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Cefotaxime Diffusion into Cerebrospinal Fluid of Children with Meningitis

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Cefotaxime diffused consistently and in therapeutic levels into the cerebrospinal fluid (CSF) of 13 children successfully treated for bacterial meningitis. CSF cefotaxime levels early (6.0 μg/ml) and late (1.2 μg/ml) in treatment were severalfold the MBCs for the infecting organisms. After a single 40-mg/kg dose to each of five infants with ventriculostomies, mean CSF levels of cefotaxime were 6.4, 5.7, and 4.5 μg/ml at 2, 4, and 6 h, respectively.

The emergence of β-lactamase-producing strains of *Haemophilus influenzae* type b necessitated the inclusion of chloramphenicol for the initial therapy for childhood meningitis. Chloramphenicol is potentially toxic and produces unpredictable blood levels (13, 14), and chloramphenicol-resistant isolates of *H. influenzae* are now recognized. In addition, the combination of ampicillin and chloramphenicol may be antagonistic against some enteric gram-negative rods and group B streptococci, both of which are major pathogens in neonatal meningitis (2, 18).

Cefotaxime is a new, third-generation cephalosporin with marked antimicrobial activity against the common bacteria of childhood meningitis and against most enteric gram-negative bacilli that may cause neonatal meningitis (3, 8, 19). The aim of the present study was to assess the diffusion of cefotaxime into cerebrospinal fluid (CSF) and its efficacy in the treatment of childhood bacterial meningitis.

Of 20 patients with meningitis enrolled in the study, 14 had positive CSF cultures for bacteria, and 13 of these completed a full antibiotic treatment course. The age range of the patients was 9 days to 5 years. Cefotaxime was the only antibiotic used; it was administered intravenously at a dosage of 40 mg/kg every 6 h, usually for 14 days.

Spinal taps were performed 36 to 48 h after starting treatment in 19 patients (14 with bacterial and 5 with aseptic meningitis) and at the end of treatment in 13 patients. Simultaneous CSF and venous blood samples were collected 3 h after a dose. Plasma and CSF samples were frozen at −70°C until assayed.

Each of five infants (1 to 19 months old) with external ventriculostomy drainage tubes received a single dose of 40 mg of cefotaxime per kg intravenously over 30 min. The standard antibiotic therapy these patients received for shunt infection was not modified. CSF samples were obtained from the ventriculostomy tubing at 2, 4, and 6 h after the dose.

Levels of cefotaxime and its derivative desacetyl cefotaxime were assayed by high-pressure liquid chromatography as described by Lecaillon et al. (15) with minor modifications. The sensitivity of the method was 0.05 μg/ml, and the coefficient of variation was 1 to 3%.

The MIC and the MBC of cefotaxime for the various bacteria were determined in 0.5-ml portions of Mueller-Hinton broth by serial twofold dilutions with an inoculum of 10^5 to 10^6 CFU/ml. The MBC was the lowest concentration that produced 99.9% bacterial killing. Serum and CSF bactericidal titers against the various organisms were also determined by using serial twofold dilutions of 0.5 ml of serum or CSF and an inoculum of 10^5 to 10^6 CFU/ml. A bactericidal titer was the lowest dilution producing 99.9% killing.

All 13 patients treated with cefotaxime had sterile CSF after 36 to 48 h of treatment, and all recovered. None of the patients had significant hemopoietic, hepatic, or renal side effects.

The cefotaxime MBC for each of eight *H. influenzae* type b strains (including two β-lactamase positive) and two *Streptococcus pneumoniae* strains was ≤0.03 μg/ml. The MBC for each of two *Salmonella* species was 0.125 μg/ml, and for a group B streptococcus the MBC was 0.06 μg/ml. *Listeria monocytogenes* isolated from the CSF of a 16-day-old infant was resistant to cefotaxime (MBC ≥ 64 μg/ml) but was susceptible to ampicillin. Although this infant was improving clinically, ampicillin was added to the treatment on day 2 of hospitalization, and cefotaxime was discontinued on day 3 when the antibiotic susceptibilities became available.

