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Ceftazidime Therapy of Serious Bacterial Infections

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Ceftazidime, a new broad-spectrum cephalosporin, was administered to 30 patients with serious bacterial infections in a randomized dosing trial with daily doses of 1.5 or 3 g. Both regimens were equally efficacious, with satisfactory clinical responses in 28 instances (93%) and microbiological eradication of 79% of initial bacterial isolates. The development of resistance to ceftazidime during therapy was observed in three cases (*Enterobacter agglomerans, Enterobacter cloacae*, and *Pseudomonas aeruginosa*) and superinfection by a resistant *Enterobacter agglomerans* strain occurred in one case. Adverse reactions of clinical significance included one case each of leukopenia, azotemia, diarrhea (*Clostridium difficile* toxin positive), and rash.

With new β-lactam antibiotics, we now are able to treat infections due to cephalothin-resistant bacteria that ordinarily require aminoglycoside therapy. Because many of these infections occur in patients who may have some degree of renal impairment, the additional nephrotoxicity of aminoglycosides may be undesirable in this setting. The new β-lactams, including ceftazidime (GR 20263), appear to be free of this side effect (3). Moreover, ceftazidime has markedly increased activity in vitro against most gram-negative bacilli, especially *Pseudomonas aeruginosa* and *Serratia marcescens* (4, 5). Therefore, we evaluated the efficacy and safety of ceftazidime in a randomized dosing trial.

MATERIALS AND METHODS

Patient selection. Patients were admitted to the study if they had clinical symptoms and signs of infection of bone, soft tissue, or respiratory tract, which were confirmed by isolation of a ceftazidime-susceptible culture immediately preceding the initiation of therapy. If cultures obtained at the initiation of therapy were sterile or yielded ceftazidime-resistant organisms, the patient was dropped from the study while safety testing was continued. Susceptibility to ceftazidime was determined for each isolate by the Kirby-Bauer method with a 30-μg ceftazidime disk. A 17-mm zone of inhibition was considered to indicate susceptibility. Soft tissue infections and abscesses consisted of cellulitis or deep open wounds surrounded by cellulitis. Bone infections showed inflammatory changes within bone on X ray, scan, or biopsy. Lower respiratory tract infections were diagnosed in febrile patients when infiltrates were present on X ray. In all cases, the proof of the role of the organisms in the pathogenesis of the infections was based on the finding in Gram-stained specimens of purulent material from wounds or sputum of leukocytes and homogeneous populations of organisms. However, in cases of polymicrobial infection, it could not always be determined on microscopic exam of Gram-stained specimens that all organisms cultured were pathogens.

Patient treatment. Patients aged 15 to 85 years (mean, 49 years) were hospitalized at one of three Northern Virginia hospitals: The Fairfax Hospital (Falls Church), The Alexandria Hospital (Alexandria), and The Commonwealth Hospital (Fairfax). They had infections in which ceftazidime was expected to be effective as a sole agent. After written consent was obtained, they were sequentially randomized according to a computer-generated schedule (Glaxo, Inc.) to receive daily either 1.5 (group A) or 3 g (group B) of ceftazidime given intravenously in three divided doses. Patients were treated for a mean of 16 days (range, 3 to 57 days).

Patient evaluation. An investigator examined each patient before beginning therapy, daily during therapy, and after therapy. The following studies were done before therapy, weekly during therapy, and at the conclusion of therapy: urinalysis, complete blood count, platelet count, prothrombin time, blood urea nitrogen, serum creatinine, serum glucose and electrolytes, serum calcium and phosphorus, and liver function tests. In patients with pneumonia and osteomyelitis, X rays were obtained at the initiation and completion of therapy. Minimal inhibitory concentrations (MICs) were measured for most isolates by a standard twofold serial dilution method with tryptic soy broth and the conventional inoculum of 10^5 organisms per ml (2). Serum levels of ceftazidime were determined by the agar well method with *Escherichia coli* ATCC 1345 (1).

