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Ceftriaxone: In Vitro Studies and Clinical Evaluation

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The in vitro activity of ceftriaxone against 437 clinical isolates of gram-negative bacilli was determined. Ceftriaxone was found to have high in vitro activity against *Enterobacteriaceae*, with the exception of *Enterobacter cloacae*. Ceftriaxone was only minimally active against *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus*. We evaluated the clinical efficacy and toxicity of ceftriaxone in 55 adult patients. Bacterial infection was confirmed by the isolation of etiological bacteria in 30 patients. Infectious disorders treated included 10 pneumonias, 13 urinary tract infections, and 7 soft tissue or bone infections. Pathogens identified were 25 isolates of gram-negative bacilli, 5 isolates of *Staphylococcus aureus*, 5 isolates of pneumococci, and 4 isolates of other streptococci. The overall efficacy of ceftriaxone was excellent. The clinical cure rate was 93%, and the bacteriological cure rate was 93%. A total of 30 adverse reactions were noted in 22 of 55 patients receiving ceftriaxone, but only one necessitated discontinuation of treatment. Adverse effects frequently noted were elevated hepatic enzymes (16%), thrombocytosis (16%), and eosinophilia (8%). Ceftriaxone is an effective and well-tolerated antimicrobial agent that appears promising for the treatment of serious gram-negative bacillary infections.

Since introduction of the parent compound cephalothin in 1962, cephalosporins have been popular with physicians because of their relatively broad range of antibacterial activity and lack of serious toxicity. Ceftriaxone (Ro 13-9904), a 2-aminothiazolyl methoxyimino cephalosporin derivative, is one of several "third-generation" cephalosporins developed in recent years. Included in this group are the currently marketed drugs cefotaxime (10) and moxalactam (13), as well as the investigational agents cefoperazone (16), ceftazidime (20), cefmenoxime (28), and ceftizoxime (12). All possess excellent activity against many gram-positive and gram-negative bacteria, including a number of species not susceptible to earlier cephalosporins. Cefsulodin (25), a related drug, has activity directed against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

The chemical manipulations that have resulted in the extension of antimicrobial activity have generally not resulted in substantial changes in pharmacokinetic properties. The serum half-lives of cefotaxime and moxalactam are 1.25 h (14) and 2.73 h (30), respectively, which do not differ substantially from the half-life of cefazolin, which is 1.8 h (3). In contrast, ceftriaxone, which is structurally somewhat similar to cefotaxime but has a triazine substituent at the 3 position on the nucleus (21), has a serum half-life of 6.5 to 8.6 h (22, 26). Thus, ceftriaxone has the longest half-life of any cephalosporin.

After examination of the in vitro susceptibility of a large number of clinical isolates of gram-negative bacilli to ceftriaxone, we undertook a clinical trial to evaluate the efficacy of ceftriaxone in the treatment of a variety of bacterial infections.

MATERIALS AND METHODS

In vitro studies. Sterile standardized ceftriaxone powder was provided by Hoffmann-La Roche Inc. Minimum inhibitory concentrations (MICs) were determined by a standard microdilution technique (2). A total of 437 gram-negative aerobic bacillary isolates collected from clinical sources over the last 2 years were tested for susceptibility to ceftriaxone. We also tested six strains of *Listeria monocytogenes* and 15 strains of group B streptococci. MICs were also determined on all isolates identified in the study population. Species with MICs of ≤16 μg/ml were considered susceptible to ceftriaxone (criterion established by the manufacturer).

Clinical trial. The trial was designed as an open, noncomparative study of parenteral ceftriaxone in serious bacterial infections. Patients hospitalized at the University of Alabama Medical Center and at the Veterans Administration Medical Center, Birmingham, Ala., were available for treatment. House officers at these institutions identified potential subjects and notified one of the investigators, who then interviewed and examined the patients. If eligibility criteria were fulfilled, written informed consent was obtained, and the patient was enrolled.

Any adult with suspected or proven serious bacterial infection of the blood stream, skin, soft tissue, bone,

joint, genitourinary tract, gastrointestinal tract, or hepatobiliary tract was eligible for enrollment in the study, with the following exceptions: (i) minors under 18 years of age; (ii) patients with a history of hypersensitivity to beta-lactam antibiotics; (ii) patients with infections caused by bacteria presumed or proven resistant to ceftriaxone; (iv) patients receiving other effective antibiotic therapy; (v) patients at risk for life-threatening *Pseudomonas* infections (e.g., patients with leukemia or granulocytopenia); (vi) patients with central nervous system infections; (vii) patients with severe renal insufficiency (serum creatinine greater than 5.0 mg/dl), and (viii) pregnant or lactating females.

