ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1982, p. 421–425
0066-4804/82/030421-05$02.00/0
Vol. 21, No. 3

Cefotaxime Therapy of Serious Bacterial Infection in Adults

DENNIS T. MULLANEY AND JOSEPH F. JOHN, JR.*

Veterans Administration Medical Center, Medical University of South Carolina, Charleston, South Carolina 29425

Received 2 September 1981/Accepted 28 December 1981

We evaluated the efficacy, safety, and tolerance of cefotaxime in 35 adults (25 with pleuropulmonary infections, 7 with genitourinary tract infections, and 3 with soft tissue infections). Of these 35 patients, 18 (51.4%) were seriously or critically ill. In vitro susceptibility testing revealed that 90.4% of the pathogens isolated were susceptible to cefotaxime (minimal inhibitory concentration, <8 μg/ml), 4.8% were intermediately susceptible (minimal inhibitory concentration, 8 to 32 μg/ml), and 4.8% were resistant (minimal inhibitory concentration, >32 μg/ml). A total of 34 of the 35 patients (97%) were clinically and bacteriologically cured of their infections. Adverse reactions occurred in two patients, but these reactions did not require interruption of therapy.

Cefotaxime is a new broad-spectrum derivative of 7-aminocephalosporanic acid which has marked in vitro activity and a high level of resistance to hydrolysis by β-lactamases (3–5, 7–9, 11). In this study we evaluated the efficacy, safety, and toxicity of cefotaxime as single-drug therapy of serious bacterial infections in hospitalized adults.

MATERIALS AND METHODS

The patients included in this study were adults (12 to 90 years old) who were hospitalized in the Charleston Veterans Administration Medical Center, Charleston Memorial Hospital, or the Medical University of South Carolina Hospital. Any patient with an infection that required parenteral antibiotics was a potential candidate for the study and was referred to the investigators by the house staff for evaluation. Patients excluded from the study included (i) pregnant or lactating women, (ii) recipients within the previous 72 h of an antimicrobial agent to which the pathogen was susceptible, (iii) subjects hypersensitive to cephalosporins or with type I hypersensitivity to penicillins, (iv) recipients of probenecid therapy during the preceding 2 weeks, and (v) individuals with serious hepatic disease or a rapidly fatal underlying illness. Patients were not excluded on the basis of the severity of their infectious process, and every effort was made to treat patients with life-threatening infections. All patients admitted to the study gave informed consent.

Before initiation of therapy, we obtained specimens for appropriate cultures, including two blood samples. In addition, we obtained a complete blood cell count and platelet count and performed direct and indirect Coombs' tests, urinalysis, and tests for blood urea nitrogen, creatinine, calcium, inorganic phosphorus, glucose, total protein, albumin, total bilirubin, aspartate, aminotransferase (glutamic-oxalacetic transaminase), alanine aminotransferase (glutamic-pyruvic transaminase), lactic dehydrogenase, and alkaline phosphatase. These laboratory tests were repeated on day 5 of therapy, every seventh day thereafter, and at the conclusion of therapy. Cultures of infected sites were repeated routinely on day 3 of therapy and after therapy was completed. In patients with genitourinary tract sepsis, follow-up cultures were also obtained 10 to 14 days after therapy ended.

Pretreatment specimens for bacteriological diagnosis were obtained personally by us, and these specimens were Gram stained and plated onto appropriate media within 20 to 30 min of collection. Sputum specimens from patients with lower respiratory tract infections were obtained by transtracheal aspiration or with a sterile Lukens trap immediately after intubation whenever possible. Expectorated sputum specimens were considered adequate if there was no more than one epithelial cell per low-power field and numerous polymorphonuclear leukocytes, with a marked predominance (>90%) of a single bacterial form as determined by oil immersion examination.

Organisms were identified by using the API system (Analytab Products, Plainview, N.Y.) or the Dyntech MIC 2000 system (Dyntech Laboratories, Inc., Alexandria, Va.) or both. Minimal inhibitory concentrations (MICs) were determined by serial twofold dilutions in the appropriate broth, using an inoculum of 10^6 organisms per ml and an 18-h incubation. The minimal bactericidal concentrations (MBC) of a drug was considered that concentration which produced two or fewer colonies when 0.001 ml of broth was subcultured onto agar. Anaerobic MICs and MBCs were determined by the disk broth method (12).

