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Use of Ceftazidime in the Therapy of Serious Infections, Including Those Due to Multiresistant Organisms

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Ceftazidime was administered intravenously or intramuscularly or both in doses of 1 to 6 g per day to 33 patients with serious gram-negative bacillary infections (12 pulmonary, 10 urinary tract, 4 soft tissue, 4 intraabdominal, and 3 miscellaneous infections). Twenty-one patients were septicemic. We identified 20 isolates of members of the family *Enterobacteriaceae* and 13 isolates of *Pseudomonas aeruginosa*. Seventeen patients had failed to respond to previous antimicrobial therapy. A total of 23 patients were clinically cured, 7 patients improved, and 3 patients failed to respond to therapy. The selection or emergence of resistant organisms during treatment (mostly *Candida* spp., *Staphylococcus aureus*, and enterococci) was noted in 11 patients. Toxicity was minimal (reversible mild liver function abnormalities and eosinophilia). The results of this study suggest that ceftazidime is an effective and well-tolerated new cephalosporin for the therapy of serious infections due to susceptible gram-negative organisms.

Ceftazidime is a newly developed cephalosporin which, like the other new cephalosporins moxalactam and cefotaxime, is highly active against members of the family *Enterobacteriaceae* and resistant to their β-lactamases (8, 9, 15). Against *Pseudomonas aeruginosa*, however, there are major differences which make ceftazidime the most potent antipseudomonal cephalosporin to reach clinical trial (4). Indeed, in vitro studies have shown that 90% of the strains are inhibited at a concentration of 2 to 4 mg/liter (13), which can easily be reached in human serum (5, 16), sputum (2), pus from osteomyelitis, and bile (3).

In contrast to its antipseudomonal effect, the activity of ceftazidime against *Staphylococcus aureus* is poor compared with those of the earlier cephalosporins (8).

We report the results of an open study in patients with severe underlying diseases who had infections due to aerobic, multiresistant, gram-negative bacilli. Particular interest was taken in the efficacy of ceftazidime against *P. aeruginosa* infections and the problem of resistant organisms emerging during therapy.

MATERIALS AND METHODS

Thirty-three in-patients of St. Pierre Hospital (Brussels, Belgium) who had bacteriologically proven gram-negative infections were included in the study after informed consent was obtained. The group included 20 men and 13 women whose ages ranged from 16 to 85 years (mean, 53 years). Of these patients, 14 had severe underlying diseases, including extended burns over more than 40% of the total body surface (six cases), neoplastic disease (three cases), diabetes mellitus (four cases), and cystic fibrosis (one case). In addition, 12 of the 33 patients were under mechanical ventilation as a consequence of major surgical procedures or metabolic coma.

The admission criteria for this study included fever and other signs and symptoms of bacterial infection (pneumonia, urinary tract infection, cellulitis, intraabdominal infection, thrombophlebitis, and septicemia) and the isolation, within 24 h of the start of ceftazidime therapy, of a pathogen susceptible to ceftazidime (>23 mm) by standardized disk testing. Patients who had received antibiotics previously were included if the infecting organisms isolated just before the start of ceftazidime therapy were resistant to previously used agents and if the patient had failed to respond to therapy, as demonstrated by clinical deterioration. We excluded from the study (i) patients with organisms resistant to ceftazidime, (ii) patients with a history of significant allergic reaction to penicillins or cephalosporins, (iii) patients with a neutrophil count of <1,000 cells per mm^3, and (iv) moribund patients.

The criteria used to diagnose pneumonia included (i) fever, sputum production, and leukocytosis; (ii) roentgenological evidence of a new infiltrate; and (iii) isolation of organisms from transtracheal aspirate and endotracheal suction in patients under mechanical ventilation or suitable expectorated sputum (leukocytes present with few or no squamous epithelial cells). Urinary tract infections were diagnosed by the presence of $>10^5$ organisms per ml in clean-catch or catheterized urine specimens, accompanied by fever, chills, frequency of urination, and dysuria. Identifica-

tion of cellulitis required isolation of organisms from wound drainage, accompanied by evidence of soft tissue infection. Patients with intraabdominal infections had cultures taken from the peritoneal level at the time of surgery and had active signs and symptoms of infection. Patients treated for septic thrombophlebitis had organisms isolated from the catheter and from blood 24 h after the removal of the catheter, together with signs of infection (local pain, inflammation, fever, and chills). The criteria used for identifying septicemia were positive blood cultures accompanied by fever, chills, or hypotension (blood pressure, ≤90 mmHg [11,997 Pa]).

