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Clinical Efficacy of Cefotaxime in Serious Infections

PETER H. KARAKUSIS,* JOSEPH M. FECZKO,† LARRY J. GOODMAN, DONNA M. HANLON, ALAN A. HARRIS, STUART LEVIN, AND GORDON M. TRENHOLME

Section of Infectious Disease, Department of Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612

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Thirty-five patients underwent 38 treatment courses with cefotaxime. Documented infections included 11 bacteremias, 7 cases of nosocomial pneumonia, 6 surgical wound infections, 3 bone infections, 1 biliary infection, and 1 urinary tract infection. Granulocytopenic patients with fever received 15 courses of empiric cefotaxime therapy alone; in 8 courses, no definite site of infection or pathogen was isolated. Broad-spectrum antibiotics had been administered to 23 patients before cefotaxime. Thirty-seven bacterial pathogens were isolated from 25 patients. Three such pathogens were resistant to cefotaxime and required alternative therapies. Pathogenic isolates included 13 *Serratia marcescens*, 12 *Pseudomonas aeruginosa*, 4 *Escherichia coli*, 2 *Klebsiella pneumoniae*, 2 *Providencia stuartii*, 1 *Enterobacter cloacae*, 1 *Haemophilus influenzae*, 1 *Enterococcus*, and 1 *Staphylococcus aureus*. Of the treatment courses, 25 of 38 resulted in a favorable response to cefotaxime, including 9 of 15 in granulocytopenic patients. Superinfection was seen in one patient. The emergence of resistance was documented in another patient. Of 15 patients with multiply resistant pathogens, 12 improved with cefotaxime. Of 12 patients with *Pseudomonas aeruginosa*, 6 favorably responded. Possible complications of cefotaxime were observed in 14 of 42 treatment courses. Cefotaxime is most useful in the treatment of infections due to multiply resistant, gram-negative pathogens other than *Pseudomonas aeruginosa*.

Serious infections in hospitalized patients frequently require the use of broad-spectrum antimicrobial therapy. Aminoglycosides in combination with other agents traditionally have been used for these infections (8, 12, 17). However, the toxicity of aminoglycosides and the emergence of resistant nosocomial pathogens can limit their use. The recent development of numerous cephalosporins with expanded spectrums parallels the growing need for alternatives to aminoglycosides. One such agent, cefotaxime (Claforan, HR756; Hoechst-Roussel Pharmaceuticals, Sommerville, N.J.), has been shown to have excellent in vitro activity against *Enterobacteriaceae* and good activity against gram-positive cocci (4, 5, 7, 20, 23). In vitro activity against strains of *Pseudomonas aeruginosa* has been comparable to that of ticarcillin, whereas the susceptibility of strains of *Bacteroides fragilis* has been variable (2, 4, 14, 22, 25). Published information regarding the clinical efficacy of cefotaxime is limited. We report our experience with this drug in the therapy of serious infections.

† Present address: Mount Sinai Hospital, Department of Medicine, Section of Infectious Disease, Chicago, IL 60608

MATERIALS AND METHODS

Patients were enrolled in the study exclusively through consultation with the Infectious Disease Service of Rush-Presbyterian-St. Luke's Medical Center. Informed consent was obtained from each patient or next of kin. Patients with infections due to multiply resistant strains of *Serratia marcescens* and patients with granulocytopenia and fever were particularly sought. Cefotaxime was administered to 40 patients; 3 patients received the drug twice. Of 43 courses of therapy, 5 were excluded from analysis. Three of these exclusions resulted when no bacterial pathogen could be isolated. Disseminated infection due to *Mycobacterium kansasii* and pneumonia due to *Aspergillus* species, cytomegalovirus, and Herpes simplex virus were present in two such patients. The third patient had pulmonary lymphocytic vasculitis at postmortem examination. No evidence of active infection was found. No antemortem response to broad-spectrum antibiotics was observed. A fourth exclusion was due to the concurrent use of another effective antibiotic with cefotaxime. The final exclusion dealt with a patient who received less than 24 h of therapy. Four of the five excluded cases died; in three cases, the deaths were related to infection.