There were 27 paired CSF and plasma samples available for study. Of these, 14 pairs were drawn early (after 36 to 48 h), and 13 pairs were drawn at the end of the 14 days of treatment. Cefotaxime and desacetyl cefotaxime levels are summarized in Table 1. Plasma and CSF cefotaxime levels were significantly lower at the end of treatment than they were early in treatment ($P < 0.05$), but the CSF diffusion ratio did not change significantly ($P = 0.79$). Early in treatment all patients, except the two with *Salmonella* meningitis, had CSF cefotaxime levels that were 25- to 275-fold (mean, 121) the MBCs for the infecting organisms. Late in treatment these levels were 17- to 97-fold (mean, 42) the respective MBCs. In the two patients with *Salmonella* meningitis, the CSF mean levels were 13-fold the MBC early in treatment and 5-fold the MBC late in treatment. Similarly, the mean blood and CSF levels and the CSF diffusion ratio of desacetyl cefotaxime were significantly lower at the end of treatment than early in treatment ($P < 0.05$).

Early in treatment, CSF was bactericidal to the 13 susceptible organisms at dilutions of 1:32 to 1:256 (mean titer, 1:108). At the end of treatment, CSF was bactericidal at dilutions of 1:8 to 1:128 (mean titer, 1:46).

The CSF leukocyte count and protein content were signi-

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TABLE 1. Cefotaxime and desacetyl cefotaxime plasma and CSF levels in 14 children with bacterial meningitis

Drug	Drug level (μg/ml)[a]					
	Early (36 to 48 h)			Late (14 days)		
	Plasma	CSF	Diffusion ratio (%)	Plasma	CSF	Diffusion ratio (%)
Cefotaxime	5.1–55.7 (16.7 ± 14.7)	0.74–38.8 (6.0 ± 10.2)	7.0–69.7 (27.7 ± 16.2)	1.7–13.6 (6.6 ± 4.3)	0.6–3.1 (1.2 ± 0.9)	4.5–64.7 (25.7 ± 21)
Desacetyl cefotaxime	2.5–20.1 (8.1 ± 4.2)	0.89–27.4 (4.6 ± 7.0)	12.2–219 (51.9 ± 54.5)	1.5–9.5 (5.4 ± 1.9)	0.5–2.1 (1.1 ± 0.8)	8.9–40.0 (20.8 ± 9.3)

[a] Values in parentheses represent the mean ± standard deviation.

ficantly lower and the sugar was significantly higher at the end of treatment. The concentration of cefotaxime in CSF correlated inversely with the CSF sugar level ($r = -0.66$). There was no demonstrable correlation with the CSF protein or leukocyte count.

Paired CSF and plasma samples obtained on day 3 of treatment from each of five children with aseptic meningitis showed a mean plasma cefotaxime level of 12.3 μg/ml (range, 1.3 to 32.7 μg/ml) and a mean CSF level of 1.4 μg/ml (range, 0.43 to 3.4 μg/ml). The mean CSF diffusion ratio was 17.3%. This ratio was lower but not significantly different ($P = 0.44$) from the ratio (27.7%) noted early in treatment of the 14 patients with bacterial meningitis.

Serial cefotaxime and desacetyl cefotaxime levels after a single 40-mg/kg dose in each of five infants with ventriculostomies are shown in Table 2. Highest cefotaxime levels in plasma and CSF occurred at 2 h. Cefotaxime mean half-life in four of these infants was 1.15 ± 0.58 h (range, 0.6 to 1.7 h) in plasma and 4.3 ± 3.1 h (range, 2.5 to 9 h) in CSF. At 6 h after a dose, the cefotaxime CSF level in each infant was still severalfold the MBC for the usual organisms of childhood meningitis.

The spectrum of antimicrobial activity of cefotaxime in this study is consistent with previous in vitro activity data (3, 8). In addition to its activity against the usual organisms of childhood meningitis, cefotaxime has been shown to be effective against many enteric gram-negative bacilli, including *Escherichia coli* and *Klebsiella*, *Proteus*, and *Serratia* species (4, 19). The antibiotic has low activity against *Pseudomonas aeruginosa* and is ineffective against enterococci and *L. monocytogenes* (16).

