Efficacy of a Twelve-Hourly Ceftriaxone Regimen in the Treatment of Serious Bacterial Infections

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Eighteen patients with 21 serious infections were treated with ceftriaxone, 1 g intravenously every 12 h, for a mean duration of 8 days. Eighteen gram-negative and two gram-positive organisms were isolated. Sites of infection included blood (three patients), urinary tract (six patients), respiratory tract (seven patients), biliary tract (three patients), ascitic fluid (one patient), and skin (one patient). Serum, bile, and ascitic fluid concentrations of ceftriaxone were in excess of the minimal bactericidal concentration required for the infecting organism in all cases. A bacteriological response was demonstrated in 94% of the infections. A clinical response occurred in four infections from which no pathogens were recovered. In one patient, ceftriaxone failed to eradicate a peritoneal infection due to Bacteroides fragilis. In two patients, superinfection with enterococci developed both during and after therapy. Systemic tolerance to ceftriaxone was excellent.

Ceftriaxone (Ro 13-9904) is a new parenteral cephalosporin which is stable against β-lactamases and has enhanced activity against a wide range of organisms, including Enterobacteriaceae, Haemophilus influenzae, Neisseria species, and non-enterococcal streptococci (1, 3, 5, 9, 11). Pharmacokinetic data from humans show that ceftriaxone, as compared with other cephalosporins, has an unusually long half-life of 6 to 8 h (7, 8; A. Pollock, P. Tee, I. Patel, J. Spichandler, M. Simberkoff, and J. Rahal, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 806, 1981), allowing extension of the dosage interval to 12 h.

This report details the results of therapy with ceftriaxone, administered every 12 h, in 18 patients with acute bacterial infections.

MATERIALS AND METHODS

Eighteen males, 53 to 80 years of age, were treated with ceftriaxone for suspected or documented acute bacterial infections. Most of these patients had underlying diseases such as diabetes, cirrhosis, atherosclerotic heart disease, chronic obstructive pulmonary disease, and malignant disease. Ceftriaxone was administered as a 30-min intravenous infusion at a dose of 1 g every 12 h for a mean duration of 8 days (range, 3 to 14 days). One patient (patient 15) with pneumonia caused by two gram-negative organisms received a larger dose (2 g every 12 h) because of overwhelming disease.

Patients with bacteremia had at least one positive blood culture in association with chills and fever. Those with pneumonia had radiographic infiltrates and both leukocytes and bacteria on Gram stains of deep-suctioned sputum. Urinary tract infection was defined by the presence of >10³ organisms per ml of urine with associated pyuria. Cirrhotic patients with peritonitis had ascitic fluid leukocytosis (>300 leukocytes per ml) and a positive culture from this fluid. Cholecystitis was defined as right upper quadrant pain in association with fever, leukocytosis, and cholelithiasis, as demonstrated by ultrasound, radioisotope scan, or endoscopy. The diagnosis of skin infection was based on local suppuration, induration, a positive Gram stain of the exudate, and a positive culture.

Appropriate cultures were obtained before therapy, 48 h after therapy was begun, and after treatment was completed. Additional cultures were obtained 4 to 6 weeks after treatment from patients with urinary tract infections. Bacteriological response was defined as elimination of the initial pathogen within 48 h after therapy was begun and for the duration of the follow-up period. Bacteriological improvement was defined as eradication of the pretreatment pathogen, with subsequent appearance of one or more new pathogenic species susceptible to ceftriaxone. Persistence of the initial pathogen after 48 h of therapy was considered to indicate bacteriological failure. Clinical response was defined as complete resolution of abnormal findings. Clinical improvement was defined as incomplete resolution of abnormal findings or as a relapse during the follow-up period. No apparent response to therapy was considered to indicate clinical failure.

Complete blood count, platelet count, serum electrolytes, blood urea nitrogen, creatinine, serum bilirubin, alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and prothrombin and partial thromboplastin times were obtained before, during, and after therapy.

