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Ceftazidime as Initial Therapy for Suspected Bacterial Infections in Hospitalized Pediatric Patients

MICHAEL D. REED, CHERYL A. O'BRIEN, STEPHEN C. ARONOFF, JEFFREY D. KLINGER, AND JEFFREY L. BLUMER*

Division of Pediatric Pharmacology and Critical Care and Infectious Diseases, Rainbow Babies' and Children's Hospital, and Departments of Pediatrics and Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106

Received 13 January 1984/Accepted 27 June 1984

Ceftazidime, a new β-lactam antibiotic, was used to treat 60 children with suspected bacterial infections occurring outside the central nervous system. The patients ranged in age from 0.1 to 21 years and received 30 mg of ceftazidime per kg up to a total single dose of 1 g administered every 8 h. Fifty-three pathogens were isolated from 43 children before the initiation of therapy. All children responded clinically, although one child failed bacteriologically and five children were considered colonized at the end of ceftazidime therapy. Adverse reactions associated with ceftazidime administration were primarily alterations in laboratory parameters and were clinically insignificant. Ceftazidime administered on an 8-h dosing regimen is effective monotherapy for the treatment of childhood infections.

Initial antibiotic therapy for most hospitalized pediatric patients generally consists of more than one drug. The more common regimens for empiric therapy include an aminopenicillin or an antistaphylococcal penicillin combined with chloramphenicol or an aminoglycoside (3, 13). With the availability of the new third-generation cephalosporins, the need for combination therapy in pediatric infections beyond the newborn period needs reevaluation.

Ceftazidime is a new β-lactamase-stable third-generation cephalosporin currently in clinical trials. The drug possesses a broad spectrum of antibacterial activity including the pathogens most frequently associated with serious infections in children (8, 15, 16, 18, 20, 23). Single-dose pharmacokinetic studies in infants and children have shown that serum and cerebrospinal fluid ceftazidime concentrations exceed the MIC for inhibition of the majority of pediatric pathogens over an 8-h period (10; J. Blumer, M. Reed, S. Aronoff, and C. Myers, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 830, 1983). The present study was designed to evaluate the safety and efficacy of ceftazidime as initial therapy for hospitalized pediatric patients with suspected moderate to severe bacterial infections.

MATERIALS AND METHODS

Patient inclusion and exclusion criteria. Infants and children older than 1 month of age admitted to Rainbow Babies' and Children's Hospital with a presumed bacterial infection were eligible for enrollment into this study. Patients were excluded if there was a history or documentation of: (i) allergy to β-lactam antibiotics, (ii) previous antimicrobial therapy within 48 h of presentation to the hospital, (iii) evidence of involvement of the central nervous system, (iv) granulocytopenia (absolute neutrophil count, <1,000/mm), or renal (serum creatinine, >2 mg/dl) or hepatic (serum aspartate aminotransferase, >200 IU/liter, or serum bilirubin, >3 mg/dl, or both) impairment. This study was approved by the Institutional Review Board for Human Investigation of the University Hospitals of Cleveland, and written informed consent was obtained from each family or patient or both.

* Corresponding author.

Diagnostic criteria. The diagnosis of infection was based upon both clinical and bacteriological evaluation. Symptomatic, physical, laboratory, and radiographic findings consistent with a specific diagnosis (see below) and the isolation of a pathogen from an appropriate source were required to make a definite diagnosis. A clinical diagnosis was made in those children in whom a pathogen was not identified.

Fever and respiratory symptomatology accompanied by new infiltrates upon chest roentgenogram defined pneumonia. In all cases, sputum for Gram stain and culture were obtained. A bacterial etiology for the pneumonia was confirmed when a new bacterial pathogen was grown from sputum culture.

A diagnosis of osteomyelitis was based upon the presence of fever, inability to bear weight, gait disturbances, localized pain, focal changes demonstrated by plain radiographs or technetium 99m scans or both, and an elevated erythrocyte sedimentation rate. Fever, gait disturbances, localized pain, and tenderness in the presence of purulent synovial fluid established the diagnosis of infective arthritis. Cellulitis was diagnosed on the basis of fever, localized tenderness, erythema, and induration in the absence of underlying bony abnormalities. Urinary tract infections were defined as frequency, dysuria, or pyuria accompanied by a clean voided urine yielding $>10^5$ CFU of a single organism per ml which was confirmed by a catheterized specimen. Fever along with a toxic appearance including tachypnea, tachycardia, and altered mental status in the presence of one or more positive blood cultures obtained from percutaneous punctures of peripheral veins supported a diagnosis of septicemia.