Response to therapy was determined on microbiological and clinical grounds for all infections. Cure was defined as the complete resolution of signs of infection accompanied by sterilization of the infected site (wound, sputum, blood) 24 h after the termination of therapy. When culture specimens were no longer

available, the assessment of response was made solely on clinical grounds. In the case of osteomyelitis, initial cultures were taken from bone, and follow-up cultures were obtained from deep within the wound. Expectorated sputum samples or endotracheal specimens obtained from deep within the bronchial tree from intubated patients were analyzed as to suitability by finding polymorphonuclear leukocytes but no epithelial cells in the specimens. For pneumonia, radiological clearing was required for cure, whereas signs of healing were required for cure of osteomyelitis. Clinical improvement was defined as the waning of signs of infection with the need for further therapy such as drainage, debridement, or a second antibiotic.

RESULTS

Ceftazidime was administered according to a randomized dosing schedule to 30 patients with infections. Patients were fairly equally distributed as to age, sex, underlying disease, bacterial isolate, and duration of treatment. In group A, there were 16 cases, versus 14 cases in group B. The types of infections are shown in Table 1.

In group A, there were nine males and seven females, ages 20 to 84 (mean, 45 years). Group B consisted of nine males and five females, ages 15 to 85 (mean, 56 years). The duration of treatment was a mean of 14 days in group A (range, 3 to 37) and 19 days in group B (range, 8 to 57). Seven patients in group A suffered from underlying diseases which could be considered as interfering with their ability to fight infection. They included two cases of cystic fibrosis, one of peripheral vascular disease in a stump infection, diabetes mellitus in a case of otitis externa, dexamethasone therapy in a case of osteomyelitis, and acute renal failure in four infections. Group B similarly included seven patients with underlying diseases: one comatose patient with a tracheostomy and pneumonia, gastric carcinoma in a patient with a postoperative polymicrobial hepatic abscess, peripheral vascular disease in a patient with an infected plantar ulcer, rheumatoid arthritis and chronic renal failure in a case of osteomyelitis, acute renal failure in a case of septicemia from mediastinitis, and an obstructed common bile duct (with an external drainage tube) in a case of polymicrobial cholangitis.

The infections varied in severity, however, between the two groups. Group A consisted of three patients with osteomyelitis, two with respiratory tract infections, and 11 with skin and soft tissue infections. Group B consisted of two patients with osteomyelitis and one with septic arthritis, two with respiratory tract infections (including one with septicemia) and one with empyema, four with skin and soft tissue infections (including one with septicemia), and four with intraabdominal infections, including a subhepatic abscess, an intrahepatic abscess, a diverticular abscess, and cholangitis. Thus, group B contained more severe infections—the intraabdominal infections and septicemias.

Bacteria cultured initially were comparable in both groups. Group A consisted of 23 isolates, including *Pseudomonas aeruginosa* (9), *Serratia marcescens* (4), *Enterobacter cloacae* (1), *Enterobacter aerogenes* (2), *Staphylococcus aureus* (2), and single isolates of *Morganella osloensis, Morganella morganii, Proteus vulgaris, Klebsiella pneumoniae*, and *Acinetobacter calcoaceticus*. Group B consisted of 19 isolates, including *Pseudomonas aeruginosa* (6), *Serratia marcescens* (1), *Enterobacter cloacae* (1), *Staphylococcus aureus* (1), *Escherichia coli* (3), *Proteus mirabilis* (3), *K. pneumoniae* (3), and a single isolate of *Aeromonas hydrophila*. No anaerobic bacteria were isolated from these wounds, and this fact reflects our intentional selection bias towards aerobic and facultative gram-negative bacilli in this study. These bacteria were all shown to be ceftazidime-susceptible by disk testing. MICs were determined for most isolates (Table 1). The MICs (in micrograms per milliliter) were as follows: *Pseudomonas aeruginosa*, 0.6 to 6.2 (mean, 3.0); *Enterobacter* species, 1.2 to 2.5 (mean, 1.6); *Serratia marcescens*, 1.5; *Proteus* species, 0.6 to 1.5 (mean, 1.0); *K. pneumoniae*, 0.5 to 1.5 (mean, 0.9); *Escherichia coli*, 0.8 to 1.5 (mean, 0.9); *Aeromonas hydrophila*, 0.8; and *M. morganii*, 1.3. A total of seven infections were polymicrobial (five in group A and two in group B).