Specimens were processed routinely in the bacteriology laboratory of the Veteran’s Hospital and identified by standard techniques. Susceptibility of isolated
pathogens to ceftriaxone was determined by the disk method of Bauer et al. (2) and by the broth dilution method. An 18-h culture of the organism grown in Mueller-Hinton broth was diluted to a final concentration of $10^5$ organisms/ml. 0.5-ml amounts were inoculated into serial twofold dilutions of ceftriaxone to give a final volume of 1.0 ml. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of antibiotic preventing visible turbidity. The minimal bactericidal concentration (MBC) was defined as the lowest concentration of antibiotic resulting in no bacterial growth after a subculture of 0.01 ml onto antibiotic-free Mueller-Hinton agar.

Blood specimens were obtained 1 and 12 h after an infusion of ceftriaxone on days 1 and 4 of the study. Serum specimens were frozen at -20°C. Antibiotic assays were performed within 2 weeks by using a modified agar well diffusion technique in Mueller-Hinton agar, with Escherichia coli 1346 as the standard.

RESULTS

Microbiology. Among 20 organisms isolated, 18 were gram negative, and 2 were gram positive. Sites of infection included blood (three patients), urinary tract (six patients), respiratory tract (seven patients), biliary tract (three patients), ascitic fluid (one patient) and skin (one patient). The same E. coli biotype was isolated from both the bile and the blood of patient 1. Four patients were infected with two different organisms. For 19 organisms (95%), the MIC of ceftriaxone was 12.5 µg/ml or less. The MBC of ceftriaxone for the majority of strains was equal to or within two tube dilutions of the MIC. The MBC of ceftriaxone for one Serratia marcescens isolate was three dilutions greater than the MIC. Clinical and laboratory data from the 18 patients are presented in Table 1.

Bacteriological and clinical outcome. Twenty-one infections were treated with ceftriaxone, and results of therapy are presented in Table 2. Bacteriological response occurred in 16 of 17 infections (94%) from which pathogens were recovered. One patient in this group died of an underlying disease after the infecting organisms were eradicated. Bacteriological improvement occurred in one patient with peritonitis resulting from small-bowel perforation; E. coli was eradicated, but Bacteroides fragilis was present after 48 h of therapy. This patient died of Candida albicans peritonitis.

Pretreatment pathogens were not recovered from four patients. Clinical response occurred in 100% of these infections during ceftriaxone therapy.

Specific infections. (i) Bacteremia. E. coli was isolated from the blood of two patients, and Proteus mirabilis was isolated from the blood of another. Bacteremia was eradicated by ceftriaxone in each instance. One patient had the same organism recovered from both bile and blood. Blood cultures obtained 24 to 48 h after therapy were sterile in all cases. One patient died after blood cultures had become negative.

(ii) Urinary tract infection. Six patients were treated for urinary tract infections, and all showed a bacteriological response. Two individuals were infected with two different gram-negative organisms. Enterococcal infection developed in one patient during treatment and in another patient within 1 week after completion of therapy.

(iii) Respiratory infection. Six patients had pneumonia, and one patient had purulent tracheobronchitis. Sputum was obtained from four patients by nasotracheal suctioning, and expectorated sputum was evaluated in the remaining three patients. Species of known virulence were considered invasive if they predominated in purulent specimens and if correlation existed between Gram stain and clinical findings. Pathogens were recovered from five patients, all of whom showed a bacteriological response. Patient 15 died of hepatic failure after a bacteriological response was demonstrated. The remaining two patients had infiltrates, fever, leukocytosis, and organisms seen on Gram stain (gram-positive diplococci in patient 10 and gram-negative coccobicilli in patient 16); however, only normal flora were isolated from sputum cultures. Both patients showed clinical and radiographic resolution of their infections.

