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Clinical Evaluation of Cefotaxime for Therapy of Lower Respiratory Tract Infections

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A clinical trial was designed to evaluate the efficacy and safety of cefotaxime, a new semisynthetic, broad-spectrum cephalosporin, in the therapy of community- and hospital-acquired pneumonias. Thirty-nine males (mean age, 65 years) were treated for 41 episodes of pneumonia. Only five patients did not have a serious underlying disease; 15 had two or more significant disorders. Sixty-six percent of these pneumonias were due to *Streptococcus pneumoniae* or *Haemophilus influenzae*. The minimal inhibitory concentrations for all bacterial isolates ranged from 0.008 to 4 μg/ml. Peak serum cefotaxime levels during therapy ranged from 12 to 124 μg/ml 1 h after a 1-g dose. Satisfactory bacteriological and clinical responses were observed in 85% of the cases. Four episodes of pulmonary superinfections due to cefotaxime-resistant gram-negative bacilli were noted, each in a patient being mechanically ventilated. Pseudomonas was involved in each of these superinfections, and three were fatal. No serious toxicity or adverse reaction to cefotaxime was seen. The results of this study suggest that cefotaxime is an effective and well-tolerated new cephalosporin antimicrobial agent for the therapy of pneumonia due to susceptible organisms.

The first generation cephalosporins are active against most gram-positive organisms but possess a limited gram-negative spectrum (25). The subsequently developed cephalosporins, cefamandole and cefuroxime, and the cephamycin, cefoxitin, display broader gram-negative antibacterial spectra but do not inhibit many important hospital-acquired pathogens, including *Serratia* sp. and *Pseudomonas* sp. (8, 13, 21, 24, 25). Cefotaxime (HR-756) is a third-generation semisynthetic cephalosporin with markedly enhanced in vitro antibacterial activity (5, 11, 15, 18, 20; J. R. Hamilton, J. Engle, and C. J. Schleupner, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, abst. no. 131, 1979). Although cefotaxime is cidal for gram-positive organisms at two- to fourfold-higher concentrations than previous cephalosporins, its gram-negative spectrum is enhanced to include most indole-positive *Proteus* sp., as well as *Providencia* sp., most *Citrobacter* sp., and many *Serratia* sp. and *Pseudomonas* sp. In addition to inhibiting both β-lactamase-positive and negative *Neisseria gonorrhoeae* and *Haemophilus influenzae*, cefotaxime is much more active than previous cephalosporins against members of the *Enterobacteriaceae* which are usually susceptible to cephalosporins.

Because of this broad in vitro antibacterial activity, cefotaxime has been evaluated in the therapy of serious infections. We report the results of a clinical trial designed to assess the efficacy and safety of cefotaxime for the treatment of community- and hospital-acquired pneumonias.

MATERIALS AND METHODS

Patients. Hospitalized patients 18 years of age or older were enrolled for this study at the Veterans Administration Medical Center in Salem, Va. This research proposal was reviewed by the institutional review committee and its human rights committee. All patients (or their legal guardians in the case of incompetency) gave informed consent before enrollment in the study.

Patients reported in this paper include a group of 24 treated with cefotaxime on a nonblinded, nonrandomized protocol for pneumonia. An additional group of 41 patients was enrolled in a single-blind, randomized study comparing cefotaxime (28 patients) with cefazolin (13 patients) for the therapy of pneumonia. Due to the randomization profile (a 2:1 ratio of enrollees treated with cefotaxime compared with those treated with cefazolin) and the nonevaluability of a number of patients receiving cefazolin in this latter study, too few patients treated with this drug were available for a valid comparison to patients receiving cefotaxime. In this report, patients receiving cefotaxime in the single-blind study will be combined with those enrolled in the nonrandomized study.