For retention in the study, the etiological bacteria had to be isolated, identified, and proved susceptible to ceftriaxone by disk diffusion criteria (resistant <12 mm, intermediate 13 to 15 mm, sensitive >16 mm).

Ceftriaxone (supplied by Hoffmann-La Roche Inc., Nutley, N.J.) was administered by intravenous infusion (except in one patient, who also received the drug intramuscularly after hospital discharge). The standard dose of ceftriaxone was 1 g diluted in 50 ml of either normal saline or 5% dextrose in water and infused over 20 to 30 min. The dose was repeated every 12 h for a minimum of 5 days. No other antibacterial agents were administered concomitantly.

Aerobic and anaerobic blood cultures were obtained from each patient before initiation of therapy. In patients with pneumonia, expectorated sputum or nasotracheal aspirate was obtained for Gram stain and culture. In patients with urinary tract infections, urine was collected for microscopic analysis and quantitative culture. In patients with soft tissue or bone infections, inflammatory material was obtained for Gram stain and culture by surgical drainage or needle aspiration. Cultures were collected on all patients before therapy, after 48 h of therapy, and after completion of therapy.

All patients were closely monitored to determine bacteriological and clinical outcome. Bacteriological cure was defined as follows: for patients with bacteremia, a sterile blood culture; for patients with pneumonia, elimination of the etiological agent from sputum; for patients with soft tissue or bone infections, elimination of the etiological bacteria from wounds or drainage; for patients with urinary tract infections, a sterile urine culture (<1,000 colonies per ml).

The following criteria were used to define clinical cure: for patients with pneumonia, defervescence of fever and improvement of cough, dyspnea, and signs of consolidation together with radiographic improvement; for patients with soft tissue or bone infections, resolution or improvement of inflammation and healing of wounds (plus radiographic improvement of osteomyelitis); for patients with urinary tract infections, resolution of fever, costovertebral angle tenderness, dysuria, frequency, and urgency; for patients with bacteremia, resolution of signs and symptoms of sepsis.

Subjects were questioned and examined daily for evidence of drug toxicity. Complete blood counts, hepatic enzymes, clotting studies, renal function tests, and urinalysis were obtained twice weekly during therapy.

Ceftriaxone plasma levels were measured in most patients on the 1st and 4th days of therapy. Peripheral venous blood was collected in a heparinized tube 30 min and 12 h after infusion of a dose. An agar plate bioassay technique was utilized. A 2,000-μg/ml stock solution of ceftriaxone was prepared in sterile water. Working standards were prepared in pooled human plasma, ranging in concentration from 2.0 to 200.00 μg/ml. Standards and patients specimens were deproteinized by adding 2.0 ml of acetonitrile to 0.25 ml of plasma and 0.75 ml of sterile water. The samples were blended in a Vortex mixer for 15 s and centrifuged at 100 g for 6 min. A bioassay plate was prepared by mixing melted antibiotic medium no. 1 and *Escherichia coli* 1346 in a transparent polystyrene tray (23 by 23 cm) with lid and allowing the agar to harden. Wells were cut into the agar with a 3.0-mm well cutter, and supernatants from the centrifuged samples were inoculated into the wells with microcapillary pipettes. Standards and patient samples were tested in duplicate. The plate was incubated overnight, and the diameter of the zone of inhibition around each was measured with calipers. A graph of the zone on inhibition (in millimeters) versus drug concentration (in micrograms per milliliter) for the standards was plotted on semilogarithm paper for each plate. The concentration of ceftriaxone in the clinical specimens was then read from this curve.

Peak and trough plasma specimens from five patients were assayed by high-pressure liquid chromatography (kindly performed by Hoffmann-La Roche Inc.). Results were compared with levels determined by the bioassay technique.

RESULTS

In vitro studies. The activity of ceftriaxone against 437 gram-negative bacillary isolates is shown in Table 1. The drug was extremely active against *E. coli, Proteus mirabilis*, and indole-positive *Proteus* sp. Activity was very good against *Klebsiella* sp., *Enterobacter aerogenes, Serratia marcescens*, and *Providencia* sp. Several strains of *Enterobacter cloacae* and *Citrobacter* sp. were relatively resistant to ceftriaxone. The MIC_{90} for *P. aeruginosa* was 25.0 μg/ml; 15% of the *P. aeruginosa* strains tested were clearly resistant to ceftriaxone (MIC >16 μg/ml). *Acinetobacter calcoaceticus* (biotypes not identified) also demonstrated significant resistance to ceftriaxone.

