

## Penetration of Ceftazidime into Cerebrospinal Fluid of Patients with Bacterial Meningitis

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Four 2-g doses of ceftazidime were infused intravenously over 30 min at 8-h intervals, first between days 2 and 4 and again between days 11 and 20, in 11 patients with bacterial meningitis undergoing treatment with other antibiotics. Concentrations of ceftazidime in serum and cerebrospinal fluid samples obtained 120 or 180 min after dose 4 were measured by high-pressure liquid chromatography. Concentrations in cerebrospinal fluid ranged from 2 to 30  $\mu\text{g/ml}$ , depending on the sampling time and the time elapsed since the onset of the disease.

Ceftazidime, a new  $\beta$ -lactam antibiotic, is active in vitro against most bacterial species that cause meningitis, including pneumococci, meningococci, *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa*, and  $\beta$ -lactamase-producing *Haemophilus influenzae* strains. The penetration of ceftazidime into the cerebrospinal fluid (CSF) of patients with bacterial meningitis undergoing concurrent treatment with other antibiotics was evaluated in this study.

A total of 11 hospitalized patients with bacterial meningitis, 4 females and 7 males, were included in the study. Their mean age was 46 years (range, 16 to 78 years). All had macroscopically purulent CSF, with leukocyte counts ranging from 500 to 14,900 cells per  $\text{mm}^3$ , 60 to 100% of which were polymorphonuclear leukocytes. The protein concentrations in CSF were elevated (180 to 480 mg/dl), and the ratio of glucose in CSF and blood was decreased in all of the patients.

Eight of the patients were undergoing treatment with ampicillin in daily doses of 10 to 16 g. One patient was receiving a daily combination of cefotaxime (6 g) with gentamicin (15 mg/kg). One patient was receiving a daily combination of cefotaxime (6 g) with metronidazole (1.5 g), and one patient was receiving a daily combination of oxacillin (10 g) with netilmicin (5 mg/kg).

Each patient received four 30-min infusions of 2 g of ceftazidime at 8-h intervals in addition to the above regimens. These doses were administered twice, once between days 2 and 4 and again between days 11 and 20 of treatment with the other antibiotics.

The nature of the study was explained to each patient, and informed consent was obtained.

The concentrations of ceftazidime in serum and CSF were measured in samples drawn 120 or 180 min after ceftazidime dose 4. In all cases, lumbar puncture was performed only when clinically indicated; in no case was it done purely for the purpose of this study. All patients were monitored for possible adverse reactions.

The concentrations of ceftazidime in serum and CSF were determined by high-pressure liquid chromatography. The mobile phase of the chromatography procedure was a reverse-phase system consisting of sodium dihydrogenophosphate in water (0.05 M) and acetonitrile-acetic acid (91.5:8.5 [vol/vol]). The column was a  $\mu$ -bondapak C18 (Waters Associates, Milford, Mass.). The flow rate was set at 2 ml/min, and detector was fitted at 254 nm on a 0.05 absorbance unit. The retention time of ceftazidime was 5.5 min in this system. The peak height was used for quantitation, and two calibration curves were used, one for CSF and one for serum. The sensitivity limit was evaluated to be 0.1  $\mu\text{g}$  for 1 cm on the strip chart recorder. The reproducibility and recovery error of the procedure were <8.5% under these conditions. Standard dilutions were prepared with drug-free serum or CSF and stored at  $-30^\circ\text{C}$  with unknown samples. No degradation of the drug was observed over a 3-month storage period. The drug in unknown samples or in standard solutions remained unchanged when solutions were stored at  $-4^\circ\text{C}$  for 7 days. Perchloric acid (0.3 ml) was added to 0.3 ml of a standard or unknown sample in a polypropylene tube, and this preparation was then mixed for 5 min. The tubes were centrifuged for 10 min at  $2,000 \times g$  and  $4^\circ\text{C}$ . To 0.16 ml of supernatant was added 0.02 ml of potassium carbonate (1/10 dilution of a saturated

