

Cerebrospinal Fluid Bactericidal Activity against Cephalosporin-Resistant *Streptococcus pneumoniae* in Children with Meningitis Treated with High-Dosage Cefotaxime

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We determined cefotaxime and desacetyl-cefotaxime concentrations in children with bacterial meningitis receiving high-dose cefotaxime (300 mg/kg of body weight/day) and concomitant dexamethasone therapy. The median peak cerebrospinal fluid cefotaxime and desacetyl-cefotaxime concentrations were 4.7 and 8.1 µg/ml, respectively. In vitro bactericidal activity (>99.9% killing in 6 h) was found in 17 (94%), 13 (72%), and 8 (44%) of 18 cerebrospinal fluid specimens against cefotaxime-susceptible, -intermediate (MIC, 1 µg/ml), and -resistant (MIC, 4 µg/ml) strains, respectively. High-dose cefotaxime, while safe, is not reliably sufficient therapy for cephalosporin-nonsusceptible pneumococcal meningitis, and combination therapy is recommended.

The extended-spectrum cephalosporins are widely used for empiric therapy of meningitis. The emergence of cephalosporin-resistant *Streptococcus pneumoniae* (CRSP) has led to treatment failures in children (11, 13) and adults (16) with pneumococcal meningitis. However, there are also descriptions of treatment successes with the extended-spectrum cephalosporins in patients with CRSP meningitis (20, 22). The National Committee for Clinical Laboratory Standards has recommended that pneumococcal strains for which MICs are 1 or ≥2 µg/ml be considered intermediately or highly resistant, respectively (17). Because experience with CRSP meningitis is anecdotal, it is unknown what proportion of patients with meningitis caused by intermediately or highly CRSP are likely to fail therapy with a cephalosporin alone.

The efficacies of different regimens that have been proposed for the treatment of CRSP meningitis are unknown. In areas where CRSP occurs with some frequency, it is recommended that an extended-spectrum cephalosporin be combined with vancomycin as empiric therapy for meningitis (9). This combination appears to be additive or even synergistic in vitro and in vivo (6, 8). In the few patients treated with this regimen reported to date, treatment was effective (7, 19). Another strategy that has been suggested for managing CRSP, especially intermediately CRSP, is to use larger dosages of an extended-spectrum cephalosporin (22). Experience with high-dose therapy is limited.

This study was undertaken to determine the bactericidal activity of high-dose cefotaxime in CRSP meningitis. We sought to evaluate the concentrations of cefotaxime and its metabolite, desacetyl-cefotaxime, in cerebrospinal fluid (CSF) when the drug was administered at a high dosage (300 mg/kg of body weight/day) to children with meningitis receiving concurrent steroid therapy and to assess the bactericidal activity of the children's CSF against an intermediately and a highly CRSP strain and a cephalosporin-susceptible control strain.

MATERIALS AND METHODS

This study was modified from a previous study of bactericidal activity in the CSF of children with meningitis (14). In the present study, cefotaxime (300 mg/kg/day) was administered intravenously every 8 h to 20 children with bacterial meningitis. All children also received dexamethasone at 0.3 mg/kg every 12 h intravenously. Dexamethasone therapy was started at the same time as antibiotic therapy and was continued for 4 days. Children who received antibiotics, other than cefotaxime, that are active against pneumococci were excluded from the study. After 24 to 48 h of therapy a lumbar puncture was repeated at either 2, 4, 6, or 8 h after the administration of a dose of 100 mg of cefotaxime per kg. Aliquots of CSF were immediately frozen at -70°C until they were analyzed. After the repeat lumbar puncture, if the causative organism was found to be cefotaxime susceptible, the daily dose of cefotaxime was reduced to 200 mg/kg. The concentrations of cefotaxime and desacetyl-cefotaxime in CSF and serum were determined by high-performance liquid chromatography (15). The lower limit of detectability of the assays was 0.5 µg/ml.

In vitro bactericidal activity. The bactericidal activity against each of three pneumococcal strains in CSF specimens was determined. The strains used have been described previously (14) and included a fully β-lactam-susceptible strain (strain S40), an intermediately CRSP strain (strain CTXi; MIC, 1 µg/ml), and a highly CRSP strain (strain CTXr; MIC, 4 µg/ml). Each pneumococcal strain was incubated in Mueller-Hinton broth with 10% bovine serum for 3 h to concentrations of approximately 10⁸ CFU/ml. From each CSF specimen, aliquots of 140 µl were placed in three microtiter wells, to each of which 10 µl of one of the pneumococcal suspensions was added. The resultant bacterial concentration in each well was approximately 5 × 10⁶ CFU/ml. Microtiter plates were incubated at 35°C for 6 h; 10 µl was drawn from each well after 2 and 6 h, and 10-fold dilutions were made in a 10% serum-saline mixture. Bacterial concentrations were determined by plating 10 µl from each dilution and from undiluted cultures on 5% blood agar plates containing β-lactamase (20 µl of β-lactamase per 20 ml of blood agar mixture). The lower limit of detection of the bacterial concentration was 100 CFU/ml. Bactericidal activity was defined as a >3 log₁₀ reduction in the bacterial concentration (>99.9% killing) in 6 h.