Thirty-five evaluable patients received 38 courses of therapy. The mean age of patients included in the study was 55.2 years (range, 17 to 88). There were 19 males and 16 females. Associated conditions were present in 32 patients (Table 1). Of the 38 infections, 29

TABLE 1. Associated conditions in 32 patients who received cefotaxime[a]

Condition	No. of patients
Organic heart disease	7
Mechanical ventilation	9
COPD[b]	2
Renal failure	4
Malignancy	19
Hematopoetic	8
Reticuloendothelial	3
Carcinoma	8
Granulocytopenia	14[c]
Postoperative state	16
Cardiovascular	6
Thoracoabdominal	4
Other	6
Diabetes mellitus	2

[a] Three patients had no associated conditions.
[b] COPD, chronic obstructive pulmonary disease.
[c] One patient received two courses of cefotaxime.

were acquired in the hospital. Broad-spectrum antibiotics had been given to 23 patients before cefotaxime therapy.

Cefotaxime was administered by intravenous infusion for 30 min. A dose of 8 to 12 g daily was given to all but one patient. One patient with acute renal failure and severe azotemia received 4 g of cefotaxime daily. The mean duration of therapy was 14.7 days (range, 2 to 48 days). Serum drug levels were measured by the agar-well microbiological method with *Escherichia coli* 3898 as the assay organism and Difco No. 2 (Difco Laboratories, Detroit, Mich.) as the medium (3, 9). The mean serum level obtained 30 min after infusion of cefotaxime was 82.5 μg/ml (range, 13.5 to 225 μg/ml). Serum levels did not significantly differ with respect to daily dose.

Thirty-seven pathogens were isolated from blood, sputum, urine, wound, or tissue specimens before cefotaxime therapy in 28 patients (Table 2). No pathogen was identified in 10 cases. Repeat cultures from infected sites were obtained as clinically indicated and upon completion of therapy. Multiple pathogens were obtained in eight cases. Cefotaxime susceptibility studies with the modified method of Kirby-Bauer were performed with 30-μg cefotaxime discs (2, 10, 21). Cefotaxime minimal inhibitory concentrations (MIC) were determined by broth dilution technique with tryptic soy broth (24). Infections in which organisms were isolated from the blood were deemed bacteremias, irrespective of their source of origin. Infections in which pathogens were exclusively cultured from the urine, bile, or wound exudate were considered urinary tract, biliary, or wound infections, respectively. Infections in which bacteria were grown from bone biopsy cultures were designated osteomyelitis. Nosocomial pneumonias were characterized by fever, purulent sputum production, and new or progressive pulmonary infiltrates acquired 3 or more days after hospital admission. Organisms isolated from expectorated sputa or suctioned secretions from endotracheal tubes were considered pathogens in five such cases. Organisms cultured from lung tissue were considered the etiological agents in another patient. Patients who were febrile, granulocytopenic, and septic on a clinical basis and in whom no pathogen was isolated were classified as having septicemia.

The response of patients to cefotaxime was classified as good, fair, or poor. A good response was defined as clinical improvement with eradication of the pathogen on repeat culture. If no pathogen was isolated from pretreatment cultures, clinical improvement alone was considered a good response to cefotaxime. Clinical improvement was characterized by a decrease in temperature or amelioration of the signs and symptoms of infection. A fair response was defined as clinical improvement with pathogen persistence. Unless otherwise stated, good and fair responses were not associated with relapse. A poor response was defined as a lack of clinical improvement regardless of bacteriological response.

Forty-two courses of therapy were evaluated for toxicity. The patient treated for less than 24 h was excluded from analysis. Parameters assessed before cefotaxime included a complete history, physical examination, blood count, direct and indirect Coombs urinalysis, blood urea nitrogen and serum creatinine, electrolytes, calcium, phosphorus, total protein, albumin, bilirubin, alkaline phosphatase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, and glucose. These studies were repeated at weekly intervals during and upon completion of the therapy.

RESULTS

Clinical improvement was documented in 25 of 38 courses of therapy (66%). Improvement was independent of daily dose or serum level of cefotaxime. Seventeen courses resulted in a favorable clinical and bacteriological response. One course of therapy effected cure of a nosocomial pneumonia from which no organism was isolated. Five courses of therapy yielded clinical improvement in the absence of a documented site of infection or pathogen. These 23 patients were classified as having good responses to cefotaxime. Two patients exhibited fair responses. These two individuals clinically improved during therapy despite bacteriological failure. Pathogen persistence was documented in sputum and bone, respectively.

