

## Treatment of Bacterial Meningitis with Ceftizoxime

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Ceftizoxime was evaluated in the treatment of 18 patients (6 adults and 12 children) with bacterial meningitis. In seven patients *Haemophilus influenzae* was the causative agent, in three *Neisseria meningitidis*, in five *Streptococcus pneumoniae*, and in one each  $\alpha$ -streptococcus and *Escherichia coli*; one case was culture negative. Ceftizoxime was administered intravenously in doses of 200 mg/kg per day. Clinical response was appropriate in all patients with a mean time of defervescence of 3.7 days, and sterile cerebrospinal fluid was obtained from all patients at 24 to 36 h after initiation of therapy. The mean concentration of ceftizoxime in 46 cerebrospinal fluid samples obtained during therapy was 8.53  $\mu$ g/ml (range, <0.5 to 29.0  $\mu$ g/ml). Ceftizoxime concentrations in cerebrospinal fluid samples were ten- to several hundredfold the bactericidal concentrations of the pathogens isolated from the cerebrospinal fluid. Ceftizoxime penetrates the meninges well during acute infection and appears to be an excellent candidate antibiotic in the treatment of bacterial meningitis.

Ceftizoxime is a beta-lactamase resistant, parenterally administered, semisynthetic cephalosporin with broad in vitro activity against gram-positive and gram-negative organisms. The ceftizoxime 90% MICs for pneumococci and meningococci are  $\leq 0.12$  and  $\leq 0.01$   $\mu$ g/ml, respectively (1, 6, 7). *Haemophilus influenzae*, including beta-lactamase-producing isolates, are uniformly inhibited by concentrations of  $\leq 0.1$   $\mu$ g of ceftizoxime per ml (1, 10). In addition, ceftizoxime is very active against many enteric organisms and nosocomial pathogens (1).

In preliminary studies of ceftizoxime in bacterial meningitis, a mean concentration in cerebrospinal fluid (CSF) of 4.9  $\mu$ g of ceftizoxime per ml was achieved after administration of single doses of 30 mg/kg intravenously, and mean CSF-to-serum ratios were 22.5% (2). Thus, the demonstrated activity against meningeal pathogens and preliminary results of probable therapeutic concentrations in CSF warranted further study of the achievable concentrations of ceftizoxime in CSF during treatment and its efficacy and safety in patients with meningeal infections.

### MATERIALS AND METHODS

**Patients.** A total of 23 consecutive patients admitted to the Communicable Disease Service of the Los Angeles County-University of Southern California Medical Center, with a diagnosis of suspected bacterial meningitis, were enrolled in the study. One additional patient with *H. influenzae* meningitis was enrolled after unsuccessful therapy with trimethoprim-sulfamethoxazole. Informed written consent was obtained from each patient, parent, or appropriate guardian before enrollment. Patients were excluded from therapy if: (i) they were allergic to penicillins or cephalosporins; (ii) there was a requirement for concurrent antimicrobial therapy; (iii) there was the presence of significant underlying disease that would confound analysis of ceftizoxime therapy; (iv) the subsequent course proved to be due to a nonbacterial etiology; or (v) if death occurred within the first 12 h of treatment.

The diagnosis of meningitis was confirmed in all patients with a positive CSF or blood culture in association with a

consistent clinical presentation and CSF changes for acute bacterial infection. A single patient was included who had negative blood and CSF cultures but had gram-positive diplococci (i.e., "purulent unknown") on CSF smear. In addition, all patients satisfied two or more of the following criteria: (i) a predominately polymorphonuclear CSF leukocyte (WBC) pleocytosis ( $> 500$  cells per  $\text{mm}^3$ ), (ii) a protein level of  $\geq 100$  mg/100 ml, or (iii) a glucose level of  $\leq 50\%$  of a simultaneously obtained serum glucose value.