In a previous report from this laboratory, these gram-negative bacilli were tested for susceptibility to moxalactam, cefotaxime, cefamandole, cefoxitin, cefazolin, carbenicillin, ticarcillin, gentamicin, tobramycin, and amikacin (7). The activity of ceftriaxone was quite similar to that of cefotaxime and moxalactam. Ceftriaxone was less active against *E. cloacae*, slightly more active against *P. aeruginosa* and *A. calcoaceticus*, and substantially more active against *Citrobacter* sp. than cefotaxime or moxalactam.

Ceftriaxone was only moderately active against the six *Listeria* isolates (MIC_{90} 12.5 μg/ml), but showed very good activity against the group B streptococci (MIC_{90} 0.78 μg/ml). Moxa-

TABLE 1. In vitro activity of ceftriaxone against aerobic gram-negative bacilli

Species	No. of isolates tested	Range of MIC (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
E. coli	50	≤0.10–0.78	≤0.10	≤0.10
Klebsiella spp.	50	≤0.10–>100	0.20	0.78
E. aerogenes	25	≤0.10–6.25	0.39	1.56
E. cloacae	22	0.20–50.0	0.39	12.5
P. mirabilis	50	≤0.10–.20	≤0.10	≤0.10
Proteus spp. (indole-positive)	30	≤0.10–0.39	≤0.10	≤0.10
P. aeruginosa	75	3.13–>100	12.5	25.0
S. marcescens	50	≤0.10–12.5	0.39	1.56
A. calcoaceticus	50	1.56–50.0	12.5	25.0
Providencia spp.	16	≤0.10–1.56	≤0.10	0.39
Citrobacter spp.	16	≤0.10–50.0	≤0.10	6.25

TABLE 2. Patients with pneumonia treated with ceftriaxone[a]

Patient no.	Age (yr)	Underlying disease	Species isolated	Days of therapy	Outcome	
					Bacteriological	Clinical
13	76	DM, hepatic encephalopathy	*K. pneumoniae* (S)	10	Cure	Cure
19	72	DM, IHD	Group A streptococcus (S)	7	Cure	Cure
20	33	Phenobarbital overdose	*H. influenzae* (S)	7	Cure	Cure
23	53	Alcoholism	*S. pneumoniae* (S)	6	Cure	Cure
25	51	Chronic anemia	*S. pneumoniae* (S, B)	10	Cure	Cure
29	21	Quadriplegia	Group C streptococcus (S)	9	Cure	Failure
34	84	COPD, IHD	*S. aureus* (S)	20	Cure	Cure
46	79	COPD, lung cancer	*S. pneumoniae* (S)	5	Cure	Cure
52	53	Kyphoscoliosis	*S. pneumoniae* (S)	6	Cure	Cure
53	34	Quadriplegia	*S. pneumoniae* (S)	6	Final culture not collected	Cure

[a] Abbreviations: S, sputum; B, blood; DM, diabetes mellitus; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease.

lactam, tested simultaneously against the same 15 group B streptococcal isolates, was significantly less active (MIC_{90} 12.5 μg/ml).

Clinical trial. Between January and May 1981, 55 patients were treated with ceftriaxone. There were 30 males and 25 females with a mean age of 57 years (range 18 to 90 years). Duration of therapy ranged from 2 to 57 days, with a mean of 10 days. Of these 55 subjects, 30 had definite bacterial pathogens isolated and were followed for bacteriological and clinical outcome. Of the remaining group of 25 patients, 15 had no pathogen isolated, 7 subsequently received additional antibiotics (though none of these seven patients received additional antibiotics because of suspected ceftriaxone failure), and 3 were proven to have nonbacterial diseases. These 25 patients were evaluated only for drug tolerance and pharmacokinetics.

Table 2 summarizes the outcome of 10 patients with pneumonia treated with ceftriaxone. Five patients had pneumococcal pneumonia (including one with bacteremia), and two had pneumonia due to other streptococci. *Haemophilus influenzae, Klebsiella pneumoniae*, and *S. aureus* were cultured from one patient each. Nine of the ten patients were cured bacteriologically and clinically. Patient 29, a young man with group C streptococcal pneumonia requiring ventilatory support, was improving with ceftriaxone therapy. The streptococcus had been cleared from his sputum, but he developed pulmonary superinfection with a resistant strain of *A. calcoaceticus*, requiring the addition of tobramycin.