Therapeutic response criteria. To be eligible for clinical and bacteriological evaluations, patients had to receive at least 5 full days of therapy.

Clinical cure was defined as full resolution of local and systemic signs of infection with no evidence of infection at the time that therapy was discontinued. Patients in whom the clinical findings subsided significantly but with incomplete resolution of evidence of infection were considered improved, whereas no apparent response to therapy constituted failure.

Bacteriological evaluation was limited to those patients in whom a pathogen was isolated before the initiation of

TABLE 1. Therapeutic response to ceftazidime

Site of infection	No. of patients studied	No. of patients with identifiable pathogen(s)	Pathogens (no. of isolates)	Ceftazidime MIC (range)	No. of patients responding to therapy (%)	
					Clinical	Bacteriological
Pulmonary	20	14	*Staphylococcus aureus* (4)	8–16	20 (100)	13 (93)
			Enterobacter cloacae (5)	0.5–1		
			Pseudomonas aeruginosa (5)	2–4		
			Haemophilus influenzae type b (2)	0.5–1		
			Klebsiella pneumonia (2)	0.5		
			Klebsiella oxytoca (1)	1		
			Proteus mirabilis (1)	0.5		
			Proteus vulgaris (1)	4		
			Acinetobacter sp. (1)	8		
Skin and skin structure	19	13	*Staphylococcus aureus* (6)	2–32	19 (100)	13 (100)
			Staphylococcus epidermidis (1)	2		
			Streptococcus pneumoniae (3)	0.125		
			Haemophilus influenzae type b (3)	0.125–0.25		
			Pseudomonas aeruginosa (1)	≤8		
			Escherichia coli (1)	≤8		
Lower urinary tract	10	10	*Escherichia coli* (6)	0.25–0.5	10 (100)	10 (100)
			Klebsiella pneumonia (1)	0.5		
			Pseudomonas aeruginosa (1)	8		
			Neisseria gonorrhoea (1)	0.0625		
			Enterobacter cloacae (1)	0.5		
Bone and joint	10	5	*Staphylococcus aureus* (2)	4, 32	10 (100)	5 (100)
			Pseudomonas aeruginosa (2)	2		
			Streptococcus agalactiae (1)	ND[a]		
Sepsis	1	1	*Pseudomonas aeruginosa* (1)	2	1 (100)	1 (100)

[a] ND, Not done.

therapy. Repeat cultures were obtained for all patients, except those with bone and joint infections, 48 to 72 h after the initiation of therapy and every 4 to 5 days during therapy as long as cultures remained positive or a culturable focus persisted. When applicable, cultures were also obtained within 48 h of ending therapy. Cure was assessed if the initial pathogen was eradicated, the patient was clinically cured, and no bacterial pathogen was isolated at the end of therapy. Asymptomatic patients with one or more pathogens isolated at 24 to 48 h after the end of therapy were considered to be colonized. Bacteriological failure was defined as the presence of the initial pathogen during and 24 to 48 h after therapy. Children from whom no pathogen was cultured before therapy were not evaluable for bacteriological response.

Evaluation for safety. The following clinical and laboratory evaluations were performed on all children just before ceftazidime therapy and at the frequencies indicated: (i) pretherapy aerobic and anaerobic cultures of all appropriate sites including blood, sputum, urine, wounds, and bone; (ii) daily physical examination; (iii) twice weekly during the first week of therapy and at least weekly thereafter—serum sodium, potassium, calcium, phosphorous, creatinine, glutamic oxaloacetic transaminase, gamma glutamyl transaminase, lactate dehydrogenase, alkaline phosphatase, bilirubin (total and direct), total protein, albumin, cholesterol, triglycerides, urea nitrogen, and glucose; (iv) weekly complete blood count with differential and platelet counts, erythrocyte sedimentation rate, Coombs reaction, and prothrombin and partial thromboplastin times. Clinical and laboratory evaluations were repeated within 24 to 48 h of the cessation of therapy. Cultures were repeated only when a culturable focus remained.