**Administration of ceftizoxime.** Ceftizoxime was administered to all patients in a daily dose of 200 mg/kg divided into six equal doses (every 4 h); maximal single doses of 2 g (or 12.0 g daily) were not exceeded. Each ceftizoxime dose was administered intravenously in a total volume of 10 to 25 ml over a mean of 12 min (range, 5 to 30 min). Patients were treated until they were afebrile for 5 days or for a minimum duration of 10 days for patients with infections due to *Neisseria meningitidis* and *Streptococcus pneumoniae* and 14 days for those with *H. influenzae* infection. Patients were followed daily to assess clinical response. Lumbar punctures were performed on day 1 (i.e., 24 to 36 h after the initiation of therapy), 3, 7 or 10, and 14 of ceftizoxime therapy.

**CSF studies.** All CSF specimens were analyzed for cell count (WBC per cubic millimeter and differential), glucose and protein concentration (milligrams per deciliter). Samples of CSF for antibiotic assay were obtained at a mean of 133 min (range, 30 to 420 min) after administration of doses on the days of scheduled lumbar punctures. When ample serum was available, it was obtained concomitantly with CSF to determine glucose and ceftizoxime concentration in serum. A single CSF specimen was obtained at 7 h after the end of therapy, and a single subdural fluid was available from a child with *H. influenzae* meningitis. Serum and CSF specimens were stored at 4°C for up to 48 h before final storage at -20°C and thereafter for up to 60 days before antibiotic assay. There was no variation in determined antibiotic concentration in samples stored under the above conditions for up to 91 days.

**Ceftizoxime assay.** Concentrations of ceftizoxime in serum and CSF were determined by a microbiological assay with *Enterobacter cloacae* (USC strain 73-200) as the test organism. The inhibitory concentration for both ampicillin and chloramphenicol for the assay organisms was  $\geq 200$   $\mu$ g/ml,

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TABLE 1. Age, etiology, culture source, and initial CSF findings of 18 patients with bacterial meningitis treated with ceftizoxime

Age	Etiology	Culture source	CSF findings		
			WBC per mm <sup>3</sup>	Glucose (mg/dl)	Protein (mg/dl)
1 mo	<i>E. coli</i>	CSF, blood	1,150	37.0	181
1 mo	<i>H. influenzae</i>	CSF, blood	540	5.0	128
2 mo	<i>S. pneumoniae</i>	CSF, blood	1,639	36.0	144
5 mo	<i>H. influenzae</i>	CSF, blood	266	32.0	37
8 mo	<i>H. influenzae</i>	CSF	2,042	94.0	41
11 mo	<i>H. influenzae</i>	CSF, blood	3,500	5.0	146
11 mo	<i>H. influenzae</i>	CSF, blood	354	29.0	63
15 mo	<i>N. meningitidis</i>	CSF	3,925	39.0	165
19 mo	<i>H. influenzae</i>	CSF	187	7.0	37
3½ yr	<i>S. pneumoniae</i>	CSF, blood	2,290	33.0	169
6½ yr	<i>H. influenzae</i>	CSF	4,580	61.0	175
9 yr	<i>H. influenzae</i>	CSF	9,425	20.0	350
24 yr	No growth <sup>a</sup>	CSF	4,820	21.0	137
27 yr	<i>S. pneumoniae</i>	CSF	3,463	5.0	282
45 yr	<i>N. meningitidis</i>	CSF	10,800	18.0	495
49 yr	<i>S. pneumoniae</i>	CSF	3,350	10.0	408
64 yr	$\alpha$ -streptococcus	Blood	880	10.0	132
67 yr	<i>S. pneumoniae</i>	CSF	1,512	40.0	109

<sup>a</sup> CSF Gram stain revealed gram-positive diplococci.

and concentrations of 10 to 1,000  $\mu\text{g/ml}$  of either ampicillin or chloramphenicol did not alter test results. Assay organisms were seeded onto plates of antibiotic medium 1 (Difco Laboratories) with 50- $\mu\text{l}$  agar wells. Standard ceftizoxime curves were constructed on each plate (1.6, 3.13, 12.5, and 50  $\mu\text{g/ml}$ ), and all control and unknown samples were run in duplicate wells. Results of assays were read at 4 h after incubation at 37°C. Ceftizoxime in CSF was detectable at concentrations of  $\geq 0.5$   $\mu\text{g}$  of ceftizoxime per ml, and concentrations of  $< 0.5$   $\mu\text{g/ml}$  were recorded as nondetectable.