To be enrolled in these studies, a patient was required (i) to have evidence of a lower respiratory tract (LRT) infection demonstrated by fever, cough, sputum production, leukocytosis, or a chest radio-

graph consistent with pneumonia, (ii) to have a pneumonia caused by a bacterium presumed or known to be susceptible to cefotaxime (and cefazolin for patients enrolled in the randomized study), after examination of a sputum specimen or LRT secretions obtained by endotracheal suction (ETS) or transtracheal aspiration (TTA), and (iii) to have received no antibiotics for 72 h before enrollment. Specific factors excluding patients from the study included (i) hypersensitivity to cephalosporins or type I hypersensitivity to penicillins, (ii) pregnancy, (iii) requirement for other antibiotic therapy concurrent with cefotaxime, (iv) having received other investigational drugs within 2 weeks of therapy, (v) having received probenecid within 2 weeks of therapy, (vi) significant renal impairment (blood urea nitrogen, >35 mg/dl; serum creatinine, >2.5 mg/dl; or creatinine clearance, <40 ml/min per 1.73 m^2 of body surface area), (vii) severe hepatic disease, and (viii) rapidly progressing fatal disease.

Laboratory tests. Laboratory studies required before entry of each patient into the study included aerobic and anaerobic blood cultures and an adequate specimen of LRT secretions. Sputa and ETS specimens were required to be of group 5 quality as defined by Murray and Washington (17); if such a specimen could not be obtained, a TTA was performed. Laboratory determinations obtained before, during, and at the completion of therapy were a complete blood count with differential leukocyte count, a platelet estimate or count, if judged to be decreased by estimation, a direct Coombs test, urinalysis, blood glucose, blood urea nitrogen, serum creatinine, total serum protein, serum albumin, serum uric acid, serum total bilirubin, serum alkaline phosphatase, serum aspartate aminotransferase, serum lactic dehydrogenase, serum phosphate, and serum calcium. After the first 28 patients had been studied, the prothrombin time and partial thromboplastin time were also determined for each patient subsequently entered into the study.

Drug. Cefotaxime was provided in sterile vials containing 1 g of dry powder. For intravenous (i.v.) administration, each gram was reconstituted with 10 ml of sterile saline for injection and further diluted to 50 ml in sterile water for injection containing 2.5 g of dextrose. For intramuscular (i.m.) administration, each gram was reconstituted to 3 ml with sterile water for injection. Such solutions were used within 4 h. The drug was administered in doses of 1 to 2 g every 4 to 8 h. Intravenous infusions were given intermittently over 30 min. The site of i.v. administration was changed every 48 h.

Patient evaluation. A complete history and physical examination of each patient were performed at the beginning and end of therapy. Vital signs (peak temperature and pulse rate, lowest blood pressure) were recorded, and abbreviated physical examinations were performed daily to monitor for responses to therapy. The previously listed laboratory studies were repeated on day 5, day 10, and/or the last day of therapy. Chest radiographs were repeated at least on the last day of therapy, and usually once or more during treatment. A repeat culture of LRT secretions was also sought at the end of treatment. At least 2 days after the start of therapy, blood specimens were obtained from most patients for peak and trough serum antibiotic levels. Specimens for trough levels were obtained within 30 min before a scheduled dose of cefotaxime, and specimens for peak levels were drawn 60 min after the start of an i.v. infusion or after an i.m. injection of cefotaxime. Sera were promptly separated and frozen at −20°C until assayed for antibacterial activity.

Efficacy. Generally, for a patient to be considered evaluable, cefotaxime must have been administered for at least 5 days. Furthermore, a pathogen isolated from LRT secretions obtained before the start of therapy had to be susceptible to cefotaxime. Other antimicrobial therapy given during cefotaxime therapy also excluded the patient from evaluation.

The therapeutic efficacy of cefotaxime was evaluated by clinical and bacteriological criteria. The clinical response to therapy was considered satisfactory if, at the end of therapy, there was resolution or improvement of (i) the infiltrate present on chest radiograph, (ii) the clinical signs and symptoms consistent with pneumonia (e.g., pulmonary findings, fever, toxicity, cough), and (iii) peripheral blood leukocytosis. The bacteriological response was considered satisfactory if, upon posttreatment culture of LRT secretions, the causative pathogen had been eradicated. If lack of sputum production precluded culture of LRT secretions after therapy, the bacteriological response was also considered satisfactory if the clinical response was satisfactory. If LRT specimen cultures obtained after therapy contained one or more new potential pathogens without clinical evidence of infection, the patient was considered colonized as a result of therapy. If such posttreatment cultures contained new potential pathogens concomitant with clinical evidence of recurrent respiratory infection, superinfection as a complication of therapy was diagnosed.

