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Ceftriaxone (Ro 13-9904) Therapy of Serious Infection

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Ceftriaxone (Ro 13-9904), a newly developed cephalosporin with a long half-life, was evaluated for efficacy and safety in 19 patients with serious infections. Underlying illnesses were present in 16 patients. Ceftriaxone was given intravenously every 12 h. Infections treated included gram-negative bacillary pneumonias (two cases), staphylococcal and streptococcal soft tissue-skeletal infections (six cases), spontaneous peritonitis (two cases), and complicated urinary tract infections (nine cases). Bacteremia was present in three patients. Microbiological and clinical cures were achieved in all but one case, although three patients with urinary infection had recurrences 6 weeks posttherapy. The only failure occurred in a patient with pneumonia who had a *Pseudomonas aeruginosa* isolated from sputum with an initial minimal inhibitory concentration of 4 μg/ml, but after 9 days of therapy, a repeat isolate had a minimal inhibitory concentration of 32 μg/ml. The minimal inhibitory concentrations for the other isolates ranged from ≤0.6 to 8.0 μg/ml. The mean peak plasma level of ceftriaxone was 99.9 μg/ml, whereas ceftriaxone levels obtained 12 h after a dose had a mean of 37.3 μg/ml. The only side effects noted were drug fever in one patient, phlebitis in two patients, and thrombocytosis in four patients.

Cephalosporin antibiotics are widely used to treat serious infections because of the spectrum of activity and the relative safety compared with other types of antibiotics. Several newly developed cephalosporins have increased potency against *Enterobacteriaceae* while maintaining activity against streptococci and staphylococci. Ceftriaxone (Ro 13-9904) is a 2-aminothiazolyl methoxyimino cephalosporin which inhibits most gram-negative enteric bacilli and streptococci at concentrations of less than 1 μg/ml (3, 5, 12). It has a potential advantage over other recently discovered β-lactam antibiotics because of a contrast in pharmacokinetics. Ceftriaxone has a serum half-life of 8 h compared with 1 to 3 h for cefotaxime, cefoperazone, moxalactam, and other investigative third-generation cephalosporins (10). This prolonged serum half-life apparently is related to a high degree of protein binding and a different excretion pattern for ceftriaxone compared with the cephalosporins listed above (11, 16). In an open trial, the safety and clinical and bacteriological efficacy of ceftriaxone therapy of serious bacterial infection at a dosage of 1.0 g twice a day were evaluated.

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MATERIALS AND METHODS

Patient population. Adult patients with suspected serious bacterial infection, hospitalized at the University of Arkansas for Medical Sciences from December 1, 1980 through July 31, 1981, were evaluated for enrollment. Exclusions were patients who had received antibiotics during the previous 72 h and patients with either renal failure, meningitis, pregnancy, lactation, neutropenia, or significant penicillin hypersensitivity. After written informed consent was obtained, cultures of both blood and the site of infection were collected as were base-line laboratory data including radiographs, if clinically indicated.

Antibiotic administration and levels. One gram of ceftriaxone was infused intravenously in 100 ml of 5% dextrose in water over 30 min every 12 h. Since no patients with renal failure were enrolled, dosage alteration was unnecessary. Peak and trough plasma concentrations of ceftriaxone were obtained at the times of the third and seventh doses of ceftriaxone. Peak levels were obtained 30 min after the completion of infusion, and trough levels were taken immediately preceding the dose. Selected body fluid ceftriaxone levels were also performed. Values were measured with the standard agar well diffusion method by using a susceptible *Escherichia coli* after dilution of the specimen with pooled plasma (1).

Bacteriology studies. Specimens for culture were processed in the usual way by the clinical microbiology laboratory. Susceptibility testing to ceftriaxone was performed on all isolates by both disk diffusion and minimal inhibitory concentration (MIC) determination by a microtiter technique by using 10^5 colony-forming

TABLE 1. Characteristics of patients at initiation of ceftriaxone and response to therapy