Thirteen patients were treated for urinary tract infections, including three with bacteremic illness (Table 3). Eleven patients had clinical signs and symptoms consistent with pyelonephritis (fever, costovertebral angle tenderness, and leukocytosis in addition to dysuria, frequency, and urgency). *E. coli* was isolated from the urine of nine patients, including all three patients with bacteremia. Two patients had urinary tract infections due to multiply resistant gram-negative bacilli (patient 22, *S. marcescens*; patient 36, *Providencia stuartii*) that were susceptible only to third-generation cephalosporins. Patient 40 had *E. coli* and enterococci isolated from her

TABLE 3. Patients with urinary tract infections treated with ceftriaxone

Patient no.	Age (yr)	Infection[a]	Underlying disease[b]	Species isolated[c]	Days of therapy	Outcome	
						Bacteriological[d]	Clinical
1	77	Cystitis	DM, CHF, CRF	*E. coli* (U)	11	Cure	Cure
9	72	Pyelonephritis	CVA	*P. aeruginosa* (U) *P. stuartii* (U)	2	Failure	Failure
17	21	Pyelonephritis	None	*E. coli* (U)	7	Cure	Cure
21	70	Pyelonephritis	COPD, HTN	*E. aerogenes* (U)	8	Cure	Cure
22	82	Cystitis	DM, dementia, atrial fibrillation	*S. marcescens* (U)[e]	7	Cure	Cure
24	59	Pyelonephritis Bacteremia	DM, HTN	*E. coli* (U, B)	14	Cure	Cure
28	26	Pyelonephritis	Ureterolithiasis	*E. coli* (U)	6	Cure	Cure
30	24	Pyelonephritis Bacteremia	SLE	*E. coli* (U, B)	14	Cure	Cure
33	68	Pyelonephritis Bacteremia	DM, CRF	*E. coli* (U, B)	14	Cure	Cure
35	90	Pyelonephritis	CHF, CVA, seizures	*E. coli* (U), *P. mirabilis* (U)	5	Cure	Cure
36	18	Pyelonephritis	Rhabdomyosarcoma	*P. stuartii* (U)[e]	10	Cure	Cure
37	19	Pyelonephritis	Sickle trait	*E. coli* (U)	5	Cure	Cure
40	88	Pyelonephritis	IHD, PTE, dementia	*E. coli* (U), Enterococcus (U)	7	Cure	Cure

[a] Clinical impression of site of urinary tract infection.
[b] Abbreviations: DM, diabetes mellitus; CHF, congestive heart failure; CRF, chronic renal failure; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; HTN, hypertension; SLE, systemic lupus erythematosus; IHD, ischemic heart disease; PTE, pulmonary thromboembolus.
[c] U, Urine; B, blood.
[d] Multiply resistant species.
[e] Follow-up cultures taken 1 day after completion of therapy.

urine (obtained by catheterization). Follow-up urine cultures were sterile, despite in vitro resistance of the enterococcus to ceftriaxone. Patient 9 had pyelonephritis due to *P. stuartii* (susceptible) and *P. aeruginosa* (resistant). Urine cultures remained positive for *P. aeruginosa* after 2 days of ceftriaxone therapy, so gentamicin was substituted. In all, 12 of the 13 patients were considered cured clinically and bacteriologically (on the basis of urine cultures obtained 1 day after completion of therapy). Only 3 of 13 patients returned for follow-up urine cultures at 1 week after completion of therapy, and only 2 patients returned at 1 month post-therapy; all follow-up cultures obtained were sterile.

The outcome of 7 patients with soft tissue and bone infections is summarized in Table 4. Three patients with cellulitis of the lower extremity due to gram-positive bacteria were cured clinically and bacteriologically. Patient 2, an intravenous drug abuser, presented with gram-negative cellulitis of her left forearm and was begun on ceftriaxone. She improved clinically, and follow-up cultures were negative, but she left the hospital against medical advice after 8 days of therapy. Patient 12 presented with a 2-year history of recurrent osteomyelitis of the left femur after a motor vehicle accident. Bone cultures taken at surgery revealed *S. marcescens* and *P. mirabilis*. He received 2 weeks of intravenous ceftriaxone followed by 6 weeks of ceftriaxone given intramuscularly, resulting in an apparent clinical cure. However, 2 months after completion of therapy, he presented with a relapse of osteomyelitis. *S. marcescens* was again isolated and again was susceptible in vitro to ceftriaxone. Patient 32, with chronic maxillary sinusitis (characterized by fever, tenderness, and nasal drainage) due to *S. aureus* and *P. aeruginosa*, was responding well but developed a rash requiring that the drug be stopped.

In summary, among 30 evaluable patients, a bacteriological cure rate of 93% and a clinical cure rate of 93% were achieved (Table 5). The susceptibility of the clinical isolates to ceftriaxone is shown in Table 6.