Susceptibility testing and antibiotic levels. All clinical bacterial isolates from patients in this study were initially tested for susceptibility to cefotaxime with a 30-μg disk, using a standard disk diffusion technique (2). The interpretive criteria for disk diffusion susceptibility tests were those recently published (9). Additionally, agar dilution minimal inhibitory concentration (MICs) for cefotaxime were determined in Mueller-Hinton agar (BBL Microbiology Systems) for all but three isolates according to techniques defined by the International Collaborative Study (6). Cefotaxime serum levels were determined in antibiotic medium no. 11 (Difco Laboratories) by the agar well diffusion method (3), using a multiply antibiotic-resistant strain of *Klebsiella pneumoniae* (ATCC 1296). Assay for the desacetyl derivative of cefotaxime was not performed. The *Klebsiella* strain 1296 used in this assay was fourfold less susceptible to the desacetyl derivative than to cefotaxime.

RESULTS

Between February 1980 and January 1981, 52 patients were enrolled in this study to receive cefotaxime. Of the 24 patients entered into the nonrandomized protocol, 19 were evaluable. Among the five nonevaluable patients, three were determined to be uninfected after entry into the study; two of these patients died subsequently of their underlying diseases (histiocytic lymphoma and vasculitis) and had sterile lungs at postmortem examination, whereas the third recovered from congestive heart failure without

antibiotics. The other two patients omitted from evaluation had positive cultures before therapy; one had a cefotaxime-resistant organism isolated by TTA, and the second died 2 days after initiation of therapy from complications of a preceding stroke.

Of the 28 episodes of pneumonia treated with cefotaxime in the randomized protocol, 22 were evaluable. Among the six patients withdrawn from the study, LRT specimens from four of these patients contained no pathogen, and evidence for pneumonia was lacking on early follow-up evaluation. The fifth patient was withdrawn from the study because his chest radiographic abnormality was determined to be malignant, and the sixth patient was withdrawn because a cefotaxime-resistant organism was isolated by TTA.

A total of 41 cases of pneumonia treated with cefotaxime were evaluated. All had clinical, chest radiographic, and laboratory findings, including purulent LRT secretions, consistent with pneumonia. Two patients were treated twice, each during two distinct episodes of pneumonia. Table 1 shows the clinical characteristics of these 41 patients. All patients were male with a mean age of 65 years (range, 37 to 86 years); 88% of the patients were 50 years of age or older. Thirty-six of the patients (88%) were white, and five (12%) were black. Only five patients lacked a significant predisposing underlying disease, and 37% suffered with two or more of the conditions noted in the table. Chronic lung disease, alcoholism, and ischemic heart disease were the most common of these underlying processes. At the time of entry into the study, most patients (56%) were considered to be in fair clinical condition, 42% were in serious condition, and one was critical.

Table 2 shows the bacterial etiology of these 41 episodes of pneumonia, the MICs of the associated pathogens, and the success of therapy. Twelve of these 41 episodes were caused by *Streptococcus pneumoniae*. Three of the 12 instances of pneumococcal pneumonia were bacteremic. Additionally, the five episodes of pneumonia listed with an unknown bacterial etiology each had a predominance of gram-positive diplococci in specimens of LRT secretions which were examined microscopically. (These five cases were included in the evaluation of the efficacy of cefotaxime because pneumonia was unquestionably present clinically in each instance.) *H. influenzae* was the next most common pathogen, with nine cases, one of which was bacteremic. Including the five pneumonias of unknown etiology as pneumococcal and the one pneumonia documented by TTA as a mixed pneumococcal-*H. influenzae* infection, these two pathogens accounted for 66% of the episodes of pneumonia. Other pathogens occurred less frequently. Four episodes of pneumonia were associated with two gram-negative pathogens each documented by TTA (two cases) and ETS (two cases) specimens. Overall, 12 of these 41 episodes of pneumonia were diagnosed etiologically by TTA, and 7 were bacteremic.

TABLE 1. Characteristics of 41 evaluable male patients with bacterial pneumonias treated with cefotaxime

Characteristic	No. (%) of patients
Age	
<50	5 (12)
50–70	22 (54)
>70	14 (34)
Underlying disease[a]	
None	5 (12)
Chronic lung disease	17 (41)
Alcoholism	10 (24)
Ischemic heart disease	8 (20)
Malignancy	3 (7)
Organic psychosis	8 (20)
Cavitary lung disease	2 (5)
Postoperative	1 (2)
Quadraparesis	1 (2)
Rheumatoid arthritis	1 (2)
Diabetes mellitus	1 (2)

[a] Fifteen of these patients had two or more significant underlying diseases.