Efficacy. There was a satisfactory clinical response in 15 of 16 infections in group A (94%) and 13 of 14 infections in group B (93%). Of these infections, 10 were cured and 5 improved in group A, whereas 9 were cured and 4 improved in group B. In group A, cures were achieved in five *Pseudomonas* infections, one *Morganella* infection, one *Serratia* infection, one *Staphylococcus aureus* infection, and three polymicrobial infections. The patients regarded as improved instead of cured in group A required either discontinuation of the antibiotic owing to an adverse drug reaction (leukopenia in patient S-25) or, for outpatient therapy (Bactrim in case S-3 and tobramycin in patient R-4), further surgical debridement (patient S-16), or they expired from other causes (renal failure in patient S-2). In group B, cures were effected in four *Pseudomonas* infections, one *Staphylococcus aureus* infection, one *Klebsiella* infection, one *Proteus mirabilis* infection, one *Enterobacter cloacae* infection, and one polymicrobial infection. The patients who were regarded as improved instead of cured required further local care after discontinuing the drug (patients S-5, S-8, S-9, and S-23).

There were two clinical failures on ceftazi-

TABLE 1. Response of infections to ceftazidime

Group (daily dose) and patient no.	Age and sex	Type of infection	Bacteria isolated before therapy	MIC (μg/ml)	Underlying disease	Days of treatment	Response to therapy	
							Clinical	Bacteriological
A (1.5 g)								
R-2	21, F	Pneumonia	*P. aeruginosa*	1.2	Cystic fibrosis	14	Cured	Persisted
R-4	22, F	Pneumonia	*P. aeruginosa*	1.3	Cystic fibrosis	3	Improved	Persisted
S-2	70, F	Postoperative stump infection	*S. marcescens* *E. aerogenes*	1.5 1.5	Peripheral vascular disease	7	Improved	Eradicated Persisted
S-3	67, M	Postoperative mediastinitis	*S. marcescens*	1.5		13	Improved	Eradicated
S-6	21, M	Traumatic wound	*P. aeruginosa* *E. aerogenes*	2.5 1.2		14	Cured	Eradicated Persisted
S-7	68, M	Otitis externa	*P. aeruginosa*	0.6	Diabetes mellitus	14	Cured	Eradicated
S-10	48, M	Postoperative wound	*M. morganii*	1.3		4	Cured	Eradicated
S-12	25, F	Traumatic wound	*S. aureus* *P. vulgaris* *K. pneumoniae* *P. aeruginosa*	10 0.6 0.6 1.25		10	Cured	Eradicated Eradicated Eradicated Eradicated
S-13	33, F	Osteomyelitis (acute)	*A. calcoaceticus* *E. cloacae*	18[a] 2.5	Dexamethasone for cerebral edema	37	Cured	Eradicated Eradicated
S-15	83, M	Postoperative wound	*P. aeruginosa*	1.25	Total hip replacement	21	Cured	Eradicated
S-16	21, M	Osteomyelitis (acute)	*S. marcescens*	30[a]		37	Improved	Eradicated
S-18	35, M	Osteomyelitis (acute)	*P. aeruginosa* *S. marcescens*	20[a] 30[a]		42	Failed[b]	Eradicated Eradicated
S-19	20, F	Cellulitis	*S. aureus*	5		4	Cured	Eradicated
S-20	43, F	Dacryocystitis	*P. aeruginosa*	28[a]		9	Cured	Eradicated
S-21	84, M	Decubitus wound	*P. aeruginosa*	6.2	Acute renal failure	7	Cured	Eradicated
S-25	52, M	Postoperative intraabdominal urinoma after ileal loop construction	*M. osloensis*	30[a]	Carcinoma of bladder, acute renal failure	14	Improved	Eradicated

dime, one in each group. In group A, a patient with osteomyelitis from whom were cultured *Pseudomonas* and *Serratia* isolates at first improved but then developed a superinfection by *Enterobacter agglomerans*, initially susceptible to ceftazidime, but which in turn developed resistance during therapy (patient S-18). In group B, a patient with *Serratia* septicemia and post-sternotomy mediastinitis (patient S-17) suffered a relentlessly downhill course and expired from renal failure. Although the organism was eradicated from the blood, it persisted in the wound drainage.

