Once-Daily Ceftriaxone Therapy for Serious Bacterial Infections in Children

BLAISE L. CONGENI,1*, TASNEE CHONMAITREE,1 TAMARA A. RAKUSAN,2 AND QUELLIN T. BOX2

Department of Pediatrics, Northeastern Ohio Universities College of Medicine at Children's Hospital Medical Center of Akron, Akron, Ohio 44308;1 and Department of Pediatrics, University of Texas Medical Branch, Galveston 775502

Received 8 August 1984/Accepted 9 November 1984

Ceftriaxone administered as a single daily dose of 50 mg/kg was evaluated in the treatment of 35 children with a variety of nonmeningitic bacterial infections. In two of the patients, the drug was discontinued before the trial could be evaluated. All of the remaining patients had a satisfactory response. In 22 of the patients, plasma was available for the determination of ceftriaxone levels 1 h after a dose and immediately before the next dose. All but one of these patients had trough ceftriaxone levels which exceeded the MIC of the infecting organism, although marginally so for Staphylococcus aureus. Ceftriaxone appears to be safe and effective in the treatment of a variety of bacterial pathogens in children when administered at a single daily dose of 50 mg/kg. This drug may be especially useful in those patients in whom outpatient antibiotic therapy is contemplated or in whom maintenance of intravenous access is difficult.

Ceftriaxone is a new expanded-spectrum cephalosporin possessing properties which make it particularly useful in the treatment of pediatric infections. First, it has excellent activity against the major pediatric pathogens including Haemophilus influenzae type b, Streptococcus pneumoniae, Streptococcus pyogenes, group B streptococcus, and Neisseria meningitidis (11). Second, it has a prolonged half-life of between 4 and 7 h (5, 12). In addition, it has modest central nervous system penetration, making it useful in the treatment of bacterial meningitis (7, 13). Several investigators have previously demonstrated its efficacy when used at a dose of 75 mg/kg per day in two divided doses (1, 4, 6, 8, 9, 14). In this study, we evaluated the clinical efficacy and pharmacokinetics of ceftriaxone when administered as a single daily dose for children with serious bacterial infections.

MATERIALS AND METHODS

Hospitalized children suspected of having bacterial infections with susceptible organisms were eligible for enrollment between July 1983 and June 1984. Children with meningitis or allergy to the penicillins or cephalosporins were excluded from this study. After informed consent was obtained, cultures of blood and other infected body sites were prepared. Ceftriaxone was administered intravenously in a 10-min infusion or intramuscularly at a dose of 50 mg/kg.

Forty-eight hours after the initiation of therapy, cultures of blood and other infected body sites were repeated. The cultured specimens were processed in the standard fashion by the clinical microbiology laboratories. Susceptibility testing of the bacterial isolates was performed initially by the standard disk diffusion method. The MICs were determined by the tube dilution technique with Mueller-Hinton broth and a 104-CFU inoculum. Peak ceftriaxone levels were obtained 1 h after the completion of the infusion, and trough levels were obtained immediately preceding the next dose. Ceftriaxone levels were determined by the modified agar well diffusion assay method with Escherichia coli 1346 (Hoffman-La Roche, Inc., Nutley, N.J.) in Mueller-Hinton agar (Galveston patients) or nutrient agar (Difco Laboratories, Detroit, Mich.) (3).

Pretreatment laboratory studies included a complete blood count, urinalysis, blood urea nitrogen, creatinine, and liver enzymes studies including a determination of serum glutamic oxalacetic transaminase levels, serum glutamic pyruvic transaminase (SGPT) levels, alkaline phosphatase levels, and prothrombin time. These tests were repeated every 4 days during therapy and at the completion of therapy.

RESULTS

Forty-four children between the ages of 3 weeks and 13 years (mean, 3.7 years) were enrolled in the study. Nine of these children had negative pretreatment cultures and were excluded from the study except for evaluating the safety of ceftriaxone. The remaining 35 patients were treated for 2 to 9 days (mean, 5.1 days). Only a single patient received two doses because he developed hives after the second dose. Six of the patients received between 2 and 5 doses (mean, 3.2 doses) intramuscularly.

The types of infections, the etiologic agents, and the clinical outcome are shown in Table 1. In 10 of the patients, 7 with H. influenzae type b, the organism was recovered in the pretreatment blood culture. Three patients, one with mastoiditis and two with cellulitis and abscess formation, had surgical drainage as well as ceftriaxone therapy.

Clinically, all the patients responded to therapy except for three. The one patient with nonenterococcal group D streptococcal bacteremia had systemic lupus erythematosus. He remained febrile during therapy, but his follow-up blood culture was sterile. The one patient with mastoiditis developed hives after his second dose, and his clinical response could not be evaluated. An additional patient with pneumonia and empyema due to H. influenzae type b remained febrile, and the SGPT level increased to 150 U/ml. She was switched to ampicillin therapy. She became afebrile after 1 week, and her lack of clinical improvement was felt to be due to the presence of loculated pleural fluid.