Drug administration. Ceftazidime pentahydrate (GR 20263; Glaxo, Inc., Research Triangle Park, N.C.) was reconstituted with 3 ml of 5% dextrose in water or normal saline. The drug was infused intravenously via a peripheral vein over 15 min. Immediately after drug administration, the intravenous infusion tubing was flushed with 10 ml of 5% dextrose in water to ensure total drug administration. Each child received 30 mg of ceftazidime per kg up to a total single dose of 1 g administered every 8 h for a total daily dose of 90 mg/kg per day or 3 g. No other antibiotic was administered during ceftazidime therapy.

RESULTS

Sixty-two children were enrolled into the study. Two children were dropped and not included in the data analysis. These children had periorbital cellulitis and showed dramatic improvement with ceftazidime therapy. Both were discharged from the hospital after receiving only 1 day of parenteral antibiotic therapy. The remaining patients ranged in age from 0.1 to 21 years, averaging 5.7 years. Thirty-five of the children were male, and 53% presented with a rectal temperature >38.5°C. The mean daily dosage of ceftazidime averaged 83 mg/kg per day (range, 44 to 97 mg/kg per day) for an average duration of 12.6 days (range, 5 to 46 days).

Forty-three children were evaluable for both clinical and bacteriological response (Table 1). From these, 53 bacterial pathogens were isolated before the initiation of ceftazidime therapy.

Staphylococcus aureus, the most common pathogen, was isolated from 12 children. All *S. aureus* isolates were resistant to penicillin, and the MIC of ceftazidime for these isolates ranged from 2 to 32 μg/ml. *Pseudomonas aeruginosa* was isolated from 10 children and the MIC of ceftazidime for

this organism ranged from 2 to 8 μg/ml. The one isolate of *Neisseria gonorrhoea* was β-lactamase producing.

Of the 43 children with identifiable pathogens, thirty-five had either no culturable focus or sterile cultures at the cessation of ceftazidime therapy. One child with pneumonia failed to improve with therapy, whereas five children (three with pneumonia) and two with skin and skin structure infections) were colonized upon discontinuation of ceftazidime. No children developed superinfection. The one failure was a 1-year-old intubated male with bronchopulmonary dysplasia and a seizure disorder. His initial tracheal culture grew *Proteus mirabilis* (MIC of ceftazidime for inhibition, 0.5 μg/ml) and *Pseudomonas aeruginosa* (MIC of ceftazidime for inhibition, 4 μg/ml). After 7 days of ceftazidime therapy, the child improved clinically and radiographically, but both organisms persisted after discontinuation of the drug. No change in the MIC of ceftazidime was observed for either organism during the 7-day treatment course.

Thirteen children were discharged from the hospital receiving oral antibiotic therapy. Of the nine in the skin and skin structure infection group, five received cefaclor, two received cephalexin, one received penicillin V-K, and one received trimethoprim-sulfamethoxazole. Only six of these patients were evaluable for bacteriological response. All of these children were observed in the hospital off all antibiotics for at least 24 h before discharge.

Two children with osteomyelitis were discharged on oral agents (cefaclor and cephalexin). Neither had a bacterial pathogen isolated at the time of diagnosis. Finally, two children with recurrent urinary tract infections were restarted on their suppressive therapy, amoxicillin and trimethoprim-sulfamethoxazole, within 24 h of discharge from the hospital. It is noteworthy that *S. aureus* was the pathogen in only three of the children receiving oral antimicrobial therapy after discharge.

Follow-up evaluations are complete in all children with urinary tract infections and range from 2 to 12 months in children with bone and joint infections.

All patients enrolled were evaluated for drug safety. Ceftazidime therapy was well tolerated by all children. Abnormal laboratory values were identified in 26 of the 60 treated children (Table 2). No relationship was observed between these laboratory abnormalities and the site of infection, ceftazidime dose, or duration of therapy. Thrombocytosis (platelet count, >300,000/mm^3) was the most common abnormality observed occurring in 13 children. One child developed mild diarrhea lasting for 5 days, but this resolved despite continuation of ceftazidime therapy. No other adverse clinical effects were observed, and none of the laboratory abnormalities were sufficiently serious to warrant discontinuation of ceftazidime therapy.