Bacteria were eradicated in 19 of 23 instances (83%) in group A. If we ignore the two instances of cystic fibrosis in which bacterial eradication is unlikely, there were only two instances of persistence, both *Enterobacter aerogenes*, which were ceftazidime susceptible at the initiation and conclusion of therapy (patients S-2 and S-6). In the first patient, persistence of the *Enterobacter* species may have prevented a cure. In group B, eradication was achieved in 14 of 19 instances (74%). In two instances (patients R-3 and S-5), the persisters (*Enterobacter cloacae* and *Pseudomonas aeruginosa*) developed resistance to ceftazidime during therapy. In the latter patient, this may have prevented a cure. In the case of *Serratia* mediastinitis (patient S-17), persistence of the organism in the wound was thought to be responsible for the patient's clinical failure.

Superinfection was a particularly disturbing

TABLE 1—*Continued.*

Group (daily dose) and patient no.	Age and sex	Type of infection	Bacteria isolated before therapy	MIC (μg/ml)	Underlying disease	Days of treatment	Response to therapy	
							Clinical	Bacteriological
B (3 g)								
R-1	85, F	Empyema	*S. aureus*	6.2		9	Cured	Eradicated
R-3	49, F	Septicemia from pneumonia	*E. cloacae*[c]	1.2		12	Cured	Persisted in sputum only
R-6	15, M	Pneumonia	*P. aeruginosa*	22[a]	Comatose with tracheostomy	8	Cured	Persisted
S-1	60, M	Postoperative subhepatic abscess	*P. mirabilis*	1.5		9	Cured	Eradicated
S-4	22, M	Traumatic wound	*K. pneumoniae*	30[a]		14	Cured	Eradicated
S-5	66, M	Postoperative hepatic abscess	*P. aeruginosa*[c]	1.5	Gastric carcinoma	14	Improved	Persisted
			P. mirabilis	1.5				Persisted
			E. coli	1.5				Eradicated
			K. pneumoniae	1.5				Eradicated
S-8	73, F	Postoperative diverticular abscess	*E. coli*	0.6		11	Improved	Eradicated
S-9	69, M	Plantar ulcer	*P. mirabilis*	1.3	Peripheral vascular disease	11	Improved	Eradicated
S-11	67, M	Osteomyelitis (acute)	*P. aeruginosa*	1.25	Rheumatoid arthritis, chronic renal failure	57	Cured	Eradicated
S-14	25, M	Septic arthritis	*P. aeruginosa*	1.25		43	Cured	Eradicated
S-17	77, M	Septicemia from mediastinitis	*S. marcescens*	30[a]	Acute renal failure	10	Failed	Persisted in wound only
S-22	55, M	Cholangitis with hepatic abscess	*A. hydrophila*	0.8	Obstructed bile duct with external drainage tube	23	Cured	Eradicated
			E. coli	0.8				Eradicated
			K. pneumoniae	0.8				Eradicated
S-23	73, M	Osteomyelitis (chronic)	*P. aeruginosa*	18[a]		20	Improved	Eradicated
S-24	38, F	Traumatic wound	*P. aeruginosa*	25[a]		13	Cured	Eradicated

[a] Kirby-Bauer zone size in millimeters (MIC not determined).
[b] Became superinfected with *Enterobacter* species, which developed ceftazidime resistance during therapy.
[c] Developed resistance to ceftazidime during therapy. Final MIC, >25.

aspect of ceftazidime therapy, especially when it was caused by *Enterobacter agglomerans*, in which case it acquired ceftazidime resistance during therapy in one patient (S-18, group A) and was resistant de novo on superinfection in a second patient (S-8, group B). Four cases of mucocutaneous *Candida* superinfection (patients R-2, R-4, and S-13 in group A, and patient S-8 in group B) and three cases of *Streptococcus faecalis* colonization (patients S-2 and S-25 in group A and S-17 in group B) were observed.

