea (three diarrheal stools or more per day) after cessation of the first 5 days of the therapy was also designated as a failure, although it must be kept in mind that the continuation of the diarrhea might also have been caused by the antibiotics used. Mild or no diarrhea (fewer than three stools per day) and absence of other signs and symptoms attributable to shigellosis were accepted as clinical cure. We defined bacteriologic failure as the isolation of Shigella organisms from stool cultures 2 weeks or longer after the patient was enrolled in the study.

In cases of clinical or bacteriologic failure, additional therapy was instituted according to the following criteria: (1) In the patients from the ampicillin group, when clinical failure occurred, ceftriaxone was to be administered for a period of 5 days; when, despite a clinical cure, bacteriologic failure was evident and the Shigella organisms excreted remained susceptible to ampicillin, a second 5-day course of ampicillin was to be given. When this therapy failed to eradicate the pathogen (positive culture after cessation of the therapy), a 5-day course of ceftriaxone was to be administered. (2) For clinical or bacteriologic failure, or both, in patients from the ceftriaxone group, retreatment according to the susceptibility of the Shigella organisms was to be instituted.

Drugs that could have affected the patients' clinical course, such as opiates, loperamide, and kaolin-pectin mixtures, were not used. Acetaminophen was given only to patients with severe toxicity associated with temperature above 38.5°C.

After the patient's condition improved clinically, usually after 2 to 3 days, therapy and follow-up were continued on an outpatient basis. The patients were scheduled to visit the hospital clinic daily for the first 7 study days, and thereafter periodically at intervals of 5 to 7 days, or more frequently if stool cultures or retreatment was needed.

Bacteriologic examinations. Stool cultures were obtained at baseline, during days 1, 2, 3, and 5, and between days 10 and 15 after admission to the hospital and thereafter at periodic intervals of 5 to 7 days, until two sequential negative cultures were obtained. For identification of Shigella and Salmonella species and pathogenic Escherichia coli strains, the specimens were plated on MacConkey and Salmonella-Shigella agars and in selenite broth. The isolates were differentiated with polyvalent and specific typing sera. The susceptibility of isolates of Shigella organisms to ampicillin and ceftriaxone was determined by means of the disk diffusion method. The disks used contained 25 μg ampicillin and 30 μg ceftriaxone. A clear zone >14 mm for ampicillin and >30 mm for ceftriaxone was used to indicate susceptibility.

Statistical methods. The significance of differences between means was tested with the use of a Student two-sample t test, under the assumption that the scores were independent observations from normally distributed populations. For evaluation of differences between two independent (noncorrelated) samples of categoric variables, the chi-square test was used, and if at least one of the cells had an expected value less than 5, the Fisher exact probability test was used instead.

The study was approved by the hospital's ethics committee; written informed consent was obtained from the parents before inclusion of each patient in the study.

RESULTS

Forty-nine patients were initially enrolled in the study, but Shigella organisms were isolated from the specimens of only 40 patients. Of these 40 patients, 20 were treated with...
ampicillin and 20 with ceftriaxone. According to the study design, the drugs were first administered intravenously, in the patients from the ceftriaxone group for a mean (±SD) of 1.5 ± 0.6 days and in the children treated with ampicillin for 2.0 ± 0.7 days. Clinical observations and laboratory determinations for patients in the two groups on admission were similar (Table I). Shigella sonnei and Shigella flexneri were recovered in an equal number of patients from each of the two groups, 12 and eight, respectively. Four strains from the ampicillin group and seven from the ceftriaxone group were resistant to ampicillin (28%). All isolates were susceptible to ceftriaxone (Table I).