Approval. Written informed consent was obtained from the parents of the study subjects. The study was approved by the Committee for Research on Human Subjects at the University of the Witwatersrand and by the Institution Research Review Board at Baragwanath Hospital.

RESULTS

The organisms isolated from the 20 children enrolled in this study included *S. pneumoniae* (*n* = 10), *Haemophilus influenzae* type b (*n* = 7), and *Neisseria meningitidis* (*n* = 2). No organism was recovered from one child (leukocyte concentration in CSF, 11,000 cells/mm³). CSF findings are summarized in Table 1.

Cefotaxime assay. CSF and serum cefotaxime and desacetyl-cefotaxime concentrations are presented in Table 2. In four

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TABLE 1. Median age and CSF indices for 20 children with meningitis^a

CSF sample	Leukocyte count (cells/mm ³)	% Neutrophils	Erythrocyte count (cells/mm ³)	Protein concn (g/dl)	Glucose concn (g/dl)	No. with the following result/total no. tested	
						Positive Gram stain	Positive culture
Initial	312 (26–11,300)	92 (10–98)	14 (0–2,480)	2.4 (1–5.1)	0.2 (0–3.2)	18/20	19/20
Repeat ^b	412 (11–10,000)	76 (0–100)	4 (0–708)	1.1 (0.6–5.4)	2.0 (0–5.2)	4/19	1/19 ^c

^a The median age was 13.5 months (range, 4 to 140 months).

^b Spinal taps were repeated 24 to 48 h after the start of therapy.

^c The organism responsible was a penicillin-susceptible pneumococcus. In vitro bactericidal activity was demonstrated in this CSF specimen.

CSF specimens (one specimen at 4 h, two specimens at 6 h, and one specimen at 8 h), cefotaxime concentrations were below the limit of quantitation (0.5 µg/ml). Desacetyl-cefotaxime was detectable in all CSF specimens.

In vitro bactericidal activity. Sufficient CSF for bactericidal activity studies was obtained from 18 children. At the start of the bactericidal studies, the concentrations of strains S40, CTXi, and CTXr were 4.2×10^6 , 5.6×10^6 , and 3×10^6 CFU/ml, respectively. The changes in bacterial concentrations of strains CTXi and CTXr after 6 h of incubation with CSF specimens are presented in Fig. 1. Bactericidal activity (>99.9% kill) against the intermediate and fully resistant strains was found in 13 (72%) and 8 (44%) of 18 CSF specimens, respectively. Bactericidal activity against strain CTXr was observed in five of nine and three of nine specimens drawn 2 to 4 and 6 to 8 h, respectively, after the administration of a dose of cefotaxime. All but one CSF specimen (which resulted in 99.4% killing) demonstrated in 6 h bactericidal activity against the fully susceptible strain (strain S40), confirming the excellent activity of cefotaxime against a susceptible *S. pneumoniae* strain. After 2 h of incubation there was limited bactericidal activity against the CTXi or the CTXr strain (mean reduction, $<2 \log_{10}$ CFU/ml) in CSF specimens, whereas the concentrations of the susceptible strain were reduced on average by 2 to 3 \log_{10} CFU/ml by CSF specimens drawn at each time point (data not shown).

There was no correlation between CSF cefotaxime or desacetyl-cefotaxime concentrations and CSF bactericidal activity. For example, bactericidal activity was observed in 3 of 7 versus 5 of 11 specimens with cefotaxime concentrations of >4 versus <4 µg/ml, respectively. The sum of cefotaxime and desacetyl-cefotaxime concentrations also did not correlate with bactericidal activity.

Adverse reactions. High-dosage cefotaxime was well tolerated. Three children developed loose stools, without dehydration, that resolved within 24 to 72 h without any change in therapy. One child developed a genital *Candida* rash that resolved with topical antifungal therapy. One child had persistent fever for 17 days (which resolved after the discontinuation of phenytoin therapy), and one child had secondary fever lasting

3 days (with no apparent source). In neither of these two children did the fever appear to be related to cefotaxime therapy.

DISCUSSION

The most appropriate empiric regimen for suspected pneumococcal meningitis remains speculative but will vary geographically, depending on the incidence of antibiotic-resistant organisms. In areas where penicillin-resistant *S. pneumoniae* and, more particularly, CRSP occur (4), standard-dosage cephalosporin therapy will be ineffective in some cases. Alternative therapeutic regimens, such as the use of combination therapy or increased dosages of cephalosporins, have been proposed.

This study demonstrates that in children with meningitis who receive large dosages of cefotaxime, concentrations of the drug in CSF frequently exceed the MIC cutoff for cephalosporin resistance in *S. pneumoniae* (2 µg/ml). Even 8 h after the administration of a dose of cefotaxime, the concentrations in CSF exceeded 2 µg/ml in some children, indicating that concentrations in CSF can be above the MIC for resistant organisms for an entire dosing interval. These results explain the observation that some patients with highly CRSP meningitis have responded satisfactorily to cephalosporin therapy (12, 20, 22). The large variation in antibiotic pharmacokinetics in the CSF of humans with meningitis, observed in this and other studies (3), further explains the differences in response to infections caused by organisms with similar in vitro susceptibilities.