Adverse reactions to ceftriaxone. Seven patients developed apparent hypersensitivity responses while receiving ceftriaxone (Table 7). In five patients this was manifested by asymptomatic eosinophilia with a mean eosinophil count of 8% (range 6 to 9%). Patient 11 maintained a low-grade fever (about 38°C) during the last week of her course of therapy which resolved 2 days after the ceftriaxone was discontinued. Patient 32, previously mentioned, developed a diffuse, pruritic maculopapular rash on the 5th

TABLE 4. Patients with miscellaneous soft tissue and bone infections treated with ceftriaxone

Patient no.	Age (yr)	Infection	Underlying disease[a]	Species isolated	Days of therapy	Outcome	
						Bacteriological	Clinical
2	35	Cellulitis (arm)	IV drug abuse	*A. calcoaceticus* *S. marcescens*	8	Cure	Course not completed
10	72	Cellulitis (leg)	COPD, CHF	*S. aureus*	10	Cure	Cure
11	61	Cellulitis (leg)	COPD, chest trauma	*S. aureus*	10	Cure	Cure
12	29	Osteomyelitis	Trauma	*S. marcescens* *P. mirabilis*	57	Failure	Failure
15	74	Periurethral abscess	BPH, COPD, AF	*E. coli*	9	Cure	Cure
32	78	Chronic sinusitis	IHD, HTN	*S. aureus* *P. aeruginosa*	7	Drug discontinued	Drug discontinued
51	58	Cellulitis (leg)	COPD, alcoholism	Group A streptococcus, *S. aureus*	12	Cure	Cure

[a] Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; BPH, benign prostatic hypertrophy; AF, atrial fibrillation; IHD, ischemic heart disease; HTN, hypertension; IV, intravenous.

TABLE 5. Outcome of bacterial infections in 30 patients treated with ceftriaxone

Diagnosis	No. of patients	Bacteriological result (no.)			Clinical result (no.)		
		Cure	Failure	Unevaluable	Cure	Failure	Unevaluable
Pneumonia							
With bacteremia	1	1			1		
Without bacteremia	9	8		1	8		1
Urinary tract infections							
With bacteremia	3	3			3		
Without bacteremia	10	9	1		9	1	
Miscellaneous soft tissue and bone infections	7	5	1	1	4	1	2

day of therapy. This was the only instance in which ceftriaxone had to be discontinued because of an adverse reaction.

Elevated hepatic enzymes were noted in 9 of 55 patients (16%), all of whom had normal liver functions when therapy was initiated. The mean peak transaminase in these patients was 144 IU/liter (range 54 to 360 IU/liter); the mean peak alkaline phosphate was 285 IU/liter (range 151 to 400 IU/liter). Follow-up testing, available in only three cases, revealed the enzyme abnormalities returning toward normal within 2 days after ceftriaxone was discontinued.

Hematological abnormalities developed in 13 patients. Patient 13 had a leukocyte count of 7,800/mm^3 at the start of therapy which fell to 3,100/mm^3 by the completion of therapy 9 days later; no follow-up leukocyte count was available. Two patients (patients 12 and 26) had minor (2 s) prolongations of their prothrombin times, which reverted to normal despite continuation of ceftriaxone. Nine patients (16%) developed thrombocytosis with a mean peak platelet count of 546,000/mm^3 (range 406,000 to 824,000/mm^3). All of these patients had platelet counts of less than 350,000/mm^3 at the start of therapy, and none had a primary hematological disease. Unfortunately, post-therapy platelet counts were not available for most of these patients. An additional patient (patient 39, pneumonia and sickle cell anemia) had a platelet count of 495,000/mm^3 on the 4th day of therapy which rose to 1,300,000/mm^3 on day 8 and to 1,500,000/mm^3 on day 12. During the same interval, her hematocrit remained stable at 22% and her leukocyte count fell from 16,600/mm^3 to 12,500/mm^3. No clotting or bleeding abnormalities were noted in our patients with thrombocytosis.

Patient 7 (who had chronic obstructive pulmonary disease and pneumonia) experienced 1 day of diarrhea while receiving ceftriaxone. No renal function abnormalities were documented in any of the 55 patients. No phlebitis or pain with infusion was noted. Patient 12 took 6 weeks of intramuscular ceftriaxone (reconstituted in 1% lidocaine) and reported no excess pain with injections.

