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Efficacy and Safety of Ceftriaxone in Serious Pediatric Infections

STEPHEN C. ARONOFF, D. MURDELL, CHERYL A. O'BRIEN, JEFFREY D. KLINGER, MICHAEL D. REED, AND JEFFREY L. BLUMER*

Department of Pediatrics, Division of Pediatric Pharmacology and Critical Care and Division of Infectious Disease, Rainbow Babies and Childrens Hospital, and Department of Pharmacology, Case Western Reserve University, Cleveland, Ohio 44106

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Thirty-four patients aged 1 month to 19 years were treated with ceftriaxone for suspected bacterial infections. Bacterial pathogens were isolated from 25 children. The overall bacterial cure rate was 88%, with an overall clinical response rate of 96%. No side effects requiring cessation of therapy were observed. Ceftriaxone proved to be safe and effective in the treatment of serious infections in children.

Ceftriaxone is a new parenteral cephalosporin with distinctive antimicrobial and pharmacokinetic properties. The drug displays a high level of in vitro activity against members of the family *Enterobacteriaceae* (1, 7, 8) but simultaneously retains potency against *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae*, and *Streptococcus pneumoniae* (1, 7, 8). In adult patients, ceftriaxone has been used successfully in the treatment of a variety of systemic and localized infections (2).

In contrast to most β-lactam antibiotics, the biodisposition of ceftriaxone is characterized by a prolonged elimination half-life and extensive tissue distribution, including the cerebrospinal fluid. In older patients, the half-life of the drug exceeds 6 h after a single intravenous dose (3). In children, serum half-lives have been reported to range from 3.7 to 6.7 h (4, 10).

This study was designed to evaluate the safety and efficacy of ceftriaxone in children with serious non-central nervous system infections when treated at 12-h intervals.

MATERIALS AND METHODS

Thirty-four children aged 1 month to 19 years with suspected non-central nervous system bacterial infections were prospectively enrolled in the study. Written consent was obtained from parents and from those children old enough to write their names. Children were excluded if they had a history of hypersensitivity to β-lactam agents or if there was any clinically significant degree of hepatic, renal, or bone marrow impairment.

Bacterial cultures were obtained before the first dose of ceftriaxone, and minimal inhibitory concentrations (MICs) of ceftriaxone for each isolate were determined by the broth dilution method. Drug safety was ascertained through serial determination of routine laboratory analysis and daily interviews with patients, parents, and nursing staff regarding possible drug-related side effects.

Bacterial pathogens isolated from blood, urine, abscesses, or bone were considered causative. Clinical signs and symptoms were used to localize the site of infection to a particular tissue or organ system.

Ceftriaxone was administered intravenously in a total daily dose of 70 to 100 mg/kg divided every 12 h. The drug was infused over 10 to 15 min. In those cases in which the intramuscular route was used, the drug was mixed with lidocaine (9).

RESULTS

The median age of the children included in the study was 2.5 years (range, 1 month to 19 years). The mean dosage of ceftriaxone was 76 mg/kg per day (range, 68 to 100 mg) for an average duration of 9.6 days (range, 5 to 30 days). All courses were initially administered intravenously; two children completed therapy by the intramuscular route. Two children proved to have an illness of noninfectious origin, and one child had an initial isolate resistant to ceftriaxone. Thus, all three were excluded from clinical and bacteriological evaluation; however, they were evaluated for their safety.

Twenty-seven isolates were obtained before therapy from 25 patients. *Staphylococcus aureus*, the most common isolate, required for inhibition a mean MIC of 4.5 μg/ml, with a range of 2 to 16 μg/ml. The *Enterobacteriaceae* isolates were markedly susceptible to ceftriaxone, requiring for inhibition MICs ranging from 0.0156 to 0.03 μg/ml. Both strains of *Haemophilus influenzae* type b were not beta-lactamase pro-

TABLE 1. Clinical summary of 32 children treated with ceftriaxone

Site of infection	No. of patients	No. of patients without initial pathogen	Pathogen (no. of isolates)	Clinical response (%)[a]	Bacteriological response (%)[b]
Facial and periorbital cellulitis	10	4	*Staphylococcus aureus* (2) *Streptococcus pneumoniae* (2) Non-group A streptococci (1) *Streptococcus pyogenes* (1)	10 (100)	6 (100)
Skin and skin structures	7	0	*Staphylococcus aureus* (6) *Streptococcus pyogenes* (1) *Pseudomonas aeruginosa* (1)	6 (86)	6 (86)
Pulmonary	4	1	*Escherichia coli* (1) *Pseudomonas aeruginosa* (1) *Pseudomonas cepacia* (1)	4 (100)	1 (33)
Bone and joint	3	1	*Staphylococcus aureus* (1) *Haemophilus influenzae* type b (1)	3 (100)	2 (100)
Lower urinary tract	3	0	*Klebsiella pneumoniae* (1) *Staphylococcus epidermidis* (1) *Escherichia coli* (1)	3 (100)	3 (100)
Bacteremia	2	0	*Salmonella mbandaka* (1) *Klebsiella pneumoniae* (1) *Staphylococcus aureus* (1)	2 (100)	2 (100)
Otitis media	2	0	*Haemophilus influenzae* type b (1) *Staphylococcus aureus* (1)	2 (100)	2 (100)

[a] Clinical efficacy was determined by daily physical examination and review of safety data. Clinical response was defined as resolution of initial clinical findings during therapy without further evidence of infection during the subsequent 1- to 2-week follow-up period.