The 1-g and 500-mg ampoules of cefotaxime that were used for injection and for in vitro studies were supplied by Hoechst-Roussel Pharmaceutical Co., Somersville, N.J. For intravenous (i.v.) administration, 1 to 3 g of cefotaxime was dissolved in 10 to 30 ml of sterile water. These doses, diluted to 100-ml volumes in 5% glucose, were infused over a 10- to 15-min interval every 6 to 8 h. Whenever possible (in more than 90% of the cases), the site of i.v. administration was changed every 48 h. For intramuscular administration cefotaxime was prepared by diluting 1 g of antibiotic in 2 ml of sterile water. Doses were injected into the lateral buttocks every 6 to 8 h.

TABLE 1. Patients, infecting organisms, therapy, and responses of patients

Target disease	Patients						Infecting organism
	Total no.	No. of males	No. of females	Age (yr)		No. seriously ill	Taxon
				Range	Mean		
Pulmonary							
Pneumonia	19	17	2	19–81	47	7	*S. pneumoniae* *Haemophilus influenzae* *K. pneumoniae* *Micrococcus parainfluenzae* *E. coli* Group C streptococci *P. aeruginosa*
Empyema	3	3		34–64	52.3	3	*S. faecalis* Gamma *Streptococcus* *S. aureus* *H. influenzae*
Bronchitis	2	2		47–65	56	0	*Haemophilus parainfluenzae* *S. pneumoniae*
Lung abscess	1	1		52		0	*Fusobacterium* *Peptostreptococcus* Anaerobic *Streptococcus* *Bacteroides* sp.
Genitourinary							
Pyelonephritis	6	2	4	15–65	40.8	5	*E. coli* *K. pneumoniae* *P. aeruginosa*
Epididymitis	1	1		16		1	*P. aeruginosa*
Miscellaneous							
Septic thrombophlebitis	1	1		70		0	*S. aureus*
Perirectal abscess	1	1		40		1	*Peptostreptococcus micrus*
Stump wound infection	1	1		67		1	*E. cloacae* *S. faecalis* *E. cloacae*

We saw all of the patients daily and evaluated the therapeutic efficacy by clinical, laboratory, and bacteriological criteria. Patients were considered clinically cured if all signs and symptoms of infection resolved, if laboratory indices returned to normal or base-line values, and if the radiographic studies showed definite improvement or resolution. Patients were considered bacteriologically cured if the causative organism(s) was eradicated from the infected site during and after completion of therapy. In one patient with a perirectal abscess and one patient with an empyema not associated with a pulmonary parenchymal infection, it was not possible to obtain posttreatment cultures, and clinical cure was taken to imply bacteriological cure.

Potential adverse effects of cefotaxime were detected by the previously mentioned laboratory tests and daily questioning and examination of each patient for adverse effects.

RESULTS

Table 1 provides data on the patients, the sites of infection, the MICs and MBCs of the pathogens isolated, the therapy, and the responses of the patients to therapy. A total of 35 patients (29 males and 6 females), who ranged in age from 15 to 81 years (mean age, 47.2 years), were included in the study. Of these 35 patients, 18 (51.4%) were seriously or critically ill upon entry into the study, and 7 of the 35 patients (20%) had positive pretreatment blood cultures. All 35 patients received at least 5 days of therapy. Most patients were treated with 1 g of cefotaxime i.v. every 6 to 8 h for 5 to 10 days. Patients with empyema, a lung abscess, or meningitis and patients from whom *Staphylococcus aureus, Streptococcus faecalis*, or *Pseudomonas aeruginosa* was isolated were treated with a larger dose of cefotaxime (2 to 3 g i.v. every 6 to 8 h) for a longer period of time (10 to 25 days). A total of 24 patients received all of their therapy i.v., and 8 patients received most (>75%) of their therapy i.v. before being switched to intramuscular therapy at the request of the physician in charge. Two patients received intramuscular therapy because of obesity, and one patient received intramuscular because he refused i.v. therapy.

