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Ceftazidime as Single-Agent Therapy for Gram-Negative Aerobic Bacillary Osteomyelitis

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The cases of 28 patients who received ceftazidime as single-agent therapy in prospective clinical trials for biopsy culture-proven osteomyelitis were reviewed. These cases all involved infection caused by gram-negative aerobic bacilli, the most frequent agent (83% of patients) being *Pseudomonas aeruginosa*. Posttreatment follow-up for patients with acute osteomyelitis was continued for at least 6 months, while follow-up for at least 12 months was done for patients with chronic osteomyelitis. A regimen of 2 g of ceftazidime intravenously every 12 h was used for most patients. The overall cure rates were 77% (acute disease) and 60% (chronic disease). Development of resistance to ceftazidime was not problematic, and the drug was well tolerated. Ceftazidime is effective for serious gram-negative bacillary osteomyelitis, including that due to *P. aeruginosa*. The twice-daily regimen did not cause major organ toxicity, eliminating the need for concentration monitoring and making it feasible to use the drug for home parenteral therapy.

Osteomyelitis due to gram-negative bacilli commonly occurs following direct traumatic introduction of contaminated matter into bone or by contiguous spread from a soft tissue infection adjacent to bone. It is rarely caused by hematogenous dissemination (14). Puncture wounds of the feet are commonly found to be associated with *Pseudomonas aeruginosa* (3, 13). Diabetic patients and those with peripheral vascular disease are often found to have ulcerations of the lower leg or foot which may progress to secondary contiguous osteomyelitis. Here, the infection may be polymicrobial and include both gram-negative and gram-positive organisms (12, 18).

In general, the therapy of osteomyelitis involving gram-negative organisms consists of a combined medical and surgical approach of appropriate surgical debridement of diseased bone, removal of foreign bodies, and prolonged parenteral administration of an antibiotic active against the offending pathogen. The current therapeutic standard is intravenous (i.v.) administration of a combination containing an aminoglycoside for 4 to 6 weeks. In some cases, even longer therapy or repeated courses of therapy may be necessary. Since aminoglycosides are associated with ototoxicity and nephrotoxicity, and patients receiving these agents often require monitoring of drug concentration in the blood and in-hospital drug administration, there has been marked interest in the development of effective agents that can be given safely, especially in the home setting.

Ceftazidime is a new broad-spectrum cephalosporin with excellent in vitro activity against most gram-negative aerobic bacilli, including *P. aeruginosa*, *Enterobacter* species, and indole-positive *Proteus* species (16, 17, 23). Ceftazidime distributes throughout the extracellular fluid space (1, 15, 22, 24) and thus penetrates in high concentrations into the fluids bathing the site of bone infection (25). The pharmacokinetic properties of ceftazidime and its low MIC for common pathogens enable the drug to be administered every 12 h to treat osteomyelitis. Because of its lower toxicity relative to aminoglycosides, distribution into bone and extracellular fluids, and broad gram-negative spectrum, ceftazidime was evaluated in the therapy of serious bone infections caused by aerobic gram-negative and gram-positive organisms, including *Pseudomonas* spp. This report presents the results for patients with gram-negative osteomyelitis who were monitored for substantial periods posttreatment.

MATERIALS AND METHODS

Patients with bacteriological proof of osteomyelitis due to gram-negative aerobic bacilli were selected from the U.S. clinical trial data collected in support of the new drug application for ceftazidime (Fortaz; Glaxo Inc., Research Triangle Park, N.C.). Each patient was enrolled in a study designed to evaluate the effectiveness of the dosage regimen (2 g i.v. every 12 h) proposed for inclusion in the package insert. In addition, patients were selected only if posttreatment follow-up was available for at least 6 months for patients with acute osteomyelitis and at least 12 months for patients with chronic osteomyelitis.