Patient	Age	Coexistent diseases	Significant daily medication	Temp (°C)	Leukocyte count ($\times 10^3$)	Site of infection	Clinical response		Cure	Organism	MIC (μg/ml)	Bacterial response
							Temp[a]	WBC[b]				
1	51	Cirrhosis		38.7	14.2	Peritoneal fluid	4	10	Yes	*E. coli*	0.375	Eliminated (4)[c]
2	65	Esophageal carcinoma		37.1	14.4	Peritoneal fluid, blood		8	Yes	*K. pneumonia*	≤0.06	Eliminated (2, 2)
3	24	Diabetes, influenza	Insulin (21 U)	38.9	20.1	Lung	3	8	Yes	*Haemophilus influenzae*	≤0.06	Eliminated (4)
4	66	Lung and sinus carcinoma		39.2	16.0	Lung	NC[d]	NC	No	*P. aeruginosa*	4.0, 32.0	Persistent
5	42	Systemic lupus-erythematosus	Prednisone (40 mg), indomethacin (200 mg)	37.4	14.4	Wrist with necrotic tendons		8	Yes	*S. aureus*	0.125	Eliminated (8)
6	57	Diabetes	Insulin (48 U)	39.4	20.0	Left foot	7	8	Yes	Group A streptococcus	≤0.06	Eliminated (5)
7	30	Diabetes, ketoacidosis	Insulin (55 U)	36.0	35.9	Back; 10 cm diameter abscess	5	4	Yes	*S. aureus*	4.0	Eliminated (5)
8	30	Diabetes	Insulin (90 U)	37.3	12.2	Right 1st toe, bone		8	Yes	Group B streptococcus	≤0.06	Eliminated (6), amputated toe
9	37	Diabetes	Insulin (45 U)	37.3	14.1	Left foot, bone		8	Yes	Group B streptococcus	≤0.06	Eliminated (10), debridement
10	55	Diabetes	Insulin (30 U)	38.4	26.0	Right plantar surface, bone	4	8	Yes	*S. aureus*	2.0	Eliminated (8), debridement
11	63			38.8	14.9	Urine, blood	6	4	Yes	*E. coli*	0.125	Eliminated (2, 1)
12	29			39.2	16.2	Urine	3	4	Yes	*E. coli*	≤0.06	Eliminated (2)
13	78	Hyperosmolar coma	Insulin (35 U)	38.0	13.7	Urine	3	4	Yes	*E. coli*	8.0	Eliminated (4)
14	51	Rheumatoid arthritis; prosthetic hip	Prednisone (10 mg), naproxen (500 mg)	39.0	24.8	Urine	4	8	Yes	*Proteus mirabilis*	≤0.06	Eliminated (3)
15	57	Alcoholic hepatitis		38.6	20.7	Urine, blood	2	8	Yes	*E. coli*	≤0.06	Eliminated (2, 2)
16	37	Quadriplegia, ureteral spincterotomy	Phenoxybenzamine (20 mg)	38.8	6.8	Urine	5	—	Yes	*P. rettgeri*	≤0.06	Eliminated (5)

17	41			39.4	12.8	Urine	4	4	Yes	*E. coli*	≤0.06	Eliminated (2)
18	24	Renal transplant, ureteral reflux	Methylprednisolone (8 mg), azathioprine (125 mg)	38.0	6.5	Urine	3	—	Yes	*E. coli*	≤0.06	Eliminated (2)
19	51	Cirrhosis, alcoholic hepatitis		38.9	27.1	Urine	NC	NC	NA[e]	*E. coli*	0.25[g]	Eliminated (3), NA

[a] Days for temperature to normalize.
[b] Days before normal leukocyte count was documented.
[c] Days before negative culture was documented.
[d] NC, No change.
[e] NA, Not assessable.

units as the inoculum (4). Cultures were repeated every 2 to 3 days until negative or the antibiotic was stopped at the conclusion of therapy. Patients with urinary tract infections had repeated urine culture 6 weeks after therapy.

Response evaluation. Patients were considered clinically cured if there was resolution of the signs and symptoms of infection. The days required for resolution of fever and leukocytosis were recorded. Chest radiograph changes, coughing, and sputum production were monitored in pneumonia. Signs of drainage and inflammation were graded for severity each day for skin and soft tissue infections. Urinary samples were obtained for culture and analysis for urinary infection. Peritonitis was assessed by physical examination and examination of peritoneal fluid.

Toxicity evaluation. Patients were monitored daily for signs of toxicity. Hematological, renal, and hepatic parameters were measured every 4 days during therapy and at the conclusion of therapy.