The ceftriaxone-treated patients had significantly fewer diarrheal stools than did the children from the ampicillin group on study days 2, 4, and 5 (Figure), and the mean duration of diarrhea in the patients treated with ceftriaxone was significantly shorter: mean 2.5 ± 1 versus 6.75 ± 6.3 days, with a range of 1 to 5 and 1 to 21 days (p <0.005). A significant difference was also noted with regard to continuation of fever, with a temperature ≥37.5°C, for a mean of 1.25 ± 0.55 days in the ceftriaxone, compared with 2.3 ± 0.7 days in the ampicillin-treated patients (p = 0.034). Abdominal pain and tenesmus continued for 1.5 ± 1.0 days in the ceftriaxone group versus 2.4 ± 2.3 days in the ampicillin group (p = 0.13).

During the initial course of therapy, Shigella organisms were eradicated from the stools of all patients treated with ceftriaxone after a mean of 1.85 ± 0.6 days and did not reappear in any subsequent examinations (Table II). In the ampicillin group, Shigella organisms were eradicated after 5 days of therapy in 12 patients (60%) versus all the children (100%) in the ceftriaxone group (p <0.001). In eight patients from the ampicillin group, bacteriologic relapse occurred 1 to 6 days after the cessation of therapy. The proportion of relapses did not differ statistically between the patients in whom the initially isolated strains were sensitive or resistant to ampicillin: 6 (38%) of 16 and 2 (50%) of 4, respectively (p = 0.38). During the relapses, the same serotypes as those initially cultured were isolated and the antibiotic susceptibility remained unchanged.

In five children from the ampicillin group, the bacteriologic failure was associated with a continuation of diarrhea. In these patients, retreatment with ceftriaxone given intramuscularly for a period of 5 days was associated with normalization of the stools and eradication of the Shigella organisms. Six patients, although clinically cured, continued to excrete Shigella organisms susceptible to ampicillin for more than 14 days. These patients were retreated with a second ampicillin course for 5 days. This therapy resulted in a bacteriologic cure in three of them; the other three patients continued to excrete Shigella organisms for more than 7 days. In these children, persistent eradication of the pathogen was achieved after a single 5-day course of ceftriaxone. In all eight patients retreated with ceftriaxone, persistent clearing of the Shigella organisms was observed after a mean of 2.2 ± 0.7 days in comparison with 4.3 ± 3 days in the three patients in whom the eradication of Shigella organisms was achieved by retreatment with ampicillin. In two of the patients in whom a relapse occurred, spontaneous clearing was observed before day 14 of the study.

In the ampicillin-treated patients, persistent clearing of the Shigella organisms from the stool, as a result of either the initial treatment or retreatment or spontaneously, was evident after a mean of 11.7 ± 9.4 days (range 2 to 40 days) after admission to the hospital; in the ceftriaxone group the pathogen was persistently eradicated after 1 to 3 days (mean 1.85 ± 0.6 days; p <0.0001) (Table II).

Analysis of all the evaluated factors separately for the 16 patients in the ampicillin group infected by ampicillin-susceptible strains revealed results similar to those found in all 20 patients from this group (data not shown).

No drug-related side effects were observed except that in one child a rash developed during ceftriaxone therapy.

**DISCUSSION**

This study demonstrated that administering ceftriaxone to children with severe shigellosis for 5 days was more successful in effecting a clinical cure and in persistent eradication of the pathogens from the stool than was a 5-day course...
of ampicillin. Ceftriaxone was found to be similarly efficient when administered to patients after a failure of ampicillin therapy.

Lolkeha et al.\textsuperscript{12} and Kabir et al.\textsuperscript{15} have reported that treatment of shigellosis with a single intramuscular dose of ceftriaxone, although associated with clinical improvement, was not effective in eradicating the \textit{Shigella} organisms from the stools. As the authors stated, this failure was probably related to inadequate tissue concentration of the drug after a single dose or inadequate duration of exposure to the antibiotic.\textsuperscript{15}