Patients were enrolled in a variety of either noncomparative clinical studies or randomized comparative clinical studies of osteomyelitis. Each protocol was approved by the respective institution's review board, and each patient, parent, or next of kin gave written informed consent to participate. The patients reported here were treated at the University of Texas at Galveston (J. T. Mader), Baylor College of Medicine (L. Gentry), University of Kansas Medical Center (C. Liu), Oklahoma City Clinic (D. J. Sexton), Maine Medical Center (M. C. Bach), Rainbow Babies' and Children's Hospital (J. Blumer), Fairfax Hospital (L. Eron), University of California-San Francisco Medical Center (J. E. Conte), and Good Samaritan Hospital (P. McKellar). Male and female patients at least 2 years of age were eligible for inclusion if they were hospitalized for osteomyelitis. Patients were excluded from the study if they had a history of immediate hypersensitivity to a penicillin or any hypersensitivity to a cephalosporin, a bacterial pathogen isolated pretreatment that was resistant in vitro to ceftazidime, chronic renal failure manifested by a serum creatinine concentration >3 mg/100 ml, or chronic hepatic dysfunction manifested as a serum glutamic pyruvic transaminase level >200 IU/liter and bilirubin >3 mg/100 ml or if any antimi-

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TABLE 1. Etiology of osteomyelitis and specification of bones involved

Disease parameter	No. of patients	
	Acute osteomyelitis (n = 13)	Chronic osteomyelitis (n = 15)
Etiology		
Traumatic injuries		
Puncture wound	3	0
Crushing	2	0
Other	7	12
Contiguous infection	1	1
Pin-track infection	0	2
Bones involved		
Tibia	3	7
Femur	0	3
Patella	1	1
Fibula	1	1
Tarsi	0	0
Phalanges		
Toes	3	0
Fingers	1	0
Hip	0	1
Metatarsi	1	0
Other	4	3
Underlying diseases		
Diabetes mellitus	1	0
Peripheral vascular disease	0	1
Rheumatoid arthritis	0	1
Seizure disorder	2	1
Alcoholism	1	1

crobial agent active against the bacterial pathogens had been given within 48 h prior to initiation of ceftazidime. Pregnant and lactating females were excluded.

The diagnosis of osteomyelitis was made by clinical presentation, radiographic evidence, and bacteriological confirmation. The cases were classified clinically as acute or chronic in nature. Acute osteomyelitis was defined as osteomyelitis occurring at a site where there had been no previous bone infection. Chronic osteomyelitis was defined as the presence of bacterially infected necrotic bone within a compromised envelope of contiguous tissues. Initial specimens for culture were collected prior to initiation of ceftazidime therapy and typically at the time of orthopedic surgery. Samples of bone were obtained by aseptic aspiration or bone biopsy. Sinus tract samples were not collected because of their reported poor correlation with the pathogen isolated from bone (11). In patients with clinical signs of sepsis, bacterial septicemia was considered confirmed by growth of the bacterium in at least two pretreatment blood cultures. The in vitro susceptibilities of the isolated pathogens to ceftazidime were determined by standard disk diffusion methods (9) or by MIC determinations by the tube or agar dilution method.

Ceftazidime was administered by i.v. infusion of 2 g every 12 h. Serial clinical examinations were performed to assess drug safety and efficacy. Clinical laboratory parameters (including complete blood count, blood chemistries, urinalysis, prothrombin time, and direct Coombs test) were monitored throughout the course of treatment.

The efficacy of ceftazidime therapy was assessed at the end of the posttreatment follow-up period for each patient as either cure or recurrence on the basis of clinical signs and symptoms and bacteriological test results. Efficacy was assessed after at least 6 months from end of drug administration for patients with acute osteomyelitis and at least 12 months posttreatment for patients with chronic osteomyelitis. Superinfection was considered when a new pathogen was isolated during the treatment period with the presence of clinical symptoms and radiographic evidence of osteomyelitis.

RESULTS

Thirteen and 15 patients with acute osteomyelitis and chronic osteomyelitis, respectively, met all criteria for evaluation. There was a predominance of males in both the acute (12 males) and chronic (12 males) disease groups. Patients covered a broad age range (13 to 78 years), with the patients with chronic osteomyelitis having a median age of 31 years, compared with a median age of 26 years in the acute-disease group.