Overall, 30 possible adverse reactions were noted in 22 of 55 patients. Ninety percent of the adverse reactions consisted of abnormal labora-

TABLE 6. Susceptibility of clinical isolates to ceftriaxone in 30 patients

Species	No. of isolates	MIC (μg/ml)	
		Median	Range
S. aureus	5	6.25	1.56–12.5
S. pneumoniae	5	0.1	—[a]
Streptococcus group A	2	0.1	—
Streptococcus group C	1	0.2	—
Enterococcus	1	100.0	—
E. coli	11	0.1	0.1–0.39
S. marcescens	3	0.78	0.78–3.13
A. calcoaceticus	2	18.75	12.5–25.0
P. mirabilis	2	6.3	0.2–12.5
P. stuartii	2	6.3	0.2–12.5
P. aeruginosa	2	53.1	6.25–100
E. aerogenes	1	50.0	—
H. influenzae	1	0.2	—
K. pneumoniae	1	0.1	—

[a] —, None.

TABLE 7. Adverse reactions possibly attributable to ceftriaxone in 55 patients

Reaction[a]	No. of reactions[b]
Hypersensitivity	
Eosinophilia (>5%)	5
Fever	1
Rash	1[c]
Hepatic	
Elevated SGOT (>40 IU/liter)	5
Elevated alkaline phosphatase (>115 IU/liter)	2
Elevated SGOT and alkaline phosphatase	2
Hematological	
Leukopenia (WBC <4,000/mm^3)	1
Prolonged PT (>2 s)	2
Thrombocytosis (>400,000/mm^3)	10
Gastrointestinal	
Diarrhea	1

[a] Abbreviations: SGOT, serum glutamic oxalacetic transaminase; WBC, leukocyte count; PT, pulmonary thrombocytosis.

[b] A total of 22 patients had 30 reactions.

[c] Drug discontinued.

tory test results without associated symptoms or signs. Many of these patients were seriously ill and receiving multiple medications; some of these adverse reactions were probably not caused by the ceftriaxone, but all were temporally related to ceftriaxone administration. Ceftriaxone had to be discontinued because of an adverse reaction in only one case (patient 32, rash).

Ceftriaxone plasma levels. Plasma ceftriaxone levels were determined by bioassay in 50 patients on the 1st and 4th days of therapy (Table 8). Five sets of peak and trough levels were analyzed both by bioassay and high-pressure liquid chromatography (HPLC). The mean peak level was 93.8 ± 30.5 μg/ml by HPLC and 63.6 ± 16.6 μg/ml by bioassay. The mean trough level was 32.4 ± 10.1 μg/ml by HPLC and 29.4 ± 4.4 μg/ml by bioassay.

DISCUSSION

Ceftriaxone is an investigational cephalosporin characterized by a uniquely long half-life and a broad spectrum of activity against gram-positive and gram-negative bacterial pathogens. To assess the potential clinical value of ceftriaxone, its properties must be compared with those of other third-generation cephalosporins, particularly the two agents already available for clinical use. All third-generation cephalosporins (except cefsulodin) have high in vitro activity against *Enterobacteriaceae. E. aerogenes, E. coli, K. pneumoniae, Proteus* species, *S. marcescens*, and *Providencia* species are usually quite susceptible to ceftriaxone, moxalactam, and cefotaxime (1, 7, 9, 17, 18, 23, 31). In several reports, including this one, *E. cloacae* has shown a highly variable degree of susceptibility to third-generation cephalosporins, with a number of resistant strains reported (11, 23). Ceftriaxone, cefotaxime, and moxalactam are only minimally active against *P. aeruginosa*, other *Pseudomonas* species, and *Acinetobacter* species (1, 8, 18, 23, 29). Although ceftriaxone may prove useful for treating infections due to *Pseudomonas* sp. or *Acinetobacter* sp. after in vitro testing has demonstrated susceptibility, the incidence of resistant strains is too high to permit ceftriaxone to be used alone for initial therapy of infectious disorders caused by these bacteria. Cefoperazone (16), ceftazidime (20), and cefsulodin (25) may prove to be more effective antipseudomonal cephalosporins.

Ceftriaxone, moxalactam, and cefotaxime have all proved to be extremely active against *Salmonella* species (6, 8), *Shigella* species (1, 18), *Neisseria meningitidis* (18), *Neisseria gonorrheae* (including penicillin-resistant strains) (24, 32), and *Haemophilus influenzae* (including ampicillin-resistant strains) (19, 24).