The therapeutic efficiency of ceftazidime was evaluated by clinical and bacteriological criteria. A patient was considered cured when the clinical illness resolved and one or more negative follow-up cultures (generally within 1 week of the end of treatment) were obtained. Improvement was defined as a significant clinical response, with the resolution of pyrexia and leukocytosis but with persistence of, relapse due to, or reinfection with the causal organism. We considered the case to be a failure if (i) there was clinical deterioration due to primary infection or a lack of clinical response, (ii) the patient died after ≥48 h of therapy, or (iii) resistant organisms of the original infecting species emerged during therapy and required a change in therapy. Colonization during treatment was defined as the appearance of one or more different pathogens resistant to ceftazidime in the absence of clinical deterioration. Superinfection was defined as the appearance of one or more resistant strains of different species from the original infecting species associated with a clinical exacerbation of the primary infection or the development of a new infection.

The following tests were carried out on all patients before, during, and after treatment: blood count, erythrocyte sedimentation rate, serum urea and creatinine levels, liver function tests, and urine examination.

Ceftazidime was supplied in 1-g vials. Of the 33 patients, 24 received the drug intravenously, and the requisite amount of drug (dissolved in 10 ml of sterile water per g) was added to 100 ml of 5% glucose in water and infused over a period of 30 min. The remaining nine patients received the drug intramuscularly. The dose of the antibiotic varied from 0.5 g every 12 h to 2 g every 8 h, depending on the pathogen (the highest doses were given for *P. aeruginosa* infections) and the level of renal function. Doses for most patients ranged from 2 to 4 g per day. No other antibiotics were administered concomitantly.

Susceptibility testing. Clinical isolates were identified by conventional bacteriological methods. Disk testing for susceptibility of the isolated strains was performed by the Kirby-Bauer method with a standard (30-μg) ceftazidime disk (Neo-Sensitabs; A/S Rosco, Taastrup, Denmark). A zone size of ≥23 mm was used to define susceptible organisms, and a zone of 20 to 22 mm was used to identify intermediately susceptible ones. To determine the minimal inhibitory concentrations (MICs), we used a microdilution method in liquid medium. Microtiter plates containing twofold serial dilutions of the antibiotic at concentrations ranging from 100 to 0.097 mg/liter in Mueller-Hinton broth were inoculated with an MIC 2000 inoculator (Dynatech Laboratories, Inc., Alexandria, Va.). The inoculator filled the microtiter plates with a bacterial suspension of 10^7 CFU/ml to give a final concentration of 3×10^5 CFU/ml in each well. The microtiter plates were then incubated for 24 h, the trays were examined on a viewing box (Dynatech), and the MICs were recorded as the lowest concentrations that inhibited visible growth. Organisms were considered resistant to ampicillin and cephalothin if the MIC was >12.5 mg/liter, resistant to gentamicin and tobramycin if the MIC was >6.25 mg/liter, and resistant to ceftazidime if the MIC was >12.5 mg/ml.

RESULTS

Overall clinical results. At the start of therapy, all patients were considered to be in either serious or fair condition. A total of 17 patients had failed to respond to previous antimicrobial therapy (usually cefazolin, carbenicillin, or gentamicin). Table 1 shows the types of infections treated and a summary of the responses to therapy. The duration of therapy was 3 to 42 days (mean, 14.4 days). The overall favorable response rate (number cured plus number improved) was 91%, including patients with septicemia.

***P. aeruginosa* infections.** Table 2 summarizes the data of 13 patients with *P. aeruginosa* infections. Before treatment all bacterial isolates were fully susceptible to ceftazidime. The mean MIC was 1.02 mg/liter (range, 0.39 to 3.12 mg/liter). Of the 13 strains isolated, 7 were resistant to carbenicillin and 5 were also resistant to gentamicin and tobramycin. Of the 13 patients studied, 9 were cured, 3 improved, and 1 failed to respond to therapy.