Thirteen patients had poor responses to cefotaxime (Table 3). In 2 of these 13 clinical failures, the etiological pathogen was eliminated from urine and blood, respectively. However, neither patient responded clinically and both died during therapy. Pathogen persistence was documented in seven failures. In three of the failures, *Pseudomonas aeruginosa* (two) and *Enterococcus* (one) resistant to cefotaxime were isolated and required the use of alternative therapies. Two failures with pathogen persistence resulted from an inability to resect infected necrotic tissue. Another such failure occurred in a patient with *Serratia marcescens* bacteremia after prosthetic aortic valve replacement. De-

TABLE 2. Clinical response with respect to pathogens and sites of infection in 28 treatment courses of cefotaxime[a]

Pathogen and site of infection	Zone size		MIC		Response[b]		
	Median	Range	Median	Range	G	F	P
Serratia marcescens (13)[c]	27	25–30	0.39	0.195–3.13	9	1	3
Bacteremia (4)					3	0	1
Nosocomial pneumonia (4)					3	1	0
Wound infection (3)					2	0	1
Biliary infection (1)[d]					1	0	0
Urinary tract infection (1)					0	0	1
Pseudomonas aeruginosa (12)	16	0–30	25	12.5–100	4	2	6
Bacteremia (2)					0	0	2
Nosocomial pneumonia (2)					1	1	0
Wound infection (4)					1	0	3
Osteomyelitis (3)					1	1	1
Biliary infection (1)[d]					1	0	0
Escherichia coli (4)	32	30–35	0.25	0.13–0.39	4	0	0
Bacteremia (3)					3	0	0
Nosocomial pneumonia (1)					1	0	0
K. pneumoniae							
Bacteremia (2)	33		0.195		1	0	1
Providencia stuartii							
Bacteremia (2)	32		0.78		2	0	0
Enterobacter cloacae							
Wound infection (1)	18		50		0	0	1
H. influenzae							
Nosocomial pneumonia (1)	18				1	0	0
Enterococcus							
Wound infection (1)	0				0	0	1
Staphylococcus aureus							
Nosocomial pneumonia (1)	18				1	0	0

[a] No pathogen was identified before cefotaxime in 10 treatment courses; multiple pathogens were identified in 8 courses.

[b] G, good response: clinical and bacteriological success; F, fair response: clinical improvement but bacteriological failure; P, poor response: clinical failure.

[c] Denotes number of isolates.

[d] Concurrent ampicillin therapy was given for one patient with mixed biliary tract infection with *Serratia marcescens*, *Pseudomonas aeruginosa* and *Enterococcus*.

spite the initial conversion of blood cultures to negative, fever and clinical deterioration progressed during cefotaxime therapy. Additional antibiotics were ineffective in controlling the infection. Antemortem blood cultures were again positive for *Serratia marcescens*. Patient 7 had persistent *Pseudomonas aeruginosa* osteomyelitis despite cefotaxime. No pathogen was isolated from four cefotaxime failures. One patient developed fatal sepsis, hypotension, and acute renal failure after surgical repair of an aortoduodenal fistula. Three patients suffered prolonged granulocytopenia and fever, complicating acute nonlymphocytic leukemias. Two of these patients died despite further empiric, broad-spectrum antimicrobial therapy.

Of 35 evaluable patients, 12 died during the study. Nine of 13 cefotaxime failures and 3 of the 25 favorable responders died. Infection was the cause of death in nine patients, which included eight failures and one superinfection.

Cefotaxime was used as the sole initial therapy in the treatment of suspected infection in 14 febrile granulocytopenic patients. One patient received two courses of therapy. All had less than 100 granulocytes per ml of blood. Pathogens were isolated from six patients, of whom four had gram-negative bacteremias, one had

TABLE 3. Clinical failures with respect to sites of infection and pathogens in 13 patients