Statistical evaluation. Analysis of antibiotic levels was performed by a nonparametric test, the Mann-Whitney U test, with $P < 0.05$ regarded as significant.

RESULTS

A total of 25 infections were documented in the 23 patients enrolled. One patient received only three doses of ceftriaxone until the diagnosis of pneumonia was excluded by the finding of pulmonary infarction. Three patients had culture-proven infections which were considered to be of moderate severity and are not included in this report with regard to efficacy. They are included in description of safety and plasma concentrations of ceftriaxone. The characteristics of the remaining 19 patients with serious infections are shown in Table 1. Underlying diseases which probably contributed to the infections were coexistent in 84% of the patients (Table 1). Evaluable patients were treated with at least 11 doses of ceftriaxone and received 15 to 44 mg/kg per day. The infections treated, the bacteria isolated with susceptibility to ceftriaxone, and descriptions of the severity of the infections are listed in Table 1. Only five patients were not febrile (temperature, <38°C), but the diagnosis of severe infection was secure. In each case of those patients without fever, leukocytosis was present. In addition, diabetes ketoacidosis was a result of the infection in one patient, another was treated with both prednisone and indomethacin, and a third patient was bacteremic with signs of significant peritonitis.

A bacterial isolate was obtained from each patient. Organisms responsible for the infection are shown in Table 1 along with the susceptibility to ceftriaxone. Disk diffusion susceptibilities correlated without exception to MIC determinations (data not shown).

The mean peak plasma concentration of ceftriaxone was 99.5 μg/ml, whereas levels obtained 12 h after a dose had a mean of 37.3 μg/

TABLE 2. Ceftriaxone plasma levels

	Plasma level (μg/ml) ± SEM			
	Peak[a]		Trough[b]	
	Day 1	Day 4	Day 1	Day 4
Mean (22)[c]	99.2 ± 6.8	100.5 ± 5.0	35.9 ± 3.4	38.8 ± 3.9
Corrected for body surface area (22)	96.6 ± 5.8	95.4 ± 6.6	35.0 ± 3.3	36.9 ± 3.8
Patients with ascites (4)	75.9 ± 15.9[d]	67.5 ± 11.9[e]	28.5 ± 10.8	41.2 ± 12.6
Patients without ascites (18)	107.4 ± 7.0[d]	104.6 ± 4.9[e]	36.3 ± 3.5	38.4 ± 4.2

[a] Peak, blood was obtained 1 h after a 30-min infusion was started.
[b] Trough, blood was obtained 12 h after infusion.
[c] Number in parentheses is number of patients.
[d] $P < 0.05$, Mann-Whitney U test.
[e] $P < 0.01$, Mann-Whitney U test.

ml. When levels were corrected for body surface area, similar results were obtained (Table 2). However, the four patients with ascites were found to have lower values 30 min after completion of the infusion ($P < 0.05$ for day 1, $P < 0.01$ for day 4). Three patients had determinations of ceftriaxone in body fluids. Seven hours after a dose, levels of 30 and 36 μg/ml were found in infected peritoneal and sterile peripneumonic pleural fluid, respectively. Corresponding peak plasma levels were 66 and 94 μg/ml. In another patient, a peritoneal fluid concentration 2 h after a dose was 58.7 μg/ml with a peak plasma level after the same dose of 117 μg/ml.

Of the 18 assessable patients with severe infection, 17 were clinically cured at the completion of therapy (Table 1). One patient (patient 19, Table 1) with urinary tract infection had ceftriaxone stopped for toxicity and other antibiotics started. She was not evaluable, even though her urine was sterile after only three doses of ceftriaxone. The patients with osteomyelitis required debridement for cure after resolution of drainage and cellulitis; two of these patients had completion of a 6-week course with oral antibiotics after bone cultures from surgery were negative. Both the diabetic patient with an abscess (10 by 10 cm) on his back and the patient with systemic lupus erythematosus who had a deep palmar space abscess involving tendons of the hand required a drainage procedure.