Of the three patients in the improved category, one patient (Table 2, patient 1) suffered from cystic fibrosis with bilateral pneumonia and responded clinically and radiologically to 10 days of therapy. At the end of treatment, a *P. aeruginosa* strain resistant to ceftazidime (MIC, 25 mg/liter) was isolated from sputum. No clinical deterioration was noted. This resistant strain spontaneously disappeared 3 weeks later, and the patient remained colonized with a susceptible *P. aeruginosa* strain (ceftazidime MIC, 1.56 mg/liter).

The second patient in the improved category (Table 2, patient 5) had a bronchopleuro-cutaneous fistula which failed to respond to carbenicillin and amikacin. Under ceftazidime therapy the cutaneous fistula was cured and the *P. aeruginosa* bacteremia was controlled. However, the bronchopleural fistula persisted, together with a ceftazidime-susceptible *P. aeruginosa* strain (MIC, 3.12 mg/liter).

The third patient in the improved category (Table 2, no. 6) had a urethral catheter and a vesical carcinoma, and a relapse with the original organism occurred 1 week after the end of ceftazidime therapy. The failure (Table 2, pa-

TABLE 1. Infections treated and summary of results of treatment with ceftazidime

Type of infection	No. of patients (no. septicemic)	No. cured	No. improved	No. of failures	No. of colonizations	No. of superinfections
Pneumonia	12 (7)	9	2	1	2	1
Febrile urinary tract	10 (4)	6	4	0	0	0
Soft tissue	4 (4)	3	0	1	3[a]	1
Intraabdominal	4 (3)	2	1	1	1	1[b]
Septic thrombophlebitis	2 (2)	2	0	0	0	0
Septicemia from unknown origin	1 (1)	1	0	0	0	0
Total (%) septicemic	21	16 (76)	3 (14)	2 (10)	4 (19)	2 (10)

[a] Colonizing strains were *C. albicans*, *S. faecalis*, and *S. aureus*.

[b] One patient presented two consecutive episodes of bacteremic superinfection to *S. aureus* and *Enterococcus* sp.

tient 11) was a severely burned patient who improved from her septic shock but died on the third day of ceftazidime treatment from septicemia due to *Candida albicans*.

***Enterobacteriaceae* infections.** Before treatment all bacterial isolates were fully susceptible to ceftazidime. Geometric means of the MICs were as follows: *Escherichia coli* ($n = 7$), 0.097 mg/liter (no range); *Klebsiella* sp. ($n = 4$), 0.153 mg/liter (range, 0.097 to 0.195 mg/liter); *Serratia marcescens* ($n = 3$), 0.117 mg/liter (range, 0.097 to 0.195 mg/liter); *Proteus* sp. ($n = 2$), 0.097 mg/liter (no range); miscellaneous (*Enterobacter cloacae*, *Acinetobacter anitratus*, *Citrobacter freundii*, and *Pasteurella multocida*), 0.117 mg/liter (range, 0.097 to 0.195 mg/liter). Of the 20 isolates, 15 were resistant to ampicillin and cephalothin. Six of these were also resistant to gentamicin.

Of 19 treated patients, 13 were cured, 4 improved, and 2 failed to respond to therapy.

Of seven patients with nosocomial pulmonary infections, five required mechanical ventilatory assistance during their therapy. All patients except one were septicemic at the onset of ceftazidime treatment. Six of the seven patients were cured. The treatment failure occurred in an 85-year-old patient with acute renal failure and postoperative status for an abdominal aneurysm who had a mixed *E. coli* and *S. aureus* (MIC, 3:12 mg/liter) septicemia. He died from septic shock 3 days after beginning ceftazidime therapy. At the time of death blood cultures were sterile, but *E. coli* and *S. aureus* persisted in the sputum obtained by tracheal aspiration.