Although the third-generation cephalosporins have enhanced activity against gram-negative bacilli, their activity against gram-positive cocci is inferior to that of first-generation cephalosporins. The MIC_{90} of ceftriaxone and cefotaxime for *S. aureus* (penicillin G susceptible or resistant) are in the range of 3.1 to 6.3 μg/ml, whereas moxalactam is slightly less active (1, 8, 11, 18, 23). All three of the drugs have been clinically effective in treating *S. aureus* infections, but none is as active against this bacterium as are

TABLE 8. Plasma levels of ceftriaxone in 50 patients

Day	Mean and SD of drug level in plasma (μg/ml)	
	Peak[a]	Trough[b]
1	103 ± 32	39 ± 16
4	119 ± 38	53 ± 20

[a] At 30 min after infusion.
[b] At 12 h after infusion.

the penicillinase-resistant semisynthetic penicillins or the first-generation cephalosporins (8). All cephalosporins, including these newer agents, are inactive against methicillin-resistant *S. aureus* (29). The susceptibility of *Staphylococcus epidermidis* to ceftriaxone is variable, but the overall activity is poor (18). Ceftriaxone and cefotaxime are both very active against *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae*, and viridans group streptococci (1, 8, 11, 18, 23, 29). Moxalactam, however, is significantly less active against streptococcal species, especially pneumococci and group B streptococci (8, 18). All cephalosporins are inactive against *Streptococcus faecalis* (8, 18).

Ceftriaxone and cefotaxime are frequently inactive against *Bacteroides fragilis*, the anaerobe generally considered most resistant to beta-lactam antibiotics (1, 8, 18, 23). Moxalactam, slightly more active against anaerobes than the other two drugs, has about the same level of activity against *B. fragilis* as cefoxitin (8, 18).

To summarize, ceftriaxone, cefotaxime, and moxalactam are all very active against the *Enterobacteriaceae, Neisseria* species, and *H. influenzae*. Ceftriaxone and cefotaxime are more active than moxalactam against gram-positive pathogens, whereas moxalactam has slightly better antianaerobic activity. None of these three drugs is dependably active against *P. aeruginosa, A. calcoaceticus*, or enterococci.

Ceftriaxone's principal advantage over the other third-generation cephalosporins may be its prolonged serum half-life. In this study, peak plasma ceftriaxone levels on the 4th day of therapy averaged 119 μg/ml, as determined by a bioassay. Trough levels, drawn 12 h after the preceding dose, averaged 53 μg/ml, emphasizing ceftriaxone's prolonged duration of action. When compared with HPLC, the bioassay technique may underestimate ceftriaxone plasma levels, particularly at the higher levels. Ceftriaxone is highly bound to human plasma proteins, requiring deproteinization of the samples with acetonitrile before analysis. Inadequate deproteinization could account for some of the low levels measured.

Ceftriaxone was very well tolerated in our study group of 55 patients. The adverse reactions most frequently noted (thrombocytosis, 16%; elevated hepatic enzymes, 16%; eosinophilia, 8%) were all asymptomatic laboratory abnormalities. Eosinophilia, elevated liver function tests, and thrombocytosis have been previously associated with the administration of third-generation cephalosporins. Eosinophilia has been reported in 4 to 11% of patients receiving moxalactam (13, 27) and in 8 to 10% of patients receiving cefotaxime (W. Greene, P. Inannini, M. Kunkel, A. Harmon, and V. T. Andriole, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill. 1981, abstr. no. 134; C. J. Schleupner, J. Engle, 21st ICAAC, abstr. no. 136). Transient liver function abnormalities have also been noted in 14 to 22% of patients receiving moxalactam (13, 27). Though thrombocytosis can be associated with the stress of infection, a clear temporal relationship between the onset of thrombocytosis and the initiation of ceftriaxone therapy was apparent in these cases. Thrombocytosis has also been reported in 7 of 36 patients (19%) receiving moxalactam (27).

In the clinical study reported here, ceftriaxone was effective as a single agent in treating 30 patients with pneumonia, urinary tract infections, and soft tissue infections caused by a variety of bacterial pathogens. The four patients in this series with bacteremic illnesses responded well to ceftriaxone. We did not have the opportunity to treat any patients with intraabdominal or pelvic infections. The bacteriological and clinical cure rates of 93% achieved in this clinical trial are impressive, particularly since many of the patients treated had complex underlying medical problems. Although ceftriaxone would certainly not be considered the drug of choice for some of the infections treated in this series (e.g., pneumococcal pneumonia or *E. coli* urinary tract infection), we felt that it was important to establish the safety and efficacy of the drug in treating a wide variety of infectious disorders.