Patients with shigellosis can be successfully treated with ampicillin when the infecting bacterium is susceptible to this antibiotic.\textsuperscript{26-30} Our study revealed that in the ampicillin-treated patients, despite in vitro susceptibility of the majority of the strains isolated, diarrhea persisted for a mean of 6.7 days, a period similar to that reported in children with shigellosis treated by placebo.\textsuperscript{3} In addition, we observed a low rate of eradication of the \textit{Shigella} organisms and a high proportion of relapses. Our findings indicate a low degree of efficacy of ampicillin for the management of severe shigellosis, particularly with regard to clearing the \textit{Shigella} organisms from the stool, irrespective of the susceptibility of the pathogen to ampicillin in the majority of the patients. These findings probably should be related to the specific \textit{Shigella} strains prevalent in our area. A poor correlation between the in vitro susceptibility of the pathogen to ampicillin and the clinical and bacteriologic outcome

### Table II. Bacteriologic observations in patients with shigellosis treated with ampicillin or ceftriaxone

<table>
<thead>
<tr>
<th></th>
<th>Ampicillin group</th>
<th>Ceftriaxone group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Days (±SD) until first negative stool culture</td>
<td>4 ± 3</td>
<td>12/20</td>
</tr>
<tr>
<td>Patients with negative culture at day 5</td>
<td>60%</td>
<td>20/20</td>
</tr>
<tr>
<td>Bacteriologic relapses (patients)</td>
<td>8/12</td>
<td>67%</td>
</tr>
<tr>
<td>Days ± SD until persistent negative stool culture*</td>
<td>11.7 ± 9.4</td>
<td>1.85 ± 0.6</td>
</tr>
</tbody>
</table>

*Two or more subsequent negative cultures during a period of ≥7 days, after treatment, after retreatment, or spontaneously.
has also been reported by Haltalin et al. 30 A concern that in bacterial diarrhea "drug sensitivity in vitro does not predict clinical response" 8 has been stressed recently by Keusch. The high excretion rate of ceftriaxone in microbiologically active form via the bile, 31 compared with the biliary excretion of ampicillin and other commonly used antibiotics, 32 may have importance for ceftriaxone's effectiveness in the treatment of enteric infections such as shigellosis.

Nalidixic acid has been used to treat patients with Shigella organisms resistant to the commonly used antimicrobial agents, although evidence of efficacy based on results of controlled studies is scant. 27, 33-35 Recently, Salam and Bennish 36 reported promising results with nalidixic acid for the treatment of shigellosis but gave no data concerning the eradication of the Shigella organisms after day 6 of therapy. In our study the majority of relapses occurred during this period. In addition, reports of the emergence of Shigella strains resistant to nalidixic acid have appeared, and in areas where this agent is widely used, resistance can be expected to become more common, as has been described in urinary tract infections. 36

The new fluoroquinolones are active against Shigella organisms and clinically effective when given orally, but because in juvenile animals they are capable of inducing toxic changes in the cartilage, their use has not been approved in pediatric patients. 11, 37

We conclude that treating severe shigellosis in children with a single daily dose of ceftriaxone for a period of 5 days is more effective than ampicillin therapy for clinical and bacteriologic cure. Ceftriaxone therapy was associated with persistent clearing of the Shigella organisms from the stools in most of our patients within the first few days of the therapy, suggesting that such treatment can be valuable not only for abbreviating the clinical symptoms but also for preventing the spread of infection within the community. Unfortunately, the lack of an oral preparation of ceftriaxone limits its use. Because of concern for the emergence of resistant strains, this therapy should be reserved for severely ill patients. In view of the prompt clinical response and clearing of the Shigella organisms from the stool in the majority of patients within 48 hours of ceftriaxone therapy, shorter courses may be equally effective.

We thank Hoffman-LaRoche, Basel, Switzerland, for assistance with the trial and for supplying the ceftriaxone, and Dr. A. Silbert for his editorial contribution.

REFERENCES

22. Mitra AK, Kabir I, Hossain MA. Piramцепилин-resistant
Shigella dysenteriae type 1 infection in Bangladesh. Lancet 1990;335:1461-2.