## RESULTS

Of the 24 patients enrolled in the study, 18 successfully completed treatment with ceftizoxime. Five patients were removed from further analysis when it was apparent that they did not have bacterial meningitis; three of these had aseptic meningitis, one tuberculous meningitis, and one chemical meningitis after subarachnoid hemorrhage. An additional patient was admitted in septic shock with apparent meningococemia; this patient died within 12 h of admission but was excluded from analysis since the child received only two doses of ceftizoxime.

**Patients.** Of 18 patients who completed therapy, 12 were children and 6 were adults (Table 1). Patients ranged in age from 2 months to 65 years. The etiology of bacterial meningitis proven by blood or CSF culture or both included seven due to *H. influenzae*, five due to *S. pneumoniae*, three due to *N. meningitidis*, one due to *Escherichia coli* and one due to  $\alpha$ -streptococcus. The single patient with presumptive bacterial meningitis had a CSF characterized by low glucose and high protein contents, 4,840 WBC/mm<sup>3</sup> in the presence of fever (103°F [ca. 39.4°C]), and clinical signs of acute meningitis; gram-positive diplococci were observed on a stained smear of the CSF sediment. Of the seven children with *H. influenzae* infection, two yielded beta-lactamase-producing isolates. Three patients had underlying diseases: multiple myeloma, congenital heart disease, and Down's syndrome with necrotizing enterocolitis. An additional two patients had conditions which may have predisposed them to meningeal infections; one had a suspected CSF leak, a second had

chronic otitis media. Concomitant or associated infections were noted in 13 patients. Of these, eight were bacteremic (four with *S. pneumoniae* isolates, three with *H. influenzae* isolates, and one with an  $\alpha$ -streptococcus isolate). Five patients had associated infections, one with bursitis (pneumococcal), one with septic arthritis (haemophilus), one with pneumonia (pneumococcal), and two with otitis media (pneumococcal and haemophilus).

**Response to therapy.** All 18 patients had an appropriate and satisfactory clinical response to ceftizoxime administration. The five patients with pneumococcal infections were treated for a mean of 14.6 days, the seven patients with *H. influenzae* infections for 15.8 days, and the three patients with meningococcal infections for 10.3 days. The single infant with *E. coli* meningitis arbitrarily received 21 days of therapy. An adult patient with meningitis caused by  $\alpha$ -streptococcus received therapy for 14 days, and the patient without a recovered pathogen received therapy for 10 days. Thirteen patients had received antibiotic therapy recently or were under treatment when admitted to the study. Of these, three patients had received low doses of oral penicillin or ampicillin for upper respiratory tract infections, eight had received one or two doses of penicillin or ampicillin administered parenterally in the emergency room of referring hospitals, and two were on antibiotics when meningitis developed. Of the latter two, one was a neonate who had been receiving methicillin, ampicillin, and gentamicin for presumptive sepsis when *E. coli* meningitis was diagnosed; he had positive blood cultures at the time ceftizoxime was initiated. The second patient, a child with *H. influenzae* meningitis, had been treated sequentially with ampicillin and then trimethoprim-sulfamethoxazole without success. This patient proved to have an infection due to an ampicillin-, chloramphenicol-, and trimethoprim-sulfamethoxazole-resistant *H. influenzae* isolate and subsequently was successfully treated with ceftizoxime.

The mean duration of fever after initiation of ceftizoxime therapy was 3.7 days (range, 1 to 14 days). Two patients had prolonged fevers. One patient with *H. influenzae* meningitis and associated otitis media, cholesteatoma, and cerebellar abscess had a fever for 14 days. The second patient with *N. meningitidis* infection experienced severe skin necrosis due to purpuric infarcts and had 7 days of fever. Significant neurological residua at the end of therapy were apparent in two patients, both of whom had defined neurological complications during hospitalization. A child with *H. influenzae* meningitis previously noted to have infection with an ampicillin-, chloramphenicol-, trimethoprim-sulfamethoxazole-resistant isolate had a subdural abscess. This child was taken to surgery after 8 days of ceftizoxime therapy where the empyema was drained. A second child had a *H. influenzae* infection and a cerebellar pontine abscess that was drained on day 13 of therapy; cultures of the abscess were negative at the time of surgery.