Mean ceftazidime serum levels in group A reached a peak value (30 min after infusion) of 105 μg/ml and a trough value (30 min preceding infusion) of 41 μg/ml, whereas in group B, they were 177 and 59, respectively, determined in five patients for each group.

Adverse drug reactions. In the above 30 patients, plus one patient not evaluable on clinical and microbiological grounds, there were 20 instances of laboratory or clinical reactions attributable to ceftazidime (Table 2), most of which were considered clinically insignificant. These side effects consisted of minimal eosinophilia (six patients), minor liver function abnormalities (four patients), thrombocytosis (two patients),

TABLE 2. Adverse reactions to ceftazidime

Reaction	No. of cases		% Incidence	No. of patients in which drug was stopped
	Group A	Group B		
Elevated AST[a]	4	0	13	0
Leukopenia	2	0	6	1
Eosinophilia	4	2	19	0
Thrombocytosis	1	1	6	0
Abnormal creatinine	0	2	6	1
Diarrhea	1	1	6	1
Rash	0	1	3	1

[a] AST, Aspartate transaminase.

leukopenia (two patients), abnormal creatinine (two patients), diarrhea (two patients), and rash (one patient). The eosinophilia ranged from 418 to 624/mm^3 (mean, 487) and occurred a mean of 15 days into therapy. It was not associated with rash or leukopenia. The liver function abnormalities involved clinically insignificant elevations of aspartate transaminase to a mean height of 137 IU/ml, occurring a mean of 12 days into therapy. They occurred in patients in whom the alkaline phosphatase levels were elevated at the start of therapy and therefore may not have been drug related.

In four instances, the abnormalities were considered severe enough to warrant discontinuation of the drug. One patient (R-6, group B) developed a rash after 8 days of therapy, and the drug was stopped. Two patients had diarrhea and were tested for *C. difficile* toxin in the stool; the drug was terminated in the one with the positive assay. The patient (S-13, group A) responded to oral vancomycin. Ceftazidime treatment resulted in two cases of leukopenia. In one patient (S-12, group A), the leukocyte count reached a nadir of 4,300/mm^3, with 22% polymorphonuclear leukocytes by day 11 of therapy. In the second patient (S-25, group A), the nadir of 3,100/mm^3 with 73% polymorphonuclear leukocytes occurred by day 16 of therapy, and the drug was stopped. All of the above abnormalities remitted on discontinuation of the drug.

Azotemia was observed in two patients. One patient (S-9, group B), a 68-year-old male on diuretics with an infected plantar ulcer complicated by peripheral vascular disease, developed mild azotemia while on ceftazidime. His blood urea nitrogen rose from 16 to 41 mg/dl by day 11 of therapy, with creatinine rising from 1.2 to 1.8 mg/dl. The urinary sediment was not active, except for one to three hyaline casts in one of two urinalyses, and this patient had no eosinophilia or eosinophiluria. Although there might have been underlying renal disease, the blood urea nitrogen and creatinine of this patient returned to normal when ceftazidime therapy was discontinued, seemingly implicating the drug in this abnormality. One other patient (S-17, group B), a 77-year-old male with *Serratia* septicemia from mediastinitis 6 days after coronary artery bypass grafting, developed severe renal failure before inception of ceftazidime therapy which progressed during his 10-day course of therapy and ultimately resulted in his demise. His blood urea nitrogen rose from a pretreatment level of 56 to 101 mg/dl, and his creatinine rose from 3.2 to 9.3 mg/dl. His urine sediment had erythrocytes and leukocytes with granular casts before therapy, but a Foley catheter was in place. He received Aldomet, hydralazine, furosemide, and dopamine while he was receiving ceftazidime. No eosinophilia or eosinophiluria was detected. The *Serratia* species, although eradicated from the blood, persisted in the wound, and it was probable that the patient's progressive azotemia was the result of acute tubular necrosis secondary to sepsis. However, a serum ceftazidime level (before dialysis) 8 h after a 500-mg dose was 200 μg/ml. It is therefore conceivable that high serum ceftazidime levels may have contributed to his acute tubular necrosis.