Of the six patients with urinary tract infections, three (two septicemic) were cured and three (one septicemic) improved. These last three patients had chronic pyelonephritis due to multiresistant *E. coli* strains (ceftazidime MIC, 0.097 mg/liter for the three strains) which caused reinfection 6 weeks after the end of ceftazidime therapy.

Four patients treated with ceftazidime had intraabdominal infections. Three patients (all of them septicemic) had generalized peritonitis secondary to gall bladder infection or a perforated colon, and one patient had a pancreatic abscess. All of these patients required surgery. Two of the four patients were cured; however, one of these patients developed problems with the emergence of resistant bacteremic *S. aureus* and *Streptococcus faecalis* during ceftazidime therapy and required oxacillin and ampicillin treatment. The third patient, who was diabetic, improved from septic shock due to cholangitis and a perforated gall bladder, but the infecting organism, a strain of *Klebsiella* sp. (MIC, 0.39 mg/liter), persisted at the peritoneal level during ceftazidime therapy, and cutaneous colonization with a resistant *S. aureus* strain was noted on day 10 of therapy. The treatment failure occurred in an alcoholic patient with a pancreatic abscess. The abscess was drained, and *E. cloacae* (MIC, 1.25 mg/liter) was grown on culture medium. Despite 7 days of ceftazidime treatment, clinical conditions deteriorated and bile remained infected with *E. cloacae* which was resistant to ceftazidime (MIC, 25 mg/liter). A cure was obtained with amikacin therapy.

Two patients with *Serratia marcescens* bacteremia and subclavian phlebitis due to a Swan-Ganz catheter were cured with ceftazidime.

Tolerance and adverse reactions. Patients who received intravenous injections of ceftazidime experienced no phlebitis and reported no pain during infusion. Local pain was noted by one patient who received deep intramuscular injections of ceftazidime. Three patients had a transient rise in liver transaminases, one patient had a rash, and one patient had transient eosinophilia. There was no deterioration in renal function in the 16 patients with abnormal renal function (blood creatinine, >1.5 mg/dl) before ceftazidime therapy.

Emergence of resistant organisms. During therapy, 12 resistant organisms emerged in 11 patients. Of the 11 patients, 6 were colonized but

TABLE 2. Data from 13 patients with *P. aeruginosa* infections treated with ceftazidime

Patient no.	Age (yr)	Underlying disease (other treatment procedure)	Infection	Infected material	MIC (mg/liter)	Ceftazidime		Clinical response
						Dosage (g per day)	Duration (days)	
1	23	Cystic fibrosis	Pneumonia	Sputum	1.56[a]	2	10	Improved
2	58	Severe arteritis; COPD[b] (mechanical ventilation)	Pneumonia	Tracheal aspiration	1.56	6	10	Cured; urine colonization (*C. albicans*)
3	69	Ruptured aortic aneurysm (mechanical ventilation)	Pneumonia	Tracheal aspiration	0.39	4	12	Cured; wound colonization (*Enterococcus* sp.) and urinary superinfection (*Hafnia* sp.)
4	46	Alcoholic cirrhosis; coma (mechanical ventilation)	Pneumonia	Tracheal aspiration	0.78[a]	6	12	Cured
5	68	COPD; pneumothorax bronchopleuro-cutaneous fistula	Empyema; pneumonia	Pleural; skin; blood	0.78[a]	6	17	Improved
6	65	Vesical carcinoma (urinary catheter)	Cystitis	Urine	0.39	2	25	Improved
7	26	Extended burns[c]	Cystitis	Urine	0.39	3	10	Cured
8	77	Benign prostatic hypertrophy with urinary tract obstruction	Cystitis	Urine	0.39	3	10	Cured
9	38	Extended burns[c]; renal failure	Cellulitis	Blood; skin	0.39[a]	3	11	Cured; urine colonization (*C. albicans*)
10	56	Burns[d]; benign prostatic hypertrophy	Pyelonephritis	Blood; urine	1.56	3	10	Cured
11	52	Extended burns[c]; diabetes mellitus; acute renal failure	Cellulitis; septic shock	Blood; skin	0.39	2	3	Died from *C. albicans* septicemia
12	43	Perforated gastric ulcus; peritonitis	Cellulitis; septic shock	Blood; wound aspiration	1.56[a]	3	15	Cured; skin colonization (*S. aureus*)
13	30	Extended burns[c]	Cellulitis; septic shock	Blood; skin	3.12	6	15	Cured