**Antibiotic susceptibility and microbiological response.** Of 17 isolates, 13 were available for study, including 5 *H. influenzae*, 4 *S. pneumoniae*, 2 *N. meningitidis*, 1  $\alpha$ -streptococcus, and 1 *E. coli*. Four organisms (three *H. influenzae* and one *S. pneumoniae*) were unavailable for study because they were isolated at referring facilities. For all organisms except  $\alpha$ -streptococcus MICs and MBCs were  $\leq 0.1$  and  $\leq 0.1$   $\mu\text{g/ml}$ , respectively; for  $\alpha$ -streptococcus, the MIC and MBC were 0.2 and 0.4  $\mu\text{g/ml}$ , respectively. All CSF cultures obtained at 24 to 48 h of therapy were negative. Of the 11 CSF specimens obtained at 24 h after the initiation of therapy, 2 (18%) were Gram stain positive; however, all of these 11

TABLE 2. Ceftizoxime concentration in CSF and concomitantly acquired concentration in serum for each sample by time obtained after administration of dose

Patient	Time (min) after dose	Ceftizoxime concn in serum ( $\mu\text{g/ml}$ )	Ceftizoxime concn in CSF ( $\mu\text{g/ml}$ )
1	120	22.0	8.6
	120	22.0	6.8
	90	52.0	3.4
2	95	35.0	7.8
	90	33.0	7.8
	110	21.0	3.6
3	30	67.0	18.0
	45	112.0	24.0
4	150	44.0	22.0
	45	115.0	29.0
	30	58.0	23.0
5	45	57.0	9.0
	180	50.0	8.4
6	140	36.0	11.0
	150	41.0	9.0
7	180	17.8	13.0
	90	70.0	16.0
	90	47.0	13.0
	30	84.0	11.3
8	30	118.0	7.4
	60	46.0	6.3
	180	16.0	4.0
9	120	NA <sup>a</sup>	7.2
	170	NA	3.2
10	180	20.0	3.6
	100	38.0	8.4
	90	50.0	4.2
	100	50.0	8.4
11	180	NA	10.1
	75	46.0	7.8
	240	NA	6.0
12	120	19.0	2.6
	240	8.9	1.0
13	30	100.0	17.0
	60	NA	6.0
14	120	25.0	1.3
	90	NA	ND <sup>b</sup>
15	160	50	16.5
	210	44	5.7
	240	27	2.7
16	245	5.8	8.6
	200	16.5	7.0
17	190	7.2	3.3
	260	10.1	ND
18	190	14.0	4.2
	420	NA	1.6

<sup>a</sup> NA, Not available.

<sup>b</sup> ND, Nondetectable ( $<0.5 \mu\text{g/ml}$ ).