DISCUSSION

Ceftazidime was developed to enhance the activity of cephalosporins against gram-negative bacilli, especially *Pseudomonas aeruginosa* and *Serratia marcescens*, while minimizing the inoculum effect on MICs (4, 5). When this drug was administered in this study in either of two dosage regimens, it was effective in a variety of infections. Satisfactory clinical responses were achieved in 28 of 30 instances (93%), despite the large number of *Pseudomonas* (15) and *Serratia* (5) isolates. The efficacy rates in the two dosage regimens were essentially identical (94 and 93% for groups A and B, respectively). Similarly, bacterial eradication was achieved in 79% overall (33 of 42 total isolates) combining the respective 83 and 74% rates for groups A and B. These figures compare favorably with those of one other study (6), in which moxalactam was used in the therapy of infections caused principally by *Pseudomonas* and *Serratia* species.

In our study, the two groups were not only heterogeneous as to the types of infections but also not strictly comparable, since both septicemias and all four intraabdominal infections were in one group. Because the patients in this group were initially more seriously ill with life-threatening infections, no definite conclusions can be derived regarding dosing, except that moderately ill patients can be treated with a lower dosage (1.5 g daily), whereas more critically ill patients might benefit from a higher dosage (3 g daily). However, since the serum levels (peak and trough) in the lower dosage group are so much

higher than the MICs of these cephalothin-resistant organisms, it may not matter which dosage regimen is used as long as serum levels and MICs are monitored.

The one cephalothin-resistant facultative gram-negative bacillus that may well be a problem for ceftazidime is *Enterobacter*. One of the two clinical failures occurred in a patient superinfected with a susceptible *Enterobacter agglomerans* strain that became resistant to ceftazidime during therapy. Another patient was superinfected with a de novo resistant *Enterobacter agglomerans* strain. Development of resistance during therapy was also noted in *Enterobacter cloacae* and *Pseudomonas aeruginosa*. Mucocutaneous candidiasis was a minor inconvenience in four instances, and only three cases of *Streptococcus faecalis* colonization were noted during therapy. These phenomena occurred in both dosage regimens. The phenomenon of wound colonization with resistant organisms is of potential importance to the development of a reservoir of resistant pathogens causing nosocomial infections.

The MICs of *Staphylococcus aureus* and *Bacteroides fragilis* are fairly high with respect to ceftazidime. We therefore purposefully did not treat anaerobic infections with ceftazidime and limited the number of *Staphylococcus aureus* infections. Nonetheless, in the three *Staphylococcus aureus* infections that we treated, in which the organisms were found to be susceptible, clinical cure and microbiological eradication were obtained. Both dosage regimens were effective, although we feel more comfortable with higher doses with this pathogen.

Ceftazidime was generally well tolerated except in four instances, leukopenia, *C. difficile* toxin-induced diarrhea, rash, and mild azotemia, which required discontinuation of the drug. The side effects were not dose related except possibly in the case of azotemia. Though there are other explanations as to the etiology of the azotemia, we would sound a precautionary note for monitoring renal function carefully in seriously ill patients treated with ceftazidime, based on the structural similarity at the 3-position of the dihydrothiazolidine ring between ceftazidime and cephaloridine, a cephalosporin with known nephrotoxic potential. Even though it was obviously quite effective in treating serious cephalothin-resistant gram-negative bacillary infections, we must also advise following patients especially closely for the development of resistance in *Enterobacter* and *Pseudomonas* species during treatment.

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