TABLE 1. Comparison of ceftazidime concentrations in CSF and serum

Patient no. (age [yr], sex) <sup>a</sup>	Etiological agent	Ceftazidime concn (µg/ml) from samples collected at:				% Ceftazidime in CSF from samples collected at:	
		Days 2-4		Days 11-20		Days 2-4	Days 11-20
		CSF	Serum	CSF	Serum		
1 (60, M)	<i>S. pneumoniae</i>	7.5	30	5.0	69	25	7.2
2 (16, M)	<i>Neisseria meningitidis</i>	2.5	125	2.0	123	2	1.6
3 (78, F)	<i>S. pneumoniae</i>	6.0	100	7.0	115	6	6.1
4 (54, M)	<i>Streptococcus sanguis</i>	30.0	65	ND <sup>b</sup>	ND	46	ND
5 (34, M)	<i>Listeria monocytogenes</i>	3.0	30	2.5	38	10	6.6
Mean ± SD		9.8 ± 11.4	70 ± 42	4.1 ± 2.3	86 ± 40	17.8 ± 18	5.4 ± 2.5
6 (49, F)	<i>Serratia marcescens</i>	12.5	20	21	40	62.5	52.5
7 (55, F)	<i>S. pneumoniae</i>	11	28	4	20	39.3	20
8 (55, M)	<i>Streptococcus durans</i>	10	21	3	35	47.6	8.6
9 (26, F)	<i>N. meningitidis</i>	14	56	ND	ND	25	ND
10 (68, M)	<i>L. monocytogenes</i>	5	24	5	21	29.8	23.8
11 (25, M)	<i>N. meningitidis</i>	4	15	3	25	26.7	12
Mean ± SD		9.4 ± 4.0	27.3 ± 14.7	7.2 ± 7.0	28.2 ± 8.8	37 ± 16	23.5 ± 17.5

<sup>a</sup> For patients 1 to 5, the sampling time was 120 min; for patients 6 to 11, the sampling time was 180 min.

<sup>b</sup> ND, Not determined.

solution), and 0.025 ml of this solution was injected into the chromatograph. This last solution was also stable for up to 7 days at 4°C.

Concentrations of ceftazidime in serum and CSF are shown in Table 1. Concentrations of ceftazidime in both CSF and serum at each of the sampling periods varied from patient to patient. The mean concentrations found between days 2 and 4, when the meninges were the most inflamed, were somewhat higher than those found between days 11 and 20, when the meninges were supposedly healed. By the Student *t* test for paired differences, the difference was not significant. However, when the percent penetration of ceftazidime into the CSF after 2 h (at both days 2 to 4 and days 11 to 20) was compared with that for samples collected 3 h after dosage, statistical significance was achieved ( $P < 0.1$ ). The meaning of such a difference is questionable, since it relies mainly upon the fact that levels of ceftazidime in serum were higher after 2 h than after 3 h.

No adverse reaction was noted, except in one patient who developed a skin rash. Because ceftazidime was administered only intermittently, no attempt was made to evaluate its contribution to control of the disease.

The concentrations of ceftazidime in CSFs of all patients in this study were far higher than the reported minimal inhibitory concentrations of

this drug for meningococci, pneumococci, and *H. influenzae* type b. Potentially, therefore, ceftazidime might replace ampicillin or penicillin in the treatment of infections caused by these organisms. The concentrations of ceftazidime in the CSF of most patients in this study were also within the therapeutic range against the gram-negative bacilli responsible for meningitis, including *P. aeruginosa* (2).

Krasinski and Nelson (1) studied the pharmacokinetics and the efficacy of ceftazidime in experimental *H. influenzae* type b meningitis. In infant rats, a dose of 25 mg of ceftazidime per kg yielded mean peak and trough drug concentrations in CSF of 4.8 and 1 µg/ml, respectively. Penetration of ceftazidime into CSF, expressed as the mean of all values in CSF and blood, was 22.8%. In the study of Krasinski and Nelson (1), there was no significant difference between the penetration of ceftazidime in control rat pups and in rat pups with meningitis. In experimental *Streptococcus pneumoniae*, *H. influenzae*, and *E. coli* meningitis, after a single dose of 25 mg of ceftazidime per kg, peak concentrations in CSF at 30 to 45 min were 3.2 µg/ml in *S. pneumoniae* meningitis, 5.4 µg/ml in *H. influenzae* meningitis, and 4.4 µg/ml in *E. coli* meningitis. The mean concentrations in CSF achieved after the continuous infusion of 25 mg of ceftazidime per kg/h for 9 h were 11.7, 17, and 22 µg/ml, respectively,

in each of the above meningitides (Y. Sakata, A. Boccazzi, and G. H. McCracken, Jr., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 232, 1982). These experiments in animal models suggest that ceftazidime may be useful for therapy of bacterial meningitis. However, extrapolation of animal data to humans is difficult, and therefore the penetration of ceftazidime into the CSF of humans must be studied before the drug is used in the treatment of bacterial meningitis. Our

results indicate that ceftazidime penetrates well into the CSF of patients with bacterial meningitis.

#### LITERATURE CITED

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