After parenteral administration, cefotaxime undergoes desacetylation in vivo. Approximately 20 to 36% of the administered dose is excreted unchanged in the urine, whereas 15 to 25% is excreted as desacetyl cefotaxime and 20 to 25% is excreted as two other metabolites, M2 and M3 (4, 6). Desacetyl cefotaxime possesses 1/10 of the activity of the parent compound against common gram-negative bacilli (19).

TABLE 2. Cefotaxime and desacetyl cefotaxime levels after single 40-mg/kg doses in five infants with ventriculostomy drainage

Interval postdose (h)	Cefotaxime level (μg/ml)[a]		Desacetyl cefotaxime level (μg/ml)[a]	
	Plasma	CSF	Plasma	CSF
2	9.5–59.1 (28.4)	2.3–10.8 (6.4)	6.4–13.2 (8.4)	0.4–4.6 (1.7)
4	0.8–27.0 (8.9)	2.0–10.4 (5.7)	2.8–6.0 (4.2)	1.1–4.2 (2.4)
6	0.5–4.3 (1.8)	1.8–12.0 (4.5)	0.3–4.4 (2.8)	1.4–3.0 (2.2)

[a] Values in parentheses represent means.

The lower plasma and CSF levels at the end of treatment in our patients are in contrast to the data of Neu et al. (17) in adults in whom serum levels after multiple dosages were shown to be predictable from single-dose studies. The reason for the lower levels in our patients was not clear but could be due to enhanced renal clearance.

Decazes et al. (5) have shown in an experimental animal model that a maximal bacterial kill rate was obtained when concentrations greater than 10 times the MBC were achieved in CSF. Cefotaxime levels more than 10 times the MBC for each of the infecting organisms were achieved in the CSF of all our patients early in the treatment course. Levels were also more than 10 times the MBC late in the treatment course in all patients except the two with *Salmonella* infections. Satisfactory bactericidal titers (1:8 to 1:256) were demonstrable in the CSF of all patients both early and late in treatment. It should be noted, however, that the MBC values and bactericidal titers depend on the inoculum and that bacterial densities in the CSF of some patients can be much higher than the standard 10^5 to 10^6 CFU/ml used in our studies (7).

The five children with aseptic meningitis had CSF cefotaxime levels that ranged between 0.43 and 3.4 μg/ml 36 to 48 h after initiation of treatment. This represented a mean CSF diffusion ratio of 17.3%. Cefotaxime diffused into the CSF in therapeutic quantities even in the absence of inflamed meninges, a finding in agreement with the animal studies reported by Armengaud et al. (1).

Kafetzis et al. (12) reported a cefotaxime CSF/serum ratio of 27 to 63% 1 to 2 h after a dose early in the treatment of meningitis in four neonates. In 13 additional infants and children, the diffusion ratio was lower, ranging between 3 and 37%. The CSF antibiotic level correlated with the CSF leukocyte count. In 27 adult patients treated with cefotaxime for bacterial meningitis, Humbert et al. (9) reported a CSF/plasma ratio of 4 to 42.6% early in treatment (day 1 or 3) and 4.4 to 54% late in treatment. Although the CSF antibiotic levels correlated positively with the CSF protein and leukocyte counts, there was no major decrease in the CSF level between day 3 and day 10 of treatment.

The mean plasma cefotaxime half-life in four of the infants with ventriculostomies was 1.15 ± 0.58 h. The youngest infant had the longest plasma half-life (1.7 h). Kafetzis et al. (11) reported the mean elimination half-life of cefotaxime in seven full-term neonates, 1 to 4 weeks old, to be 2.0 ± 0.4 h. These values are higher than the half-life of 1.04 ± 0.21 h reported in healthy adult subjects (10), indicating that cefotaxime elimination rate increases with age.

Our data indicate that cefotaxime diffuses sufficiently and

consistently into the CSF of infants and children early and late in the course of treatment of bacterial meningitis. Further assessment of its efficacy in the treatment of childhood meningitis, especially gram-negative meningitis in neonates, is warranted.

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