Thirty-four (83%) of these 41 cases of pneumonia were community acquired; the remainder were nosocomial. Although only one patient was felt to be critically ill at the time of enrollment, eight patients required mechanical ventilatory assistance during their therapy. Two (5%) of the 41 episodes of pneumonia were thought to be secondary to aspiration, and 3 (7%) were cavitary pneumonias.

The geometric mean MICs and the range of MICs for the clinical isolates associated with these pneumonias were within clinically achievable serum and tissue levels (Table 2). Only eight isolates had MICs of >1 μg/ml. The four *Staphylococcus aureus* isolates consistently had the highest MICs (range, 2 to 4 μg/ml). Only one *S. pneumoniae* and one *H. influenzae* isolate had a MIC of 4 μg/ml; the remainder were susceptible at 1 μg/ml or less.

The daily dose of cefotaxime used in this study varied from 3 to 12 g. Twenty-five patients received 6 g per day (1 g every 4 h), and 11 received 4 g per day (1 g every 6 h); four patients received 12 g per day (2 g every 4 h); one received only 3 g per day (1 g every 8 h). All administrations were i.v. except for one patient who received the drug i.m. late during his treatment. Patients were treated for a mean of 7.2 days (range, 2 to 14 days). Of 41 pneumonias, 35

TABLE 2. Etiological diagnoses of bacterial pneumonia in 41 patients and outcome of therapy with cefotaxime

Bacterial etiology	MIC[a] (μg/ml)		No.[b] of patients	Satisfactory response (%)
	Geometric mean	Range		
Streptococcus pneumoniae	0.13[c]	0.008–4.0	12 (3)	92
Haemophilus influenzae	0.16[d]	0.008–1.0	9 (1)	100
Staphylococcus aureus	2.4	2–4	4	75
Klebsiella pneumoniae	0.5	0.06–2	3 (1)	67
Escherichia coli	0.03		1 (1)	100
K. oxytoca	0.03		1	100
Pseudomonas aeruginosa[e]			1 (1)	0
Mixed gram negative[f]	0.38	0.016–1.0	4	75
Mixed[g]		1.0,4.0	1	0
Unknown			5	100
Totals			41 (7)	85

[a] For single organisms, actual MIC is given.
[b] Number in parentheses denotes number of bacteremic cases.
[c] Mean for 11 of 12 isolates.
[d] Mean for eight of nine isolates.
[e] Organism was susceptible to cefotaxime by disk diffusion testing.
[f] Two cases were documented by TTA, two were documented by ETS specimens. Two cases were mixed *E. coli-P. mirabilis*; one each was *E. coli-S. marcescens* and *Enterobacter agglomerans-Morganella morganii*.
[g] One case of mixed *S. pneumoniae-H. influenzae* documented by TTA.

(85%) had a satisfactory clinical and bacteriological response (Table 2). Two patients are included among the six treatment failures who received only 2 days of therapy each, because both were infected with cefotaxime-susceptible organisms. One had *K. pneumoniae* sepsis (MIC = 2 μg/ml), deteriorated rapidly from serious to critical condition, and died despite high doses of cefotaxime (2 m i.v. every 4 h). The other patient had bacteremic *Pseudomonas aeruginosa* pneumonia; the organism was susceptible to cefotaxime by disk diffusion testing (unavailable for MIC determination), but the patient was withdrawn from study after 2 days and changed to aminoglycoside therapy because of clinical deterioration while on 1 g of cefotaxime every 6 h. Of the other four patients who were cefotaxime treatment failures, all developed pulmonary superinfection with cefotaxime-resistant gram-negative bacilli while being assisted by mechanical ventilation. During three of these pulmonary superinfections, *P. aeruginosa* was the only or most likely pathogen isolated from LRT secretions; in the fourth patient, an 81-year-old male, *P. maltophilia, Enterobacter aerogenes*, and *Serratia marcescens*, all resistant to cefotaxime, were recovered from LRT secretions. One of these four patients, a 58-year-old alcoholic man, died of bacteremic *P. aeruginosa* pneumonia on the 9th day of cefotaxime therapy. The other three superinfections were nonbacteremic pneumonias developing on days 6, 7, and 10 of therapy; only one patient survived, a 64-year-old man with an organic brain syndrome who had *S. marcescens* susceptible to cefotaxime, in addition to a resistant *P. aeruginosa*, in his LRT secretions at the time of his superinfection. The other two fatal pneumonias occurred in men with serious underlying disorders; one was 66 years old with lung cancer and the other, 81 years old, had a recent nephrectomy. Aside from the patient with bacteremic *Pseudomonas* pneumonia who was receiving 2 g of cefotaxime every 4 h, the other three patients with superinfections had received 1 g every 4 h.