Twelve of the 13 patients in the acute-disease group and 12 of 15 patients in the chronic-disease group developed osteomyelitis following traumatic injury (Table 1). Many of these patients had had open reduction-internal fixation of a compound fracture. Three patients in the acute-disease group had puncture wounds. On admission, two patients in the chronic group had an in-dwelling metal appliance. Appliances were removed at the time of initiation of therapy. While the long bones of the leg and hip were the infection site in most patients in the chronic group, patients with acute osteomyelitis had a variety of smaller bones of the feet and hands involved (Table 1). This is consistent with the occurrence of puncture wounds and crushing injuries in the patients with acute disease.

Twenty patients received ceftazidime (2 g i.v. every 12 h). The dosage was increased to 2 g every 8 h for four patients with tenacious and severe disease. For the remaining four patients, the dosage was reduced to 1 g every 8 h for selected patients with some degree of renal insufficiency. Among the 13 patients with acute disease, the duration of ceftazidime therapy was 14 to 27 days for 6 patients and 28 to 41 days for 7 patients. The 15 patients with chronic disease received ceftazidime for 14 to 27 days (4 patients), 28 to 41 days (3 patients), and ≥42 days (8 patients). One patient in the chronic group received 16 weeks of therapy.

P. aeruginosa was the predominant pathogen in both groups of patients. A variety of other gram-negative bacteria

TABLE 2. Bacterial pathogens isolated from patients with osteomyelitis

Pathogen isolated	Acute osteomyelitis			Chronic osteomyelitis		
	No. of isolates	MIC (μg/ml)		No. of isolates	MIC (μg/ml)	
		Median	Range		Median	Range
P. aeruginosa	11	2.0	0.8–4.0	12	1.0	0.4–2.0
Enterobacter cloacae	5	1.6	<1–12.5			
Klebsiella sp.	2	0.8	0.5–1.0			
C. freundii	2	<0.5	<0.5			
S. marcescens				2	0.3	0.1–0.5
Other gram-negative organisms	5	2.3	0.5–6.3	4[a]		
S. aureus	1	8.0		1	4.0	
Beta-hemolytic streptococci	1[a]					

[a] —, Isolates were susceptible, but no MIC data were obtained.

TABLE 3. Efficacy assessments of ceftazidime in patients with osteomyelitis

Bacterial pathogen isolated	No. of patients			
	Acute osteomyelitis		Chronic osteomyelitis	
	Cure	Recurrence	Cure	Recurrence
P. aeruginosa alone	5	1	3	4
P. aeruginosa plus another bacterium	4	1	4	1
Subtotal rate	82%	18%	58%	42%
Other gram-negative bacteria	1	1	2	1
Total rate	77%	23%	60%	40%

were also isolated. Table 2 reports the MICs of ceftazidime for these isolates. All isolates of *P. aeruginosa* were highly susceptible in vitro. Bacteremia was documented in one patient, with *Escherichia coli* isolated from both blood and bone. Ten of the 28 patients had osteomyelitis due to multiple bacteria, of which one was *P. aeruginosa*.

Clinical follow-up data were collected for at least 6 months for patients with acute osteomyelitis and for at least 12 months for patients with chronic osteomyelitis. Ten of 13 patients (77%) were cured of acute osteomyelitis (Table 3). Among patients with chronic osteomyelitis, 9 of 15 (60%) were cured. There were six patients whose infections recurred at intervals from 1 to 19 months posttherapy.

Three patients with acute disease had recurrent osteomyelitis during the follow-up period. One patient had a recurrence 1 month after leaving the hospital against medical advice after only 17 days of parenteral therapy. The second patient had a recurrence at 20 months after treatment for 20 days. The third patient had a recurrence at 2 months after treatment for 41 days for osteomyelitis due to *P. aeruginosa*, *Citrobacter freundii*, and *Serratia marcescens*.

Six patients with chronic disease had recurrent osteomyelitis during the follow-up period. Four of the six patients had osteomyelitis of long bones. All six patients received ceftazidime therapy for at least 4 weeks, and four of the six patients received ceftazidime therapy for at least 6 weeks. Five failures occurred in patients with *P. aeruginosa* as an initial pathogen, and one patient had *Proteus mirabilis* as the sole initial isolate. Four patients had recurrences within 4 months posttreatment, while the other two patients had recurrences at 8 and 19 months posttreatment, respectively.