A total of 25 patients with acute pleuropulmonary infections were treated with cefotaxime; this included 19 patients with pneumonia, 3 patients with empyema, 2 patients with chronic obstructive pulmonary disease and superimposed acute bronchitis (increased leukocyte count, fever, increased production of purulent

TABLE 1—*Continued*

Infecting organism			Therapeutic regimen				Days of fever	
No. of patients	MIC range (μg/ml of medium)	MBC range (μg/ml of medium)	Total dose (g/day)		Days of treatment		Range	Mean
			Range	Mean	Range	Mean		
8	≤0.0015–0.097	≤0.003–0.097	2–12	5.5	6–21	9.3	1–6	2.1
5	≤0.003–0.012	≤0.003–0.012						
4	0.012–0.145	0.012–0.195						
1	0.048	0.048						
1	0.048	0.048						
1	3.12	6.25						
1	25.0	<100						
1	0.195	12.5	3–8	5.0	9–13	11.3	1–4	2.0
1	≤0.003	<0.003						
1	1.56	1.56						
1	0.015	0.015						
1	0.003	0.006	3–4	3.5	6		1	
1	0.012	0.012						
1	≤6.0	≤6.0	8		26		1	
1	≤6.0	≤6.0						
1	≤6.0	≤6.0						
1	≤6.0	≤6.0						
4	0.024–0.048	0.024–0.048	4–8	5.3	7–18	9.2	1–6	3.2
1	0.024	0.024						
1	12.5	12.5						
1	6.25	12.5	8		18		1	
1	1.56	1.56	4		9		2	
1	3.12	>25.0	4		9		5	
1	0.048	0.048	4		5		5	
1	>100	>100						
1	>100	>100						

sputum, and decreased arterial oxygenation), and 1 patient with a lung abscess. Of these 25 patients, 23 had one or more predisposing factors which made them more susceptible to serious pulmonary infection (Table 2). Of the 21 patients with pneumonia or bronchitis, 20 had a single pathogen isolated from their sputum, and 1 had a *Klebsiella pneumoniae* strain and a group C *Streptococcus* strain isolated from a transtracheal aspirate. In every case, the predominant organisms(s) cultured from the sputum was anticipated from an examination of the Gram-stained sputum. The most frequently isolated pathogens in these patients were *Streptococcus pneumoniae* (8), *Haemophilus* spp. (8), and *K. pneumoniae* (4). All 25 patients were clinically cured, and in all 25 patients the offending pathogen was eradicated by day 3 of therapy. Of particular interest was a patient with cavitary pneumonia, bacteremia, and meningitis caused by a strain of *K. pneumoniae* that was resistant to all currently available antibiotics. This patient had a prompt clinical response and bacteriological cure with cefotaxime treatment after failing to respond to high-dose ticarcillin and amikacin therapy.

The next largest group of patients included the seven patients with genitourinary tract sepsis. None of these patients had indwelling Foley catheters. Five of the seven patients had one or more predisposing factors which increased their susceptibilities to genitourinary tract sepsis (Table 2). Six patients had pyelonephritis (fever, rigors, pyuria, bacteriuria, and costovertebral angle pain to fingertip palpation), which was caused by *Escherichia coli* in four patients, *P. aeruginosa* in one patient, and *K. pneumoniae* in one patient. The seventh patient had acute epididymitis with overwhelming sepsis caused by a *P. aeruginosa* strain that was resistant to all currently available antibiotics. After failing to respond to high-dose ticarcillin and amikacin therapy, this patient showed a prompt clinical response to cefotaxime. All six patients with pyleonephritis were also clinically cured by cefotaxime treatment. In all seven patients the urine was sterile upon reculture on day 3 of therapy and again 10 to 14 days after therapy ended.

The final group consisted of three patients with miscellaneous soft tissue infections. One patient was being treated for cholecystitis when

TABLE 2. Predisposing factors in patients receiving cefotaxime

Factor	No. of patients
Pleuropulmonary infections	
Alcoholism	13
Chronic obstructive lung disease	8
Diabetes mellitus	5
Acute renal failure	2
Asthma	2
Cerebrovascular accident	2
Asplenism	1
Closed head injury	1
Congestive heart failure	1
Hemoglobinopathy	1
Carcinoma of the lung	1
Cerebral palsy	1
Rheumatoid lung disease	1
Genitourinary tract infections	
Paraplegia	2
Diabetes mellitus	2
Postcesarean section	1
Asplenism	1
Miscellaneous infections	
Alcoholism	1
Prolonged i.v. therapy	1