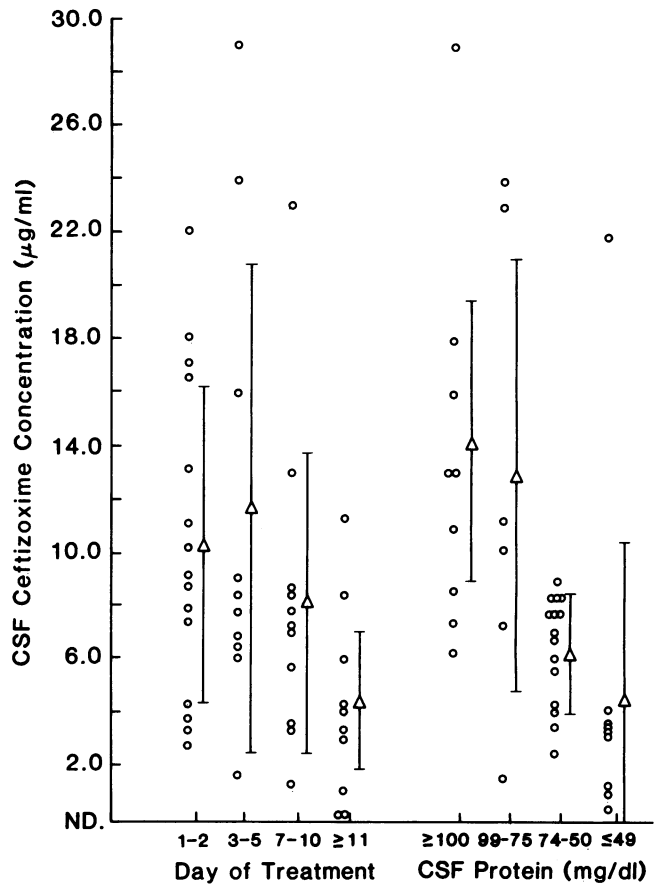


FIG. 1. Concentration of ceftizoxime in CSF by day of treatment or CSF protein concentration. The mean ( $\Delta$ )  $\pm$  standard error is displayed to the right of the individual values.

specimens were culture negative. Of six CSF specimens obtained at 36 h, all were Gram stain negative, as was a single CSF specimen obtained at 48 h. A sample of subdural empyema fluid yielded *H. influenzae* on culture at 24 and 48 h after the initiation of therapy, but it was subsequently negative at cultures obtained at 96 h.

**Ceftizoxime concentrations in CSF and serum.** A total of 46 CSF samples were collected within 30 to 420 min (mean, 133 min) after doses were administered during the course of bacterial meningitis. In 40 of these samples, a paired serum was available for analysis. The time of obtaining CSF after administration of the dose, and the concomitantly measured concentration in CSF and serum for each sample is displayed in Table 2. The mean concentration in CSF was  $8.53 \mu\text{g}$  of ceftizoxime per ml (range,  $<0.5$  to  $29 \mu\text{g/ml}$ ). Only two CSF samples had nondetectable levels of ceftizoxime, and both of these samples were collected after 11 days of therapy. The median CSF/serum ratio was 22.6% (range, 0 to 150%). A single subdural fluid concentration was  $42 \mu\text{g/ml}$ .

The concentration of drug in CSF did not correlate with the WBC count or glucose concentration in CSF (data not shown) but a trend for higher concentrations in CSF was observed in those CSF samples with higher protein concentrations or in those CSF samples obtained during the early days of treatment (Fig. 1). Of those patients with CSF collected at the time of a normal protein concentration ( $\leq 49 \text{ mg/dl}$ ) the mean level in CSF was  $4.47 \mu\text{g/ml}$  ( $n = 10$ ),

whereas in those patients with CSF obtained at the time of an abnormal CSF protein ( $\geq 50$  mg/dl) mean concentration in CSF was  $10.1 \mu\text{g/ml}$  ( $n = 31$ ).

**Adverse effects.** Possible drug complications related to the administration of ceftizoxime were minimal and reversible. Increases in transaminases (less than or equal to twofold normal) occurred in three patients, and increases in alkaline phosphatase (less than or equal to twofold normal) occurred in three; eosinophilia ( $\geq 500/\text{mm}^3$  in two) and thrombocytosis by smear evaluation ( $\geq 250,000/\text{mm}^3$  to  $\leq 750,000/\text{mm}^3$ ) occurred in nine patients. Platelet counts were not performed since smear evaluation was accurate within the limits stated and all smears returned to within normal limits at the time of discharge or the first follow-up visit (1 to 2 weeks). Clinical complications of drug administration may have included vaginal pruritis in one patient, nausea and diarrhea in one patient, and localized phlebitis in one patient.