Site of infection (no. of patients)	Pathogen	Reason for failure
Bacteremia (4)	*Serratia marcescens*	Early, prosthetic valve endocarditis
	Pseudomonas aeruginosa	Resistant organism
	Pseudomonas aeruginosa	Resistant organism
	K. pneumoniae	Persistent granulocytopenia, pseudomembranous enterocolitis
Wound infection (3)	*Serratia marcescens, Pseudomonas aeruginosa*	Failure to resect infected necrotic knee arthroplasty
	Pseudomonas aeruginosa	Inability to resect fiber implants from a severely infected scalp
	Serratia marcescens, Pseudomonas aeruginosa, Enterococcus	Polymicrobial arterial graft bed infection; resistant organism
Osteomyelitis (1)	*Pseudomonas aeruginosa*	Chronic infection with sequestrum
Urinary tract infection (1)	*Serratia marcescens*	Cholangiocarcinoma with biliary obstruction; acute myocardial infarction with cardiogenic shock
Septicemia (4)	No pathogen isolated	Persistent granulocytopenia
	No pathogen isolated	Persistent granulocytopenia
	No pathogen isolated	Persistent granulocytopenia
	No pathogen isolated	Ruptured aortoduodenal fistula; hypotension and acute renal failure

nosocomial pneumonia, and one had osteomyelitis with *Pseudomonas aeruginosa*. Three of these six patients had good responses to cefotaxime. One patient developed pulmonary infiltrates and fever without isolation of a pathogen from expectorated sputum. Resolution of clinical pneumonia succeeded cefotaxime therapy. No pathogen or site of infection was detected in eight patients. Five of these patients responded favorably to cefotaxime. Five of six patients with transient granulocytopenia (less than 14 days) had favorable responses to cefotaxime. Four of nine patients with persistent granulocytopenia improved during therapy.

The clinical response to cefotaxime with respect to pathogenic isolates is shown in Table 2. Thirteen courses of therapy were instituted for infections caused by strains of *Serratia marcescens* which were resistant by Kirby-Bauer disc susceptibility testing to all commercially available antimicrobials including amikacin. Sporadic cefoxitin (>100 μg/ml) and amikacin MICs (>50 μg/ml) were obtained to corroborate drug resistance. There were four bacteremias, four nosocomial pneumonias, three wound infections, one biliary infection, and one urinary tract infection. Multiple pathogens were isolated from 5 of 13 patients. An unusually prolonged duration of therapy (48 days) was necessary for successful treatment of one patient with an anterior thigh compartment infection due to *Serratia marcescens*. In another patient in whom *Serratia marcescens, Pseudomonas aeruginosa*, and *Enterococcus* were isolated from bile, ampicillin was given concomitantly with cefotaxime. Favorable responses were noted in 10 of 13 courses of therapy (77%). Twelve courses of therapy were given for infections due to *Pseudomonas aeruginosa*. There were two bacteremias, two nosocomial pneumonias, four wound infections, three bone infections, and one biliary tract infection. Multiple pathogens were isolated from five patients. Favorable responses were noted in six cases (50%). Of 12 infections due to *Pseudomonas aeruginosa*, 2 were caused by strains which were resistant to cefotaxime and ticarcillin. In both instances, organisms were isolated from the blood during periods of granulocytopenia and fever. No primary focus of infection was discerned. In each case, cefotaxime or ticarcillin had been administered in the 2 weeks before cefotaxime. No patient with infection due to susceptible strains had received therapy with these agents.

Twenty-three possible complications of cefotaxime were noted in 14 of 42 courses of therapy (Table 4). The majority of reactions involved skin and peripheral blood elements. In only two cases were reactions considered severe enough to warrant discontinuation of therapy. Colonic pseudomembranous changes were noted at postmortem examination in two granulocytopenic patients. In one instance, lesions were extensive and may have contributed to the death of the patient. The pathogenesis of the pseudomembranous changes could not be inferred from

TABLE 4. Possible drug-related complications in 42 patients who received cefotaxime

Maculopapular rash	5
Vesicular eruption	1
Eosinophilia	4
Coombs conversion	2
Coombs-positive hemolytic anemia	1
Fever	3
Pseudomembranous enterocolitis	2
Superinfection	1
Emergence of resistant organisms	1
Relapse	1
Pain with injection	1
Transaminase elevation	1

available data. No antemortem studies for *Clostridium difficile* were obtained. In one granulocytopenic patient, fatal superinfection with *Pseudomonas aeruginosa* bacteremia occurred. In another patient with osteomyelitis due to *Pseudomonas aeruginosa*, resistant organisms emerged during therapy. Bone biopsies performed before and during treatment with cefotaxime consistently yielded *Pseudomonas aeruginosa* serotype 4 (Bacto *Pseudomonas aeruginosa* antiserum set; Difco). The MIC of cefotaxime for the organism before therapy was 25 μg/ml. The MIC for the organism isolated during therapy was >100 μg/ml. One bacteremic patient with mesenteric endarteritis due to *Providencia stuartii* resistant to all available antibiotics relapsed after 14 days of cefotaxime. A second 25-day course was curative.