Table 3 shows serum levels of cefotaxime determined in 26 of the patients enrolled in this study. Peak and trough levels were similar for patients given 1 g every 4 or 6 h, except for a tendency for peak and trough levels around a 4-hourly dose to be somewhat higher.

In Table 4, the incidences of adverse reactions are presented for the 41 courses of cefotaxime evaluable for clinical and bacteriological responses. Included also in the evaluation for adverse effects are two patients withdrawn from the study who were treated for at least 5 days and, therefore, could be evaluated for side effects. No patient experienced a systemic reaction to the drug, including fever or skin rash (Table 4). Three episodes of phlebitis occurred. In addition to the four instances of superinfection mentioned, colonization of the respiratory tract was documented in three patients after therapy. Hemotological reactions were limited to five episodes of transient eosinophilia. Additionally, during therapy 11 patients developed positive direct Coombs tests, seven of which were only weakly reactive. Six of these 11 patients received 1 g of cefotaxime every 4 h,

TABLE 3. Mean peak and trough[a] serum antibiotic levels in patients treated with cefotaxime intravenously

Timing of level	Mean serum level (μg/ml) for each dose	
	1 g every 6 h (n = 8)[b]	1 g every 4 h (n = 18)
Peak	38 (12–68)[c]	49 (17–124)
Trough	7 (<1–20)	17 (3–116)

[a] Peak levels were obtained 1 h after the start of the i.v. infusion; trough levels were drawn just before a dose.

[b] Number of patients evaluated is given in parentheses.

[c] Range of serum levels is given in parentheses.

two received 2 g every 4 h, and three received 1 g every 6 h. The mean duration of therapy for these 11 patients was 8.4 days (range, 5 to 14 days). All of these instances of Coombs test reactivity were transient, but one was associated with an unexplained moderate fall of blood hemoglobin level from 12.3 to 9.8 g/dl.

No evidence of nephrotoxicity was detected in this study, nor were any gastrointestinal side effects documented. One patient did report an exacerbation of preexisting diarrhea during treatment with cefotaxime which resolved shortly after therapy was stopped. Four patients did show mild serum aspartate aminotransferase elevations to twofold normal. Because of the extent of underlying disease in each of these patients, a relationship of these elevations to cefotaxime therapy is unlikely.

TABLE 4. Incidence of adverse reactions and development of abnormal laboratory studies during therapy with cefotaxime

Finding	No. with indicated finding/ no. evaluated (%)
Systemic reactions	0/43 (0)
Phlebitis	3/43 (7)
Fever	0/43 (0)
Rash	0/43 (0)
Colonization	3/41 (7)
Superinfection	4/41 (10)
Hematological reaction	
Leukopenia	0/41 (0)
Eosinophilia[a]	5/41 (12)
Thrombocytopenia	0/43 (0)
Direct Coombs test[b]	11/42 (26)
Prolonged prothrombin and partial thromboplastin time	0/23 (0)
Renal dysfunction	
Abnormal urinalysis	0/43 (0)
Azotemia	0/43 (0)
Liver dysfunction; increase of:	
Serum aspartate aminotransferase	4/43 (9)
Serum alkaline phosphatase	0/43 (0)
Serum total bilirubin	0/43 (0)
Gastrointestinal disturbance	0/43 (0)

[a] Eosinophilia was defined as greater than 400/mm^3.

[b] A positive Coombs test was associated with a decreased hemoglobin (from 123 to 9.8 g/dl) in only one instance.