he developed an *S. aureus* bacteremia secondary to an infected i.v. catheter site; this patient had a prompt clinical response and bacteriological cure. Another patient appeared at a local emergency room in septic shock, and the initial catherized urine specimen reportedly showed pyuria and bacteriuria. On the basis of these findings, the patient was thought to have genitourinary tract sepsis, and cefotaxime treatment was begun. After the patient was stabilized, a more complete examination revealed the presence of a perirectal abscess, and the initial urine culture was subsequently reported as sterile. The patient had a prompt clinical response to cefotaxime treatment and on day 3 of therapy underwent surgical drainage of his abscess, from which a single anaerobe was isolated. This patient received 5 more days of cefotaxime postoperatively and was clinically cured. It was not possible to obtain a posttherapy culture from this patient. The last patient in this group developed a wound infection and overwhelming sepsis 9 days after undergoing an above-the-knee amputation. *Enterobacter cloacae, E. coli*, and *S. faecalis* were isolated from the stump wound. *E. cloacae* and *E. coli* were also isolated from the blood. After cefotaxime treatment was begun, the patient had a prompt clinical response. However, in vitro susceptibility testing indicated that the *E. cloacae* and *S. faecalis* strains were resistant to cefotaxime. In view of the favorable clinical response shown by the patient, it was decided to repeat the in vitro testing, which again indicated that the *E. cloacae* and *S. faecalis* strains were resistant to cefotaxime. Therefore, according to the protocol, cefotaxime was discontinued after day 5 of therapy, and the patient was started on carbenicillin and tobramycin. At the time that cefotaxime was discontinued, cultures of the blood were negative, and cultures of the wound revealed eradication of *S. faecalis* and *E. coli* and a marked reduction in the amount of *E. cloacae*. Thus, although this patient had an excellent clinical response, he was considered a failure.

In vitro susceptibility testing revealed that 38 of the 42 pathogens isolated were susceptible to cefotaxime (MIC, <8 μg/ml), 2 isolates were intermediately susceptible (MIC, 8 to 32 μg/ml), and 2 isolates were resistant (MIC, >32 μg/ml). The susceptible *Enterobacteriaceae* isolates had a mean MIC of 0.049 μg/ml (range, 0.012 to 0.195 μg/ml). The one resistant *Enterobacteriaceae* isolate was an *E. cloacae* strain with an MIC of 100 μg/ml. It should be noted that the initial disk susceptibility testing of this organism demonstrated a large zone of inhibition around the 30-μg disk, with several minute colonies growing within the zone. This may have been analogous to the apparent enhanced in vitro activity of cefamandole against *Enterobacter* which can be demonstrated by agar susceptibility testing methods but not by broth susceptibility testing (1). This discrepancy results from a high rate of mutation to cefamandole resistance, resulting in small-colony variants that are impossible or nearly impossible to detect by agar dilution methods (6). The *S. pneumoniae* isolates had a mean MIC of 0.020 μg/ml (range, 0.0015 to 0.097 μg/ml), and the *Haemophilus* spp. isolates had a mean MIC of 0.014 μg/ml (range, 0.003 to 0.097 μg/ml). The two *S. aureus* isolates had MICs of 1.56 μg/ml. The three *P. aeruginosa* isolates had a mean MIC of 12.5 μg/ml (range, 6.25 to 25.0 μg/ml). The two *S. faecalis* isolates had markedly discrepant MICs (0.195 and 100 μg/ml), as did the two aerobic non-group D streptococcal isolates (0.003 and 3.12 μg/ml). The five anaerobic isolates all had MICs of ≤ 6.0 μg/ml. The MBC for each isolate was equal to or within one tube dilution of the MIC, with the exception of the two *S. faecalis* isolates and one *P. aeruginosa* isolate.

Only 1 of our 35 patients had an adverse reaction that was definitely attributable to the administration of cefotaxime. This patient developed a mild phlebitis at an i.v. infusion site toward the end of her therapy for overwhelming pneumococcal bacteremia. The phlebitis resolved promptly with local therapy. Another patient with *Pseudomonas* sepsis had a mild self-limited rise in hepatic transaminases, but he was concurrently receiving a higher-than-usual dose of a phenothiazene for nausea and vomit-

ing. There were no adverse systemic reactions and no renal or hematological toxicity in our patients. No patient developed a superinfection during therapy or after completion of therapy.

DISCUSSION

The results of this clinical trial suggest that cefotaxime is a safe and effective drug for treatment of seriously ill adult patients with a variety of bacterial infections. The fact that we had no deaths and the 97% clinical and bacteriological cure rates reflect the greatly enhanced in vitro activity of this drug and the aggressive supportive care that patients receive in large university medical centers. The low incidence of adverse reactions (5.7%) may be partially explained by the relatively small number of patients studied and our meticulous attention to i.v. catheter site care and rotation.