Follow-up cultures at 48 h were sterile for all patients; however, in several of the patients with cellulitis, infected material was not available for culture at 48 h because of a prompt clinical response. One patient with a urinary tract...
were recovered from the urine. It was more concentration obtained patient, ug/ml. The triaxone had patients of transaminase leukopenia which occurred during therapy. Four patients developed thrombocytosis, TD, of systemic lupus erythematosus. Anemia and leukopenia with anemia and episodic was seen one and anemia with anemia of its failure. Although the organism to be sensitive by the disk method, the MIC of ceftriaxone for this organism was 32 µg/ml.

In the present study, patients suspected of having infections with organisms such as P. aeruginosa or enterococcus were not included. None of the patients with staphylococcal infections had life-threatening disease. Our intention was to determine whether ceftriaxone was effective when administered once daily. The ability to give a drug as a single daily dose should significantly simplify administration, especially in those situations in which the maintenance of intravenous access is difficult or outpatient antibiotic therapy is considered. The ability to give a drug once a day can result in significant savings to the patient even when outpatient therapy is not used.

The clinical efficacy of once-daily ceftriaxone treatment seen in this study appears comparable to that seen with twice-daily administration (1, 4, 6). These results are also comparable to results from two previously reported studies in which ceftriaxone was used as a single daily dose (2, 10). In the study reported by Martin (10), most of the patients had meningitis, and a variety of dosages were used. In that report, 12 of the 43 children had infections other than meningitis, and all were clinically and bacteriologically cured. Baumgartner and Glauser (2) evaluated ceftriaxone in 127 adult patients, and 65 patients were treated with a single daily dose of 2 g. In four of the five failures, the causative organism was a resistant strain of P. aeruginosa.

The pharmacokinetics previously reported and the drug levels seen in this study support the once-daily administration of this drug. Chadwick et al. (5) and Schaad and Stoekel (12) reported on the pharmacokinetics of ceftriaxone after a single dose of 50 mg/kg. Peak levels similar to ours were seen with half-lives of 4.2 and 6.5 h. Plasma concentrations 24 h after a dose were not reported in those studies, but in our study the trough concentration of ceftriaxone exceeded the MIC of ceftriaxone for the infecting organism, although marginally so for S. aureus, in all but 1 of the 22 patients for whom drug levels were available.

The major side effect seen in these and other studies has been diarrhea. This diarrhea is self-limited, frequently disappears during therapy, and is often seen in association with alterations in stool flora. Diarrhea was encountered in only two patients, but it should be noted that a lower daily dose of ceftriaxone was used in this study than in previously published studies. The other side effects encountered were generally mild and, except for two patients, were resolved either during therapy or shortly after the completion of therapy.

In summary, ceftriaxone appears to be safe and effective in the treatment of a variety of bacterial infections in children when administered once daily at a dose of 50 mg/kg. In view of its in vitro activity and the previously published reports, we do not feel that ceftriaxone can be relied on in life-threatening infections due to S. aureus. Its greatest usefulness would appear to be in those infections caused by H. influenzae type b, including beta-lactamase-producing

Table 1. Clinical illness and etiology in 35 patients treated with ceftriaxone

<table>
<thead>
<tr>
<th>Illness (no. of patients)</th>
<th>Organism (no. of patients infected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis (21) (6 facial or periorbital)</td>
<td>H. influenzae type b (6)</td>
</tr>
<tr>
<td></td>
<td>S. aureus (4)</td>
</tr>
<tr>
<td></td>
<td>S. pyogenes (2)</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis (1)</td>
</tr>
<tr>
<td></td>
<td>S. aureus + S. pyogenes (2)</td>
</tr>
<tr>
<td></td>
<td>S. aureus + H. influenzae type b (1)</td>
</tr>
<tr>
<td>Urinary tract infection (7)</td>
<td>E. coli (4)</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae (2)</td>
</tr>
<tr>
<td></td>
<td>P. vulgaris (1)</td>
</tr>
<tr>
<td>Epiglottitis (3)</td>
<td>H. influenzae type b (3)</td>
</tr>
<tr>
<td>Bacteremia (2)</td>
<td>Group D nonenterococcal streptococcus (1)</td>
</tr>
<tr>
<td></td>
<td>S. pneumoniae (1)</td>
</tr>
<tr>
<td>Mastoiditis (1)</td>
<td>S. pyogenes (1, TD)</td>
</tr>
<tr>
<td>Pneumonia (1)</td>
<td>H. influenzae type b (1, TD)</td>
</tr>
</tbody>
</table>

* TD, Treatment discontinued before response could be evaluated. All patients except the one with mastoiditis and the one with pneumonia had satisfactory outcomes.

Infection due to E. coli initially had a sterile culture at 48 h and received ceftriaxone for 5 days. At the 4-week follow-up visit, more than 100,000 colonies of enterococcus per ml were recovered from the urine.

All bacterial isolates were susceptible to ceftriaxone by the Kirby-Bauer disk method. The MIC of ceftriaxone was available for 25 isolates; for H. influenzae type b (4 isolates) it was ≤0.01 µg/ml; for Staphylococcus aureus (11 isolates) it was 1.6 to 3.1 µg/ml; for S. pyogenes (9 isolates) it was 0.008 to 0.003 µg/ml; and for Proteus vulgaris (1 isolate) it was ≤0.1 µg/ml.