DISCUSSION

Cefotaxime is a new third-generation semisynthetic cephalosporin with an enhanced intrinsic activity and spectrum compared with previous cephalosporins (5, 11, 15, 18, 20; Hamilton et al. 19th ICAAC, abstr. no. 131, 1979). Although somewhat less potent against *Staphylococcus* sp. than cephalothin and cefamandole, this compound has at least as much activity as cephalothin and cefamandole for non-enterococcal streptococcal isolates with MICs in a range easily achieved in vitro. Against *Escherichia coli, K. pneumoniae, Proteus mirabilis*, and *Salmonella* and *Shigella* isolates, cefotaxime is 10- to 100-fold more active than cephalothin. Compared with cephalothin, cefamandole, and cefoxitin, cefotaxime has at least 10-fold greater activity against indole-positive *Proteus, Enterobacter, Citrobacter*, and *Providencia* sp. and against *S. marcescens*. Additionally, cefotaxime is two to four times as potent as carbenicillin against *Pseudomonas* sp. and has activity in vitro against aminoglycoside-resistant gram-negative rods (10, 11, 15; Hamilton, Engle and Schleupner, manuscript in preparation). Additionally, for both beta-lactamase-positive and negative strains of *H. influenzae* and *N. gonorrhoeae*, cefotaxime has been shown to be much more active than currently available cephalosporins and, with the exception of *Bacteroides fragilis*, is at least equivalent to other cephalosporins in its anaerobic spectrum of activity (1, 4, 11, 12, 16, 18).

The human pharmacology of cefotaxime is similar to that of most currently available cephalosporins, but its half-life of approximately 1 h is twice as long as that of cephalothin (7, 14, 19). The serum levels after 1 g (Table 3) are in agreement with previously published findings, including the presence of residual antimicrobial activity up to 6 h after dosing (8, 14, 19). It is likely that the wide range of serum levels shown in the table after either dosing frequency reflects the diversity of patient ages enrolled in this study and the accompanying variation of their renal function. Due to the enhanced intrinsic activity of cefotaxime, its low protein binding of 36% compared with previously available cephalosporins, and the presence of detectable serum

levels for up to 6 h after i.v. or i.m. administration, cefotaxime has the potential for less frequent administration and lower dosing than other cephalosporins in the therapy of certain infections in less seriously ill patients. (8, 18, 19). Like cephalothin, cefotaxime is converted in vitro to a biologically less active desacetyl derivative, which accounts for the fact that only 60% of this drug is excreted unaltered in the urine (8, 14, 19).

In clinical studies previously reported, cefotaxime has been shown to be curative of uncomplicated gonorrhea by several groups (B. Lutz, B. Pauling, J. Kosola, and W. J. Mogabgab, 19th ICAAC, abstr. no. 674, 1979; D. J. Lancaster, S. W. Berg, and W. O. Harrison, 19th ICAAC, abstr. no. 675, 1979). High rates of clinical cure have also been observed for cefotaxime in the therapy of respiratory, urinary, gynecological, and other serious infections (C. D. Schwigon, 20th ICAAC, abstr. no. 20, 1980; J. Messihi, and L. G. Smith, 20th ICAAC, abstr. no. 765, 1980; D. L. Hemsell, F. G. Cunningham, R. P. Depalma, S. S. Kappus, and M. L. Roark, 20th ICAAC, abstr. no. 19, 1980; J., Pescina-Casas, E. Galindo, F. Vargas-Arreola, and C. Decanini-Teran, 20th ICAAC, abstr. no. 761, 1980).

Our data further substantiate these previous reports. The elderly male population (mean age, 65 years) treated in our study, 88% of whom had one or more serious underlying diseases (Table 1), underscores the significance of the 85% rate of satisfactory clinical responses resulting from monotherapy with cefotaxime. Of the two patients who failed therapy without developing superinfection, the patient with *K. pneumoniae* bacteremia probably, in retrospect, would have been a therapeutic failure regardless of the antimicrobial chosen due to the seriousness of his illness. The treatment failure in the patient with *P. aeruginosa* bacteremia is unexplained; however, this organism was unavailable for MIC determination to confirm its susceptibility to cefotaxime, and this patient is now recognized to have been undertreated (1 g every 4 h) for the organism involved. Whether the dosages used in our study are otherwise higher than necessary to treat pneumonias successfully requires further study. The report of Briggs et al. would suggest this possibility, at least in the case of pneumococcal pneumonia (M. S., Briggs, S. G. Jenkinson, and R. D. Bryn, 20th ICAAC, abstr. no. 764, 1980).