Only 4.8% of the pathogens in our study were resistant to cefotaxime in vitro. In agreement with previous preclinical in vitro studies, we found cefotaxime to be very active against members of the *Enterobacteriaceae*, *Haemophilus* spp., and *S. pneumoniae*. The limited number of isolates of the other species recovered during this study does not permit conclusions to be drawn. However, previous in vitro evaluations have indicated that cefotaxime also has good activity against *S. aureus*, aerobic non-group D streptococci, and anaerobes, with the exception of certain β-lactamase-producing strains of *Bacteroides fragilis* (10, 13). *P. aeruginosa* appears to be intermediately susceptible or resistant to this antibiotic, and the eventual role of cefotaxime in therapy, alone or with another agent, against serious *Pseudomonas* infections remains to be defined.

In view of the greatly enhanced in vitro activity of cefotaxime, trials comparing high-dose therapy (4 to 12 g/day) with low-dose therapy (1 to 2 g/day) should be undertaken to determine the appropriate dosing regimen(s) for infections of the various organ systems. Our patients with *S. pneumoniae* and *Haemophilus* spp. pneumonia, as well as our patients with pyelonephritis, might have done equally well on a lower dosing regimen. Also deserving study is the potential role of cefotaxime in the therapy of meningitis. In our patient with meningitis caused by a highly resistant *K. pneumoniae* strain, cefotaxime proved to be life saving. In addition, there is at least one published report documenting the efficacy of cefotaxime in the treatment of meningitis in children infected with resistant organisms (2).

ACKNOWLEDGMENTS

This work was supported in part by a grant from Hoechst-Roussel Pharmaceutical Co.

We thank the medical house staff for their help in patient care and Sharon Kearns for her technical work.

LITERATURE CITED

1. **Adams, H. G., G. A. Stilwell, and M. Turck.** 1976. In vitro evaluation of cefoxitin and cefamandole. Antimicrob. Agents Chemother. 9:1010–1024.
2. **Belohradsky, B. H., D. Geiss, W. Marget, K. Burch, D. Kafetzis, and G. Peters.** 1980. Intravenous cefotaxime in children with bacterial meningitis. Lancet i:61–63.
3. **Counts, G. W., and M. Turck.** 1979. Antibacterial activity of a new parenteral cephalosporin–HR 756: comparison and cefamandole and ceforanide. Antimicrob. Agents Chemother. 16:64–68.
4. **Dabernat, H. J., A. Buu-Hoi-Dang Van, C. Delmas, and R. Bauriad.** 1979. Comparative activities of cefotaxime, a new cephalosporin derivative, and of selected beta-lactam antibiotics against *Haemophilus* species. Ann. Inst. Pasteur Paris 130A:461–467.
5. **Drasar, F. A., W. Farrell, A. J. Howard, C. Mince, T. Leung, and J. O. Williams.** 1978. Activity of HR 756 against *Haemophilus influenzae*, *Bacteroides fragilis* and gram-negative rods. J. Antimicrob. Chemother. 4:445–450.
6. **Findell, C. M., and V. C. Sherris.** 1976. Susceptibility of *Enterobacter* to cefamandole: evidence for a high mutation rate to resistance. Antimicrob. Agents Chemother. 9:970–974.
7. **Fu, K. P., and H. C. Neu.** 1979. The comparative β-lactamase resistance and inhibitory activity of 1-OXA cephalosporin, cefoxitin and cefotaxime. J. Antibiot. 32:909–914.
8. **Hamilton-Miller, J. M. T., W. Brumfitt, and A. V. Reynolds.** 1978. Cefotaxime (HR 756), a new cephalosporin with exceptional broad-spectrum activity in vitro. J. Antimicrob. Chemother. 4:437–444.
9. **Neu, H. C., N. Aswapokee, P. Aswapokee, and F. Kwung.** 1979. HR 756, a new cephalosporin active against gram-positive and gram-negative aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. 15:273–281.
10. **Pechere, J. C., R. Gruay, J. Dubois, and R. Letarte.** 1980. Hydrolysis of cefotaxime by a β-lactamase from *Bacteroides fragilis*. Antimicrob. Agents Chemother. 17:1001–1003.
11. **Sosna, J. P., P. R. Murray, and G. Medoff.** 1978. Comparison of the in vitro activities of HR756 with cephalothin, cefoxitin, and cefamandole. Antimicrob. Agents Chemother. 14:876–879.
12. **Wilkins, T. O., and T. Thiel.** 1973. Modified broth-disk method for testing the antibiotic susceptibility of anaerobic bacteria. Antimicrob. Agents Chemother. 3:350–356.
13. **Wise R.** 1979. *Bacteroides fragilis* and HR 756. J. Antimicrob. Chemother. 5:115–116.