(iv) Biliary tract infection. Three patients had acute cholecystitis, and all were cured by surgery and ceftriaxone. Patient 1 had a perforated gallbladder, and E. coli was isolated from both bile and blood. Sterilization of bile was documented 2 days after surgery. The bile concentration of ceftriaxone 14 h after discontinuation of therapy was 13.5 µg/ml. Patient 18 had E. coli bacteremia and underwent surgery on day 9 of ceftriaxone therapy. The concentration of ceftriaxone in the bile was 1,600 µg/ml 5 h after a dose, and cultures were sterile. Patient 8 had right upper quadrant pain, fever, leukocytosis, and an abnormal ultrasound examination. Cholecystectomy was performed on day 2 of antibiotic therapy, at which time bile cultures were sterile. There was a fall in temperature and peripheral leukocyte count after institution of ceftriaxone treatment and before surgery was carried out.

(v) Skin infection. Patient 13 was treated with ceftriaxone for an infected diabetic foot ulcer with cellulitis. S. marcescens was isolated from the ulcer, and P. mirabilis was recovered from the blood. The patient ultimately required amputation, after a bacteriological response was demonstrated.

(vi) Peritoneal infection. Patient 14, with portal hypertension and ascites, developed E. coli peritonitis. Paracentesis after 2 days of therapy with

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| Cholecystectomy | None | Response | None | 9/30 | 62/3 | 14/26 | 3/2 | 1 | Bile | 0'0/60'0  | 20/0 | 0'0/60'0  |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cholecystectomy | None | Response | None | 4/22 | 9/30 | 52/18 | 12/4 | 1 | Blood | 0'0/60'0  | 60/0 | 0'0/60'0  |
| Cholecystectomy | None | Response | None | 9/30 | 62/3 | 14/26 | 3/2 | 1 | Blood | 0'0/60'0  | 20/0 | 0'0/60'0  |

**TABLE 1.** Clinical and laboratory data from 18 patients treated with ceftriaxone

- **No.** None cultured
- **Bile** 18
- **Blood** 17
- **Respiratory tract:** P. aeruginosa 16
- **K. pneumoniae** 15
- **P. aeruginosa** 14
- **Staphylococcus aureus** 9
- **K. pneumoniae** 8
- **E. coli** 7
- **P. aeruginosa** 6
- **E. coli** 5
- **P. aeruginosa** 4
- **B. fragilis** 3
- **K. pneumoniae** 2
- **E. coli** 1

**Patient Injury Site:** (Grams)

- **No.** None cultured
- **Bile** 18
- **Blood** 17
- **Respiratory tract:** P. aeruginosa 16
- **K. pneumoniae** 15
- **P. aeruginosa** 14
- **Staphylococcus aureus** 9
- **K. pneumoniae** 8
- **E. coli** 7
- **P. aeruginosa** 6
- **E. coli** 5
- **P. aeruginosa** 4
- **B. fragilis** 3
- **K. pneumoniae** 2
- **E. coli** 1
Ceftriaxone yielded no *E. coli* growth, but infection with *B. fragilis* and *C. albicans* was documented. A small-bowel perforation was found during surgery, and treatment was changed to clindamycin, ampicillin, amikacin, and amphotericin B. The patient died of septic shock, hepatic failure, and *C. albicans* peritonitis.

**Ceftriaxone concentrations in serum and other body fluids.** Ceftriaxone serum concentrations were determined on days 1 and 4 of therapy (Table 1). Concentrations in bile and ascitic fluid were also measured. Serum concentrations 1 h after a dose were 20 to 150 µg/ml (mean, 68.4 µg/ml) on day 1 of treatment and 50 to 180 µg/ml (mean, 120.2 µg/ml) on day 4 of treatment. Trough concentrations were <6 to 100 µg/ml (mean, 37.8 µg/ml) on day 1 of treatment and <6 to 100 µg/ml (mean, 48.7 µg/ml) on day 4 of treatment. The highest trough concentration (100 µg/ml) was obtained from a patient with moderate renal insufficiency (creatinine, 4.3 mg/100 ml).

The ascitic fluid concentration of ceftriaxone in a patient with peritonitis was 16 µg/ml 1 h after a dose. Bile concentrations of ceftriaxone were measured in two patients. In patient 1, aspiration of bile from the T-tube 14 h after the final dose yielded a concentration of 13.5 µg/ml. Patient 18 had a bile concentration of 1,600 µg/ml 5 h after a dose of 1 g on day 9 of therapy.