Although the incidence of adverse clinical reactions observed in our study is encouraging (Table 4), the incidence of superinfection is noteworthy. Collectively, five of seven instances of colonization-superinfection associated with cefotaxime therapy occurred in patients being artificially ventilated. The problem with super-infection in our study was disturbing but anticipated, because our population manifested well-recognized risk factors for such complications, viz., age greater than 60 years, serious underlying disease, and the administration of broad-spectrum antibiotics (23). Ongoing surveillance in our hospital did not identify an epidemic of nosocomial infections due to pseudomonas in association with the instances of superinfection with this organism which we observed. Whether the emergence of resistance to cefotaxime and other cephalosporins by serial in vitro passage of pseudomonas and other clinical isolates, as observed by Wise et al. (26), has any relevance to our observations of superinfections with cefotaxime-resistance gram-negative bacilli during therapy with this drug awaits further study. Furthermore, the adequacy of monotherapy with cefotaxime for serious pseudomonas and other gram-negative bacillary infections requires additional observations, despite the 70% response rate of the 10 gram-negative bacillary pneumonias which we observed. Due to our experience with superinfections related to this drug, therapy with cefotaxime is now routinely discontinued after 7 days unless continuation is clinically necessary. Appropriate clinical specimens are also cultured during therapy to monitor for colonization with new potential pathogens.

The other adverse effects observed during our study were minor and of no clinical consequence. All five episodes of eosinophilia were transient, the highest being 1,128 cells/mm^3. No episode of direct Coombs positivity was associated with recognized hemolysis, and all were transient. No nephrotoxicity was seen.

The therapeutic success which we encountered in this clinical study supports a significant clinical potential for cefotaxime in the therapy of serious infections due to susceptible bacteria. This antibiotic was well tolerated after parenteral administration. The potential for superinfection in seriously ill patients requires further evaluation in comparison with this risk associated with the use of similarly broad-spectrum antimicrobials. The future role of cefotaxime in the therapy of varied infections, especially monotherapy for serious gram-negative bacillary infections, requires further evaluation. The lack of serious toxicity and adverse reactions associated with cefotaxime confirmed in other studies, together with its broad antimicrobial spectrum, may make it in the future a suitable substitute for aminoglycosides in certain clinical settings.