TABLE 2. Adverse reactions to ceftazidime in 60 pediatric patients

Reaction	No. of cases	% Occurrence
Thrombocytosis	13	22
Esoinophilia	6	10
Coombs conversion	5	8.3
Elevated SGPT[a]	1	1.7
Elevated creatinine	1	1.7
Diarrhea	1	1.7

[a] SGPT, Serum glutamic pyruvic transaminase.

DISCUSSION

Until recently, the cephalosporin class of antibiotics offered little to the pediatric practitioner due to an unacceptably high incidence of "breakthrough" meningitis (4, 6) and the inability of these drugs, as single agents, to effectively eradicate the more common pathogens associated with childhood infections (5). For these reasons and others (1, 24), combination antimicrobial therapy has been standard practice in the treatment of serious infections in children.

Newer cephalosporin analogs including cefuroxime (14), ceftriaxone (2, 22), cefotaxime (9, 19), and moxalactam (21; M. D. Reed, S. C. Aronoff, and J. L. Blumer, Drug Intell. Clin. Pharm., in press) appear to be effective against common pediatric pathogens and adequately penetrate into the central nervous system. Ceftazidime, a new β-lactam antibiotic of the cephalosporin class, also appears to possess these desirable attributes as well as a broad spectrum of antibacterial activity (8, 10, 15, 16, 18, 20, 23; 23rd ICAAC, abstr. no. 830). The present investigation was undertaken to evaluate the efficacy and safety of ceftazidime monotherapy in the treatment of non-central nervous system pediatric infections.

Forty-three of the 60 evaluable children had at least one pathogen isolated before ceftazidime therapy was started. The initial pathogen(s) was eradicated in 42 of these 43 children. Although tracheal cultures remained positive after 7 days of ceftazidime treatment in one child, the child responded clinically and did not require further antimicrobial therapy. An additional five children were colonized at the cessation of therapy. Overall, a favorable clinical outcome was observed in all children studied (Table 1).

S. aureus, the most common pathogen isolated, was responsible for infections in 12 children. Three of these children received oral antibiotics after hospital discharge. The MIC of ceftazidime for these isolates ranged from 2 to 32 μg/ml. Although these ceftazidime MICs far exceed the 90% MIC for other β-lactam antibiotics (11, 20), all nine infected children not receiving supplemental oral therapy fulfilled criteria for both bacteriological and clinical cures. In addition, no cultures from the three children switched to oral therapy grew *S. aureus* after the children had spent 24 h off ceftazidime before the start of their at-home medication. Similar clinical and bacteriological efficacy despite high in vitro MICs has been observed with other third-generation cephalosporins (12; Reed et al., in press). Thus, although we do not believe that these agents should be used routinely to treat *S. aureus* infections, these data suggest that ceftazidime and other third-generation cephalosporins may provide effective empiric therapy even when *S. aureus* is the suspected pathogen. More data on the effectiveness of these agents is necessary to more clearly define their role in the therapy of staphylococcal disease.

No drug-associated side effects requiring discontinuation of ceftazidime therapy were observed in any child. Abnormal laboratory determinations were observed in 26 of the 60 treated children (Table 2). Thrombocytosis was the most common abnormal laboratory parameter, occurring in 13 children. This abnormality has been observed previously with ceftazidime (7) and other β-lactam antibiotics. Eosinophilia, Coombs reactivity, and abnormalities in liver function tests have also been reported in frequencies similar to those observed in the present study with ceftazidime (17). None of these abnormalities were associated with any clinical symptomatology.

The results of this study demonstrate that ceftazidime is safe and efficacious as monotherapy for the treatment of non-central nervous system infections which occur during childhood. The relatively prolonged elimination half-life of

ceftazidime compared with earlier β-lactam analogs permits drug administration every 8 h (10; 23rd ICAAC, abstr. no. 830). Resultant serum concentrations usually exceed the MIC of ceftazidime for *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b throughout most of the dosing interval.

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