Investigators from six other medical centers recently presented results of studies of the clinical efficacy of ceftriaxone (T. R. Beam, T. A. Raab, and J. M. Mylotte, 21st ICAAC, abstr. no. 814; R. W. Bradsher, 21st ICAAC, abstr. no. 813; J. S. Epstein and G. L. Simon, 21st ICAAC, abstr. no. 815; L. Eron, R. Goldenberg, and D. Poretz, 21st ICAAC, abstr. no. 810; H. Giamarellou, J. Tsagarakis, G. Petrikkos, K. Mavroudis, and G. K. Daikos, 21st ICAAC, abstr. no. 808; R. C. Trincher and J. P. Rissing, 21st ICAAC, abstr. no. 811). Ceftriaxone was evaluated in a total of 161 patients with serious bacterial infections, including 46 patients with

urinary tract infections, 40 with lower respiratory infections, 41 with soft tissue infections, 12 with bone infections, and 22 with miscellaneous infections. The overall clinical cure rate was 91%. Adverse reactions reported included phlebitis, elevated liver function tests, diarrhea, and rash, though the drug was generally well tolerated.

Additional studies will have to be undertaken to precisely define the clinical indications for ceftriaxone (and the other third-generation agents). In the treatment of pulmonary infections, ceftriaxone may have a role in treating gram-negative bacillary pneumonias and may be a reasonable substitute for the combination of a first-generation cephalosporin plus an aminoglycoside. Ceftriaxone may be an effective alternative to chloramphenicol for treating ampicillin-resistant *H. influenza* pulmonary infections.

In the treatment of urinary tract infections, ceftriaxone should be reserved for those situations where a multiply resistant gram-negative bacillus is suspected or isolated. No relapses were noted in our patients with urinary tract infections, though we were able to obtain urine cultures at 1 and 6 weeks after completion of therapy in only 23% of the patients due to failure to return for follow-up cultures. Patients with polymicrobial soft tissue infections (cellulitis, wound infections, decubitus ulcers) may be candidates for ceftriaxone therapy. With its potential for once-a-day administration, ceftriaxone could prove to be a valuable drug for the outpatient therapy of chronic osteomyelitis.

The high incidence of resistance of *B. fragilis* to ceftriaxone raises concerns about using this drug alone to treat intraabdominal or pelvic infections. Whether a third-generation cephalosporin alone will be as effective as such regimens as gentamicin plus clindamycin or gentamicin plus chloramphenicol has not yet been adequately studied.

An interesting potential use for ceftriaxone is in the treatment of gonorrhea infections. A single injection of ceftriaxone (in doses as low as 125 mg) eradicated uncomplicated urethral, anorectal, and pharyngeal gonorrhea in a series of 46 males (H. H. Handsfield, V. L. Murphy, and K. K. Holmes, 21st ICAAC, abstr. no. 812). A small dose of ceftriaxone, if proven effective, would clearly be better tolerated by the patient and possibly less expensive than the currently recommended regimen of 4.8×10^6 U of procaine penicillin plus 1 g of probenecid.

Because of its marginal activity against *P. aeruginosa*, ceftriaxone alone cannot be recommended as initial therapy in any patient in whom the risk of *P. aeruginosa* infection is great, such as the patient with granulocytopenia. Although the combination of a third-generation cephalosporin and an aminoglycoside may be effective in some patients with pseudomonal disease (R. Cleeland, W. Delorenzo, L. Gulow, and P. Russo, 21st ICAAC, abstr. no. 804), until more clinical data are available we recommend the combination of an aminoglycoside plus an antipseudomonal penicillin, such as carbenicillin or ticarcillin, for serious pseudomonal infections.

Although patients with central nervous system infections were excluded from this study, ceftriaxone may prove to be a valuable drug in bacterial meningitis. In therapy of murine meningitis due to *S. pneumoniae* or *K. pneumoniae*, ceftriaxone was superior to ampicillin or cefotaxime (4). Other investigators have confirmed the efficacy of ceftriaxone in the dog meningitis model (15) and documented effective levels of the drug in the cerebrospinal fluid of patients with meningitis (5). Though rigorous clinical assessment will be necessary, ceftriaxone appears to be a potentially effective agent for bacterial meningitis, particularly that due to gram-negative bacilli or ampicillin-resistant *H. influenzae*.

Insufficient data are currently available to indicate how effective ceftriaxone will be in patients with serious intravascular infections. We recommend that ceftriaxone not be routinely used to treat bacterial endocarditis, particularly endocarditis due to gram-positive species, until its efficacy has been documented.

Ceftriaxone has an in vitro spectrum of activity similar to the spectra of the currently available third-generation cephalosporins. However, with its substantially longer half-life, ceftriaxone appears to have a potentially significant therapeutic advantage over cefotaxime and moxalactam. The high degree of efficacy and low incidence of significant toxicity demonstrated in this study should encourage further clinical evaluation.

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