**Superinfection.** Two patients developed infections due to enterococci during or after ceftriaxone therapy. Patient 12 required a cystotomy and permanent catheter drainage for treatment of urethral strictures, and an enterococcal infection developed on day 5 of therapy. Patient 4 was successfully treated for a mixed *E. coli* and *P. mirabilis* urinary tract infection. Three days after completion of therapy, enterococci were cultured from the urine at a time when the patient was asymptomatic.

**Toxicity.** Local tolerance to intravenous injection was excellent. Transient neutropenia was noted in one patient (patient 2) whose leukocyte count decreased to 3,100/mm³ after 7 days of therapy. One day after ceftriaxone therapy was discontinued, the leukocyte count was 6,500/mm³. Patient 9 developed fever after 7 days of treatment. After ceftriaxone therapy was discontinued, the serum alkaline phosphatase and transaminase levels became elevated. Quinidine therapy was then discontinued, and both fever and hepatic abnormalities resolved.

**DISCUSSION**

Pharmacokinetic studies (7, 8) have demonstrated that the half-life of ceftriaxone is approximately 6 to 8 h. This unusually long half-life is attributed to a significant nonrenal mechanism of excretion and distribution, presumably hepatobiliary. With a dose of 1 g every 12 h, serum, biliary, and ascitic fluid concentrations of ceftriaxone were significantly in excess of the MICs and MBCs of this antibiotic for individual isolates.

Ceftriaxone has a broad spectrum of activity, especially against the *Enterobacteriaceae* and non-enterococcal streptococci. It has greater in vitro activity against non-enterococcal streptococci (particularly *Streptococcus pneumoniae*) than moxalactam (1, 6, 9, 10) and greater activity against all *Proteus* species than either cefotaxime or moxalactam (4, 9). Its enhanced activity against aerobic pathogens and unusually long half-life give ceftriaxone a potential advantage over other third-generation cephalosporins in the treatment of certain infections. Ceftriaxone may be especially useful in hospitalized patients, in whom less frequent dosing is desirable, and in the parenteral therapy of outpatients.

Exceptions to the broad spectrum of ceftriaxone are *Bacteroides fragilis*, enterococci, methicillin-resistant staphylococci, and some *Pseudomonas* species. Persistence of *B. fragilis* in the peritoneal cavity of one patient confirmed in vitro data showing ceftriaxone to be less active than cefoxitin (9), moxalactam, or cefotaxime (11) against members of the *B. fragilis* group. This drug should probably not be used as the sole therapy for serious intraabdominal infections in which *B. fragilis* may play a predominant role.

Two patients in this study developed infections with enterococci, one during and one after therapy with ceftriaxone. Thus, enterococci should be suspected when superinfections occur, especially superinfections of the urinary tract.

Hinkle and Bodey (5) showed that 98% of their penicillin-resistant *Staphylococcus aureus* species were inhibited by 6.25 µg of ceftriaxone per ml. Other investigators (11) have shown ceftriaxone to be comparable to cefotaxime.

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**TABLE 2. Outcome of infections treated with ceftriaxone**

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. of infections</th>
<th>No. of organisms isolated*</th>
<th>No. of bacteriological responses</th>
<th>No. of clinical responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Urine</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Bile</td>
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<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Skin</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Three patients had two organisms recovered from the same site, and four patients had no pathogens isolated.
against this organism and superior to moxalactam. Only one patient in this study was infected with S. aureus. Although the MIC of ceftriaxone for this organism was 12.5 \( \mu \text{g/ml} \), serum concentrations several times greater than the MIC were achieved. The patient showed complete bacteriological and clinical responses within 1 week.

In summary, this study suggests that ceftriaxone is an effective and safe cephalosporin for the treatment of urinary, respiratory, and biliary tract infections and bacteremia not due to endocarditis. Because of its long half-life and increased potency against certain pathogens, it can be administered in a lower dose and at longer intervals than currently available cephalosporins.

ACKNOWLEDGMENT

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LITERATURE CITED