In 22 of the patients, plasma was available for ceftriaxone determinations. The mean (± standard deviation) ceftriaxone concentration in plasma obtained 1 h after infusion was 189.8 ± 94.6 µg/ml. The mean trough ceftriaxone concentration obtained immediately before a dose was 8.8 ± 5.5 µg/ml. The mean half-life was 5.3 ± 1.1 h. Only one patient had a trough concentration with no measurable activity (i.e., <0.05 µg/ml), and except for this patient, all patients had trough ceftriaxone concentrations greater than or equal to 3.4 µg/ml.

When administered intravenously or intramuscularly, ceftriaxone was well tolerated. The most common side effect encountered was mild elevation of the serum glutamic oxalacetic transaminase or SGPT levels, which was seen in seven patients. One additional patient developed an SGPT elevation of 150 U/ml, and ceftriaxone was discontinued. Four patients developed thrombocytopenia, two had eosinophilia, and one patient had significant anemia and leukopenia which occurred during therapy. The patient with anemia and leukopenia was the patient with systemic lupus erythematosus. Diarrhea was seen in two youngsters. Except for the patient with hives and the one with an SGPT level of 150 U/ml, none of these side effects necessitated discontinuation of the drug.

**DISCUSSION**

Several groups of investigators have previously reported on the usefulness and efficacy of ceftriaxone in the treatment of a variety of bacterial infections in children and adults (1, 2, 4, 6, 9, 14). In these studies, ceftriaxone was not useful in the treatment of infections due to Pseudomonas aeruginosa or enterococcus or in patients with ventriculoperitoneal shunt infections. Another area of greater importance to the practitioner is the usefulness of ceftriaxone in the treatment of serious staphylococcal infections. Harrison et al. (9) had a treatment failure with ceftriaxone in a patient with a periorbital cellulitis due to a relatively resistant S. aureus strain. Although the organism appeared to be sensitive by the disk method, the MIC of ceftriaxone for this organism was 32 µg/ml.

In the present study, patients suspected of having infections with organisms such as P. aeruginosa or enterococcus were not included. None of the patients with staphylococcal infections had life-threatening disease. Our intention was to determine whether ceftriaxone was effective when administered once daily. The ability to give a drug as a single daily dose should significantly simplify administration, especially in those situations in which the maintenance of intravenous access is difficult or outpatient antibiotic therapy is considered. The ability to give a drug once a day can result in significant savings to the patient even when outpatient therapy is not used (2).

The clinical efficacy of once-daily ceftriaxone treatment seen in this study appears comparable to that seen with twice-daily administration (1, 4, 6). These results are also comparable to results from two previously reported studies in which ceftriaxone was used as a single daily dose (2, 10). In the study reported by Martin (10), most of the patients had meningitis, and a variety of dosages were used. In that report, 12 of the 43 children had infections other than meningitis, and all were clinically and bacteriologically cured. Baumgartner and Glauser (2) evaluated ceftriaxone in 127 adult patients, and 65 patients were treated with a single daily dose of 2 g. In four of the five failures, the causative organism was a resistant strain of P. aeruginosa.

The pharmacokinetics previously reported and the drug levels seen in this study support the once-daily administration of this drug. Chadwick et al. (5) and Schaad and Stoekel (12) reported on the pharmacokinetics of ceftriaxone after a single dose of 50 mg/kg. Peak levels similar to ours were seen with half-lives of 4.2 and 6.5 h. Plasma concentrations 24 h after a dose were not reported in those studies, but in our study the trough concentration of ceftriaxone exceeded the MIC of ceftriaxone for the infecting organism, although marginally so for S. aureus, in all but 1 of the 22 patients for whom drug levels were available.

The major side effect seen in these and other studies has been diarrhea. This diarrhea is self-limited, frequently disappears during therapy, and is often seen in association with alterations in stool flora. Diarrhea was encountered in only two patients, but it should be noted that a lower daily dose of ceftriaxone was used in this study than in previously published studies. The other side effects encountered were generally mild and, except for two patients, were resolved either during therapy or shortly after the completion of therapy.

In summary, ceftriaxone appears to be safe and effective in the treatment of a variety of bacterial infections in children when administered once daily at a dose of 50 mg/kg. In view of its in vitro activity and the previously published reports, we do not feel that ceftriaxone can be relied on in life-threatening infections due to S. aureus. Its greatest usefulness would appear to be in those infections caused by H. influenzae type b, including beta-lactamase-producing.
ONCE-DAILY CEFTRIAXONE FOR CHILDHOOD INFECTIONS

strains, *S. pyogenes*, *N. meningitidis*, and *S. pneumoniae*. Because of its unusually prolonged half-life and the ability to administer the drug in a single daily dose, this drug may prove particularly useful in those situations in which outpatient antibiotic therapy is contemplated or the maintenance of intravenous access is difficult.

ACKNOWLEDGMENTS

We thank Ralph Haynes for reviewing the manuscript and Sara Jane Salstrom for determining the ceftriaxone levels.

LITERATURE CITED