The only clinical failure was a patient with carcinoma of the lung who had a postobstructive pneumonia. His sputum Gram stain indicated a predominance of gram-negative bacilli, and culture revealed *Pseudomonas aeruginosa*. The initial isolate had an MIC of 4 μg/ml to ceftriaxone, but after 9 days of therapy with this agent, there was no improvement in either his respiratory symptoms, fever patterns, or chest radiograph, and *P. aeruginosa* was still isolated. The repeat isolate had an MIC of 32 μg/ml to ceftriaxone (Table 1). After administration of gentamicin and ticarcillin, he became afebrile, but radiation therapy to the chest was required before radiographic improvement was noted.

Organisms were eliminated at completion of therapy in all cases except for the *P. aeruginosa* described above (Table 1). One patient with pyelonephritis and one patient with lower urinary tract infection had symptomatic lower tract infection with a different organism isolated from the urine 6 weeks after ceftriaxone therapy. The patient with the ureteral sphincterotomy had *Providentia rettgeri* isolated in his urine again 6 weeks after therapy, even though he was asymptomatic with the relapse. One patient with *Klebsiella* peritonitis was clinically cured, but 3 weeks later had a second episode of peritonitis with enterococcus isolated from the blood and peritoneal fluid. The patient with systemic lupus erythematosus had another staphylococcal abscess at another site requiring treatment 8 weeks after completion of ceftriaxone therapy. One diabetic patient with group B streptococcal osteomyelitis had recurrence of pain, drainage, and fever within 6 weeks of completion of therapy. A *Proteus* species was isolated from a deep wound culture, and amputation of his foot was needed for cure. Certain organisms were isolated during therapy (Table 3). These were considered to be colonization rather than infection, because in each situation there were no signs or symptoms of infection in contrast to when ceftriaxone therapy was begun.

Adverse effects of ceftriaxone were minimal (Table 4) but included two episodes of thrombophlebitis and one episode of diarrhea. The diarrhea was most likely due to lactose intolerance, since it resolved when milk products were withheld while the patient continued to receive ceftriaxone. One patient was considered to have drug fever and was the only subject in whom the drug was stopped for possible toxicity. She, however, continued to have fever on gentamicin therapy. This patient died 8 days later with

TABLE 3. Colonization during ceftriaxone therapy

Organism	MIC (μg/ml)	Colonization site
Staphylococcus aureus	2.0–8.0	Skeletal[a] (2)[b], sputum (1)
Staphylococcus epidermidis	0.5–2.0	Skeletal (2), skin (1), sputum (1), urine (1)
Enterobacter agglomerans	16.0	Skeletal
Acinetobacter subsp. *anitratus*	>64.0	Skeletal
Candida albicans		Sputum (2), urine (1)

[a] Skeletal includes drainage from wound site.
[b] Number in parentheses is number of patients.

progressive liver failure due to alcoholic hepatitis. None of the other patients died during the 6 weeks after therapy.

Of interest was that four patients had a marked increase in platelet count observed on either day 4 or day 8 of therapy (Table 5). None had primary hematological disease, but one had neoplastic disease. Two others had a modest increase, but the other 15 cases had no change in platelet count. Resolution was documented after the infection in two patients, but the other patients did not have a decrease measured. No other laboratory abnormalities were observed with the hepatic, renal, or hematological monitoring.

TABLE 5. Thrombocytosis during ceftriaxone therapy

Patient	Platelet count	
	Pretherapy	Posttherapy[a]
6	572,000	814,000
9	257,000	956,000
12	662,000	1,113,000
4	546,000	946,000

[a] Posttherapy is either day 4 or 8 of therapy.

DISCUSSION

This study indicates that ceftriaxone given twice a day as a single agent was an effective antibiotic for serious infections in patients with significant underlying diseases. There was clinical cure and adequate bacteriological response to therapy in 17 of the 18 (94%) evaluable cases of serious infections.