DISCUSSION

A nosocomial outbreak of infections due to *Serratia marcescens* resistant to all commercially available antibiotics prompted an evaluation of cefotaxime in the therapy of serious infections at Rush-Presbyterian-St. Luke's Medical Center. Those patients hospitalized in intensive care units and individuals undergoing inhalation therapies had the greatest risk of acquiring the organism. Granulocytopenic patients were included in the study, due to the risk of nosocomial infection in this population.

Despite a severely ill patient population as indicated by a 34% hospital mortality, the use of cefotaxime resulted in clinical improvement in 25 of 38 cases (66%). Seven of eleven patients with gram-negative bacteremia and all 7 patients with nosocomial pneumonia improved with cefotaxime. Furthermore, five of six patients with fever and transient granulocytopenia favorably responded to cefotaxime.

In vitro susceptibility testing (4, 5, 7, 14, 20, 22, 23, 25, 26) and results obtained in this study suggest that the greatest benefit of cefotaxime might occur in the treatment of multiply resistant, nosocomial, gram-negative pathogens. Fifteen courses of cefotaxime administered for infections caused by multiply resistant *Serratia marcescens* (13) and *Providencia stuartii* (2) resulted in clinical improvement in 12 patients (80%). Of 12 infections due to *Pseudomonas aeruginosa*, 6 responded favorably to cefotaxime therapy (median cefotaxime MIC, 25 μg/ml). This data exclude one patient who was fatally superinfected with *Pseudomonas aeruginosa* bacteremia. When evaluated in light of all *Pseudomonas aeruginosa* isolates, cefotaxime cannot be considered adequate therapy for this organism unless in vitro susceptibility can be documented. Furthermore, the empiric use of cefotaxime alone for serious infections should be discouraged in individuals who have received recent therapy with beta-lactam agents active against *Pseudomonas aeruginosa*. It has been shown that strains of *Pseudomonas aeruginosa* that are resistant in vitro to carbenicillin are commonly resistant to cefotaxime (16). Support for the in vivo selection of resistant isolates by prior broad-spectrum antibiotics is offered by Kurtz et al., who found that only 5% of all *Pseudomonas aeruginosa* isolates from recently treated immunocompromised patients were susceptible to cefotaxime (15). The suggestion that the use of antipseudomonal beta-lactam agents may select resistant strains of *Pseudomonas aeruginosa* is strengthened by our study, in which two of four patients who had received these agents developed fatal *Pseudomonas aeruginosa* bacteremia resistant to cefotaxime.

The comparative toxicity of cefotaxime versus aminoglycosides may also determine which agents are used in serious gram-negative infections. Of all courses of cefotaxime evaluated in this study, 33% were associated with possible complications of therapy. As has been noted with other cephalosporins, minor hematological and dermatological abnormalities predominated (18, 19). In 4 of 42 treatment courses, complications necessitated cessation of therapy. A severe pruritic maculopapular rash and a Coombs-positive hemolytic anemia were noted in two such patients. *Pseudomonas aeruginosa* superinfection and emergence of resistant *Pseudomonas aeruginosa* during cefotaxime therapy obligated that alternative agents be instituted in the other two patients. The postmortem findings of pseudomembranous enterocolitis in two granulocytopenic patients receiving cefotaxime is noteworthy. Enterocolitis complicating cephalosporin therapy has been infrequently described (1, 11, 13). However, in one study, 69% of patients with persistent granulocytopenia had pseudomembranous changes noted at autopsy (6). Nonetheless, patients with diarrhea during cefotaxime therapy should be examined for morpho-

logical and microbiological evidence of *Clostridium difficile* infection. Of the above described complications, four occurred in patients who had favorably responded to cefotaxime. If these four instances are deemed therapeutic, limiting complications, cefotaxime was found to be safe and effective in 21 of 38 evaluable patients (55%).

This trial indicates that the new cephalosporin, cefotaxime, is most useful in the treatment of multiply resistant, nosocomial, gram-negative, bacillary infections due to organisms such as *Serratia marcescens*. Its use as an alternative to aminoglycosides may be limited by modest activity against *Pseudomonas aeruginosa*. The utilization of this agent alone or in combination with aminoglycosides in the therapy of febrile granulocytopenic patients requires further evaluation.

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