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LITERATURE CITED

1. **Baker, C. N., C. Thornsberry, and R. N. Jones.** 1980. In vitro antimicrobial activity of cefoperazone, cefotaxime, moxalactam (LY 127935), azlocillin, mezlocillin, and other β-lactam antibiotics against *Neisseria gonorrhoeae* and *Haemophilus influenzae*, including β-lactamase-producing strains. Antimicrob. Agents Chemother. **17**:757–761.
2. **Bauer, A. W., W. M. M. Kirby, J. C. Sherris, and M. Turck.** 1966. Antibiotic susceptibility testing by a standardized single disk method. Am. J. Clin. Pathol **45**:493–496.
3. **Bennett, J. V., J. L. Brodie, E. J. Benner, and W. M. M. Kirby.** 1966. Simplified, accurate method for antibiotic assay of clinical specimens. Appl. Microbiol. **14**:170–177.
4. **Borobio, M. V., J. Aznar, R. Jimenez, F. Garcia, and E. J. Perea.** 1980. Comparative in vitro activity of 1-oxa-β-lactam (LY 127935) and cefoperazone with other β-lactam antibiotics against anaerobic bacteria. Antimicrob. Agents Chemother. **17**:129–131.
5. **Counts, G. W., and M. Turck.** 1979. Antibacterial activity of a new parenteral cephalosporin-HR 756: comparison with cefamandole and ceforanide. Antimicrob. Agents Chemother. **16**:64–68.
6. **Ericsson, H. M., and J. C. Sherris.** 1971. Antibiotic sensitivity testing. Report of an international collaborative study. Acta Pathol. Microbiol. Scand. Sect. B, Suppl. 217.
7. **Fu, K. P., R. Aswapokee, I. Ho, C. Matthijssen, and H. C. Neu.** 1979. Pharmacokinetics of cefotaxime. Antimicrob. Agents Chemother. **16**:592–597.
8. **Fu, P., and H. C. Neu.** 1978. A comparative study of the activity of cefamandole and other cephalosporins and analysis of the β-lactamase stability and synergy of cefamandole with aminoglycosides. J. Infect. Dis. **137**(Suppl.):S38–S48.
9. **Fuchs, P. C., A. A. Barry, C. Thornsberry, R. N. Jones, T. L. Gavan, E. H. Gerlach, and H. M. Sommers.** 1980. Cefotaxime: in vitro activity and tentative interpretive standards for disk susceptibility testing. Antimicrob. Agents Chemother. **18**:88–93.
10. **Hall, W. H., B. J. Opfer, and D. N. Gerding.** 1980. Comparative activities of the oxa-β-lactam LY127935, cefotaxime, cefoperazone, cefamandole, and ticarcillin against multiple resistant gram-negative bacilli. Antimicrob. Agents Chemother. **17**:273–279.
11. **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.
12. **Jorgensen, J. H., S. A. Crawford, and G. A. Alexander.** 1980. Comparison of moxalactam (LY127935) and cefotaxime against anaerobic bacteria. Antimicrob. Agents Chemother. **17**:901–904.
13. **Kaiser, G. V., M. Gorman, and J. A. Webber.** 1978. Cefamandole—a review of chemistry and microbiology. J. Infect Dis. **137**(Suppl.):S10–S16.
14. **Luthy, R., R. Munch, J. Blaser, H. Bhend, and W. Siegnethaler.** 1979. Human pharmacology of cefotaxime (HR 756), a new cephalosporin. Antimicrob. Agents Chemother. **16**:127–133.
15. **Murray, P. R.** 1980. Activity of cefotaxime-aminoglycoside combinations against aminoglycoside-resistant *Pseudomonas*. Antimicrob. Agents Chemother. **17**:474–476.
16. **Murray, P. R., J. L. Christman, and G. Medoff.** 1979. In vitro activity of (HR 756), a new cephalosporin, against *Neisseria gonorrhoeae*. Antimicrob. Agents Chemother. **15**:452–454.
17. **Murray, P. R., and J. A. Washington.** 1979. Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin. Proc. **50**:339–344.
18. **Neu, H. C., N. Aswapokee, P. Aswapokee, and K. P. Fu.** 1979. HR 756, a new cephalosporin active against gram-positive and gram-negative aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. **15**:273–281.
19. **Neu, H. C., P. Aswapokee, K. P. Fu, I. Ho, and C. Matthijssen.** 1980. Cefotaxime kinetics after intravenous and intramuscular injection of single and multiple doses. Clin. Pharmacol. Ther. **27**:677–685.
20. **Sosna, J. P., P. R. Murray, and G. Medoff.** 1978. Comparison of the *in vitro* activities of HR 756 with cephalothin, cefoxitin, and cefamandole. Antimicrob. Agents Chemother. **14**:876–879.
21. **Stapley, E. O., J. Birnbaum, A. K. Miller, H. Wallick, D. Hendlin, and H. B. Woodruff.** 1979. Cefoxitin and cephamycins: microbiological studies. Rev. Infect. Dis. **1**:73–87.
22. **Stephens, M., M. Potten, and A. J. Bint.** 1979. The sensitivity of gentamicin-resistant gram-negative bacilli to cefotaxime, other cephalosporins and aminoglycosides. Infection **7**:109–112.
23. **Tillotson, J. R., and M. Finland.** 1969. Bacterial colonization and clinical superinfection of the respiratory tract complicating antibiotic treatment of pneumonia. J. Infect. Dis. **119**:597–624.
24. **Washington, J. A., II.** 1978. Differences between cephalothin and newer parenterally absorbed cephalosporins *in vitro*: a justification for separate disks. J. Infect. Dis. **137**:(Suppl.):S32–S37.
25. **Weinstein, A. J.** 1980. The cephalosporins: activity and clinical use. Drugs. **19**:137–154.
26. **Wise, R., T. Rollason, M. Logan, J. M. Andrews, and K. A. Bedford.** 1978. HR 756, a highly active cephalosporin: comparison with cefazolin and carbenicillin. Antimicrob. Agents Chemother. **14**:807–811.