[a] Multiresistant strains resistant to carbenicillin (MIC, >100 mg/liter) and gentamicin and tobramycin (MIC, >6.25 mg/liter).
[b] COPD, Chronic obstructive pulmonary disease.
[c] More than 40% of the total body surface was covered with third-degree burns.
[d] At least 20% of the total body surface was covered with third-degree burns.

not clinically infected by resistant organisms, 3 were superinfected by new organisms, and in 2 the emergence of resistance was observed in the original organism (*P. aeruginosa* and *E. cloacae*); of the latter, 1 patient improved and 1 patient failed to respond to therapy. The superinfection episodes included three episodes of septicemia (due to *C. albicans, S. aureus*, and *Enterococcus* sp.) which occurred in two patients. A third patient developed a urinary tract superinfection due to *Hafnia* sp. The most common resistant organisms to emerge during therapy were *C. albicans* (four isolates), *S. aureus* (three isolates), and *Enterococcus* sp. (two isolates).

DISCUSSION

The present study shows that ceftazidime is effective in the treatment of serious infections due to aerobic, gram-negative bacilli, including infections due to multiresistant strains which failed to respond to previous therapy. Most noteworthy were the good results obtained in cases of severe *P. aeruginosa* infections. The high doses used (between 3 and 6 g per day in patients with normal renal function), low serum binding, and the good pharmacokinetics of ceftazidime may explain these results (5). Indeed, in a previous report from this laboratory, good bronchial diffusion of ceftazidime was shown in eight

patients with cystic fibrosis (2). Ceftazidime levels of between 4 and 15 mg/liter of sputum (mean value, 9 mg/liter) were noted 1 h after intravenous injection of 0.5 to 1 g of the drug. Our experience with patients with *P. aeruginosa* pneumonia or septicemia suggests that single-drug therapy with ceftazidime may be an effective and safe alternative to antipseudomonas penicillins in allergic patients or in cases due to organisms resistant to penicillins and aminoglycosides. Before concluding that ceftazidime may be considered as first-line, single therapy against *P. aeruginosa* infection, further extended and controlled studies are needed, particularly in neutropenic or corticosteroid-treated patients, two well-known conditions associated with high mortality due to *P. aeruginosa* infections (10).

One death from septic shock occurred during treatment of a patient with pneumonia and septicemia due to *E. coli* and *S. aureus*. Like the other new cephalosporins, ceftazidime is less active in vitro against staphylococci than against gram-negative organisms (7), and it is advisable not to use ceftazidime alone in mixed infections that include *S. aureus* (3). In addition, the poor efficacy of ceftazidime against most anaerobes precludes its use for mixed anaerobic-aerobic, gram-negative, intraabdominal infections.

Although the incidence of adverse clinical reactions observed in our study is low, the incidence of colonization or superinfection is noteworthy. Emergence of resistant organisms during therapy with new extended-spectrum cephalosporins has been noted with cefotaxime (1, 11) and moxalactam (6, 12, 14, 17) and has mostly involved *P. aeruginosa*, enterococci, and *Candida* sp. We noted superinfection or colonization with *S. aureus* due to the poor activity of ceftazidime against this organism. A resistant *E. cloacae* strain emerged in one patient with an intraabdominal infection who was not responding to ceftazidime therapy. Although transient, resistance of *P. aeruginosa* also occurred in one patient (Table 2, no. 1) with cystic fibrosis. However, in our experience with ceftazidime, no colonization or superinfection with *P. aeruginosa* was noted.

The therapeutic success which we encountered in this clinical study supports a significant clinical potential for ceftazidime in the therapy of serious infections, particularly those due to *P. aeruginosa*. This drug does not appear to have significant renal toxicity and can be given in fairly high doses with few major side effects. The potential for superinfection requires further evaluation in comparison with the risk associated with the use of similar broad-spectrum antimicrobial agents.

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