These patients were seriously ill, and many would probably have responded to other antibiotics. However, several infections would have required combinations of antibiotics to adequately cover the most common pathogens until culture results were available. For example, diabetic foot ulcers with cellulitis or osteomyelitis may be caused by gram-positive cocci (*Staphylococcus aureus* or group A or B streptococci), enteric gram-negative bacilli, or anaerobic bacteria (7). An agent effective against all three types of organisms may be preferable to combinations of antibiotics specific for each bacteria. Clearly, if staphylococci or streptococci were considered the cause of infection in situations other than a study of efficacy of a drug, less expensive and more narrow-spectrum antibiotics would be used. It is important, however, to demonstrate the effectiveness of an agent before it can be suggested for empiric use while awaiting culture results. The broad spectrum of ceftriaxone does appear to allow coverage of the majority of gram-positive cocci, enteric gram-negative bacilli, and anaerobes other than *Bacteroides fragilis* (2). The cause of osteomyelitis in two diabetics was group B streptococci, which is in keeping with the frequency of this organism as a pathogen in diabetics as recently reported by Stevens et al. (13) and Tofte et al. (14). Group B streptococci is uniformly susceptible to ceftriaxone (9) but not as susceptible to another new β-lactam, moxalactam (6). Only three patients with osteomyelitis were included, and treatment of this infection with ceftriaxone must certainly be considered experimental until further studies are performed. However, an initial favorable response with the cure of the surrounding cellulitis was noted in each case.

Plasma levels of ceftriaxone were at least five times the MIC for as long as 12 h after a 1-g infusion in each patient. Significant protein binding has been described with this agent which allows the remarkably prolonged half-life. Since only the unbound fraction of the drug can act against bacteria, protein binding in antibiotic

TABLE 4. Adverse effects with ceftriaxone therapy

Reaction	Severity	Result	Resolution to drug
Thrombophlebitis	Moderate	Resolution	Probable
Thrombophlebitis	Mild	Resolution	Probable
Diarrhea	Moderate	Resolution	Remote
Pyrexia	Moderate	Drug stopped	Possible

therapy is important. However, Wise et al. have indicated that the activity of ceftriaxone in vitro is relatively unaffected by the addition of serum despite the high degree of protein binding (16). Further study is obviously required, but the unique pharmacokinetics of this agent may allow once-daily therapy of serious infections after an initial response with more vigorous treatment. This opens the potential for investigation of outpatient therapy of infections which currently require a long course of parenteral antibiotics.

Ceftriaxone is partially cleared by the liver (11) so that the finding of a significantly lower plasma concentration in patients with liver disease manifest by ascites was mildly surprising. A higher level might have been predicted based on the degree of abnormal liver function in these patients. Presumably, the lower peak value in our patients with liver disease compared with levels in patients without ascites is a reflection of a larger volume of distribution.

Thrombocytosis has been an infrequently recognized condition associated with cephalosporin therapy (10). Four of the patients studied had a marked increase in platelet count within 8 days of starting the antibiotic, and two other patients had a similar but milder increase. Although ceftriaxone is a possible cause, it is reasonable to assume that the thrombocytosis observed was in response to severe infection and not the drug. In a double-blinded randomized comparison of cefamandole and penicillin in serious infection, both agents were associated with the same magnitude of thrombocytosis (10).

Colonization with organisms that were relatively resistant to ceftriaxone occurred in some of this group of patients (Table 3), and one patient had enterococcal sepsis and peritonitis 3 weeks after being cured of *Klebsiella* peritonitis. The only failure in this series was a man with pneumonia due to *P. aeruginosa* which, although originally susceptible to ceftriaxone, was persistently isolated in the sputum. The poor drainage associated with bronchial obstruction added to the difficulty in treatment, but the susceptibility to ceftriaxone decreased eightfold while the patient was on therapy (Table 1). Although not studied in this patient, selection of resistant organisms from an original heterosusceptible population has been described in similar situations with other new β-lactam antibiotics (8, 15).

Ceftriaxone appears to be a safe and effective antibiotic for serious infection in a twice-daily regimen. Seriously ill patients were found to respond favorably to ceftriaxone. This study did not examine patients with neutropenia and included only one patient with a moderately susceptible organism, *P. aeruginosa*. However, ceftriaxone was responsible for curing infection due to susceptible gram-negative bacilli, staphylococci, and β-hemolytic streptococci of both groups A and B in patients with underlying disease processes which contributed to the severity of the infections. Certain infections are commonly caused by a wide variety of microorganisms, including severe diabetic foot ulcers, pneumonia, peritonitis, or urinary tract infection. Seriously ill patients with these infections were found to respond favorably to ceftriaxone. This study supports further investigation of this minimally toxic broad-spectrum antibiotic as a single agent for the treatment of certain serious bacterial infections when *P. aeruginosa* is not considered to be highly likely as the pathogen.

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