Superinfection occurred in three patients. One patient became superinfected with a ceftazidime-susceptible *Pseudomonas maltophilia* strain and received subsequent therapy with mezlocillin. Another patient was superinfected with *Staphylococcus aureus* (ceftazidime MIC, 8 μg/ml) which responded to a course of gentamicin plus nafcillin. The third patient was superinfected with a ceftazidime-resistant enterococcus, which was treated with ticarcillin-clavulanic acid.

There were minimal side effects from the drug. One patient developed mild liver function test abnormalities. A second patient complained of blurred vision, which resolved despite continuing treatment. In these patients, these effects did not necessitate premature discontinuation of therapy.

In two patients, the organisms causing their infection became resistant to ceftazidime during therapy. For one, a *P. aeruginosa* strain, the MIC increased from 2 to 16 μg/ml. In the other case, an *Enterobacter cloacae* strain became highly resistant; however, the bone had united with fixation.

DISCUSSION

Recently, there have been a number of studies with single broad-spectrum agents as monotherapy in the treatment of gram-negative osteomyelitis (2, 4, 6–8, 10, 20, 21). Imipenem-cilastatin was used in 34 patients, many of whom had mixed infections (10); 74% were considered cured or improved and remained well through a follow-up visit between 2 and 20 months posttreatment, while six patients showed continued presence of the pathogen at the end of therapy, and in two cases *P. aeruginosa* had become resistant.

Ticarcillin plus clavulanic acid was used to treat 47 patients with osteomyelitis; 10% of these cases were due to *P. aeruginosa* and 23% to other gram-negative organisms (6). Most patients were monitored for 3 to 11 months posttreatment. Cure was achieved in 9 of 14 patients (64%) with a gram-negative pathogen. In addition, therapy was discontinued for four patients (9%) because of hypersensitivity reactions in two and clinical bleeding in two. These previous trials with ticarcillin-clavulanic acid (6) and imipenem-cilastatin (10) are not fully comparable to our study with ceftazidime because they used shorter follow-up periods.

Several investigators have studied oral administration of ciprofloxacin (750 mg every 12 h) to patients with gram-negative bacillary osteomyelitis. One study reported a cure rate of 65% among 20 patients monitored for 7 to 21 months posttreatment (7). A second study of 30 patients who were monitored for at least 6 months posttreatment reported a 73% cure rate (21). In a randomized comparative study of ciprofloxacin versus parenteral therapies, 17 of 30 patients had *P. aeruginosa* and each of the 30 patients had at least one gram-negative isolate (8). Ciprofloxacin achieved treatment success in 71% of patients, compared with 94% in the control group (8).

Experiences with ceftazidime in the therapy of osteomyelitis have been reported by other investigators (2, 4, 5, 19, 20). Gentry (5) reviewed the cumulative international experience with ceftazidime in the treatment of bone and joint infections at the time of introduction of this drug into the U.S. market. The data reported by Scully and Neu (19) are of interest but were not included in our analysis since their patients received lower doses than ours (2 g i.v. every 12 h). The dosage regimen examined here is that approved for use in the United States.

Most of these previous studies included gram-positive as well as gram-negative infections, and the overall success rate varied between 60 and 92%. Sheftel and Mader (20) reported recurrence in three of nine patients with gram-negative osteomyelitis treated with ceftazidime (2 g i.v. every 12 h) with follow-up for at least 1 year.

Our study, involving the biopsy-proven cases of gram-negative infection with posttreatment follow-up, showed an overall cure rate of 77% in acute disease and 60% in chronic osteomyelitis. The safety profile of the drug has been impressive, and development of resistance despite single-drug therapy has been low. Ceftazidime appears to be a safe and effective drug in the treatment of gram-negative osteomyelitis, including that due to *P. aeruginosa*. The potential for its use in home therapy seems clear.

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