[b] Bacteriological efficacy was determined through serially obtained cultures of the infected site. Bacterial response was defined as eradication of the initial pathogen from the original site without recurrence during the follow-up period.

ducers and were inhibited by less than 0.02 μg of ceftriaxone per ml. The three initial isolates of *Pseudomonas* species required for inhibition MICs of 2, 8, and 16 μg/ml.

The clinical and bacteriological responses to ceftriaxone are shown in Table 1. Of the 31 children evaluated in this study, 30 (96%) demonstrated a clinical response. This rate is comparable to those previously reported in adults (2, 5). No deaths were noted. No bacterial superinfections were noted. The results from four children were considered bacteriological failures or reoccurrences (Table 2). A 4-year-old boy with presumed staphylococcal septicemia responded clinically and bacteriologically to a 2-week course of therapy. He was readmitted 2 weeks

TABLE 2. Bacteriological recurrences and failures with ceftriaxone therapy

Site of infection	No. of patients	Initial isolate (MIC[a])	Subsequent isolate (MIC[a])	Reason for failure
Osteomyelitis	2	*Staphylococcus aureus* (4) *Pseudomonas aeruginosa* (16)	*Staphylococcus aureus* (4) *Pseudomonas aeruginosa* (>128)	Only 2 wk of therapy; development of resistance
Pneumonia	2	*Pseudomonas aeruginosa* (8) *Pseudomonas cepacia* (2)	*Pseudomonas aeruginosa* (>128) *Pseudomonas cepacia* (>64)	Cystic fibrosis

[a] In micrograms per milliliter.

later with osteomyelitis and a pathological fracture of the fibula. *Staphylococcus aureus*, susceptible to ceftriaxone, was recovered from his bone. A 19-year-old adolescent with a pseudomonas wound infection improved clinically during a 4-week course of therapy. Although bacterial cultures of the wound were sterile early in therapy, he was readmitted to the hospital with pseudomonas osteomyelitis 2 months after completion of the drug administration. The isolate was resistant to ceftriaxone. Two adolescents with pulmonary exacerbations of cystic fibrosis improved clinically; however, sputum isolates at the conclusion of drug therapy yielded resistant *Pseudomonas* strains.

No toxicity requiring termination of drug administration or prolongation of hospitalization was encountered. Four children developed diarrhea during therapy, which resolved upon the completion of ceftriaxone administration. Group D streptococci (two enterococcus isolates and one non-enterococcus isolate) were recovered from stool cultures in two children, and *Staphylococcus aureus* and yeast cells were recovered from one child each. No species of the *Enterobacteriaceae* family were found in the stools after therapy. Diarrhea resolved promptly upon discontinuation of the drug in each case.

Of 34 patients, 12 (35%) developed thrombocytosis, defined as more than 500,000 platelets per mm^3. No episodes of thrombosis or thromboembolic phenomena occurred, and platelet counts returned to normal despite continued use of the drug. No correlation was noted between duration of therapy and onset of thrombocytosis. Two children developed granulocytopenia during therapy. Absolute neutrophil counts of 962 and 990 cells per mm^3 were noted 7 and 5 days into therapy. In both cases, counts returned to normal within 3 days of the cessation of drug administration.

DISCUSSION

Of 26 children with culture-proven infections, 4 had pathogens recoverable at the end of therapy or recurrence of infection during the follow-up period. The bacteriological failures of therapy were attributed to the underlying disease of the patient (two cases of cystic fibrosis) and to inappropriate duration of therapy (two cases). It was of interest, however, that each of the *Pseudomonas* species isolated required a higher MIC for inhibition by ceftriaxone after therapy.

Unlike the experience reported by Epstein et al., only one failure of therapy was associated with infection caused by *Staphylococcus aureus* (2). In our case, the duration of therapy was probably too short for his illness. In vitro susceptibility analysis of 50 isolates of *Staphylococcus aureus* demonstrated that 90% of the strains were inhibited by 4 μg or less of ceftriaxone per ml (7). Of 11 isolates in our study, 9 were inhibited at this drug concentration.

Three children with pseudomonas infections failed therapy or developed a recurrent infection. In all cases, emergence of drug resistance was a possible etiology. McNamara and his colleagues found cephalothin-resistant *Pseudomonas aeruginosa* to be resistant to the new cephalosporins and to ceftriaxone (6). The MIC of ceftriaxone required to inhibit 90% of the 71 *P. aeruginosa* isolates tested exceeded 128 μg/ml (7). The rapid emergence of resistance to ceftriaxone may well suggest the inadvisability of using this agent as a single-drug therapy in treating serious pseudomonas infections. Further observations are needed.

Thus, ceftriaxone appears to be a safe and effective broad-spectrum agent when administered to children. The prolonged half-life of the drug permits a 12-hourly dosing regimen, which is advantageous in pediatric practice. *Staphylococcus aureus, Streptococcus pyogenes, H. influenzae* type b, and *Streptococcus pneumoniae* are inhibited by readily achievable concentrations of ceftriaxone in serum. As a result, ceftriaxone may be used in place of the traditional β-lactam–chloramphenicol combinations routinely used in the initial management of serious childhood infections. We recommend cautious use of ceftriaxone when the possibility of infection with *Pseudomonas* species exists.

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