### DISCUSSION

A number of investigators have examined the expanded spectrum cephalosporins in clinical or experimental meningitis, including cefotaxime (4), cefoperazone (3), moxalactam (8), ceftazidime (9), and ceftriaxone (5). All of these agents have the advantage of low inhibitory concentrations against *Haemophilus* isolates, including those producing beta-lactamase. All have good antimicrobial activity against *N. meningitidis*. However, their activity against *S. pneumoniae* (and other gram-positive bacteria) is variable, and in particular, the activity of moxalactam may be less than adequate for clinical infections due to gram-positive cocci. Other agents, as exemplified by ceftriaxone, possess novel pharmacokinetic advantages, such as a long serum half-life, thereby necessitating fewer doses during therapy. Since most of these agents have potent activity against gram-negative bacteria, they have been viewed as a major alternative to aminoglycoside therapy in neonatal meningitis and nosocomial infections. However, the antimicrobial and pharmacological advantages and disadvantages of each drug are continuing to be assessed for each, and as yet, no single drug has emerged as clearly superior for the treatment of bacterial meningitis.

Ceftizoxime also would appear to be an excellent candidate for treatment of bacterial meningitis. It possesses equivalent or better activity against the usual agents of meningitis than previously available cephalosporins as well as many of the currently available penicillins. Of *H. influenzae* strains, 90% are inhibited at concentrations of  $\leq 0.03 \mu\text{g/ml}$ , 90% of *N. meningitidis* strains at concentrations of  $\leq 0.1 \mu\text{g/ml}$ , and 90% of *S. pneumoniae* strains at concentrations of  $\leq 0.25 \mu\text{g/ml}$  (1). Ceftizoxime also has excellent activity against many gram-negative organisms, including indole-negative and -positive *Proteus* spp. and the genera *Enterobacter*, *Citrobacter*, and *Serratia* (6, 7).

Hamilton and coworkers measured mean ceftizoxime concentrations in CSF of  $0.48 \pm 0.33 \mu\text{g/ml}$  in patients undergoing elective myelography after the intravenous administration of single doses of 30 mg of ceftizoxime per kg (R. A. Hamilton, N. J. Owens, B. Moskovitz, C. H. Nightingale, and R. Quintiliani, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 40, 1981). These investigators noted that measurable concentrations of ceftizoxime were detectable only in those samples obtained more than 40 min after intravenous infusion. In our previously completed studies (2), the mean concentration of ceftizoxime in CSF was  $4.9 \mu\text{g/ml}$  after administration of single intravenous doses of 30 mg/kg. In the same studies,

CSF/serum ratios averaged 22.5%. Higher ceftizoxime concentrations in CSF were observed in CSF with high protein concentrations, elevated WBC counts or during earlier days of therapy, and in those samples obtained at greater than 120 min after drug administration. These studies demonstrated the entry of ceftizoxime into CSF across inflamed meninges. Concentrations in CSF peak at ca. 1 to 2 h after administration of the drug.

In the current studies, 18 patients with meningitis caused by pathogens acquired in the community were treated successfully with ceftizoxime. All patients responded well clinically and yielded negative cultures after 24 to 48 h of therapy. MBCs of ceftizoxime against all recovered bacterial isolates were well below the measured concentrations of the antibiotic in the spinal fluid. Thus, the average concentrations in CSF achieved in this study were ten- to several hundredfold the inhibitory concentrations for *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*. Under the conditions of repeated intravenous doses (30 mg/kg per dose) given at 4-h intervals in the presence of inflamed meninges, ceftizoxime penetrated the meninges well, with mean concentrations in CSF of  $8.53 \mu\text{g/ml}$  and median CSF/serum ratios of 22.6%. The mean duration of fever after initiation of therapy was 3.7 days, and the incidence of neurological complications and side effects related to ceftizoxime were comparable to those which might be expected with conventional drug regimens.

The high level of activity of ceftizoxime against gram-negative pathogens and an acceptable activity against gram-positive pathogens makes this antibiotic an excellent candidate for treatment of community-acquired bacterial meningitis as well as nosocomially acquired meningeal infections. Further studies of ceftizoxime in bacterial meningitis are indicated, including comparative studies against current regimens and broad spectrum cephalosporins.

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