On the other hand, the cefotaxime concentrations in 40% of specimens were less than 2 µg/ml. In 33 and 17% of CSF specimens there was no antibacterial activity against the CTXr and CTXi strains, respectively. In such patients CRSP strains are unlikely to be cleared, especially if the drug is present at sub-MICs for a large part of the dosing interval. In addition, cefotaxime concentrations were frequently not >4 µg/ml, suggesting that more resistant strains will rarely be cleared with cephalosporin therapy alone.

The bactericidal activity of cefotaxime in CSF and the efficacy of cefotaxime against CRSP strains are greater than those

TABLE 2. Median concentrations of cefotaxime and desacetyl-cefotaxime in CSF and serum

Time (h) after dosing	Median (range) concn (µg/ml)			
	Cefotaxime		Desacetyl-cefotaxime	
	Serum	CSF	Serum	CSF
2 (n = 5)	19.7 (13.7–26.2)	4.7 (1.4–12.4)	12.7 (7.8–25.8)	8.1 (5.5–24.4)
4 (n = 6)	8.2 (3.1–38.1)	3.3 (<0.5–7.1)	9.1 (4.9–21.4)	5.7 (2.8–21)
6 (n = 5)	21 (<0.5–181)	1 (<0.5–23.7)	8.9 (<0.5–21.4)	3.7 (1.1–9.3)
8 (n = 5)	<0.5 (<0.5–11.3)	2.2 (<0.5–7.8)	1.2 (0.6–10.5)	3.4 (1.6–23.5)

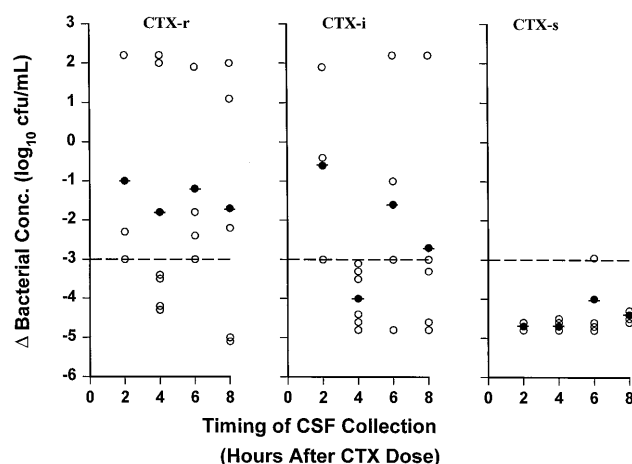


FIG. 1. Changes in bacterial concentrations after 6 h of incubation of pneumococcal strains with CSF specimens collected from children 2, 4, 6, or 8 h after the administration of a dose of 100 mg of cefotaxime (CTX) per kg. Values equal to or below $-3 \log_{10}$ CFU/ml (dashed line) indicate bactericidal activity (>99.9% killing) in the CSF specimen. Mean values are indicated by solid circles. CTX_r, CTX_i, and CTX_s indicate the highly cefotaxime-resistant (MIC, 4 μ g/ml), intermediately cefotaxime-resistant (MIC, 1 μ g/ml), and cefotaxime-susceptible strains, respectively.

predicted by the cefotaxime concentration alone because cefotaxime is metabolized to desacetyl-cefotaxime, which is less active than the parent compound but whose activity is additive or synergistic when it is present in combination with cefotaxime. A direct correlation between bactericidal activity and cefotaxime concentrations or the sum of cefotaxime and desacetyl-cefotaxime concentrations was not observed in this study, probably because of the complex interaction between cefotaxime and its metabolite.

On the basis of experiments with animals, concern has been expressed that antibiotic penetration into CSF may be adversely affected by concomitant steroid administration (2, 18). This has not been borne out by human studies with ceftriaxone therapy (10, 14). Earlier studies with children with bacterial meningitis not receiving steroid therapy reported mean peak CSF cefotaxime concentrations of 6.0 to 6.2 μ g/ml (1, 21). In those studies the dosages were smaller (160 to 200 mg/kg/day) than those used in the present study. However, in a recent French study with children with meningitis who received the same cefotaxime dosages as in the present study but without concomitant dexamethasone therapy (5), the median peak concentration in CSF was 4.4 μ g/ml, similar to the values observed in the present study. These data suggest that dexamethasone does not reduce the level of cefotaxime penetration into the CSF, but this needs to be confirmed in a randomized controlled study.

In conclusion, large dosages of cefotaxime (300 mg/kg/day) are safe in children but may not be reliably sufficient therapy for meningitis caused by CRSP strains, including intermediately resistant strains. Recommendations for cefotaxime therapy in children with meningitis will depend on the regional prevalence of resistant strains. In areas where CRSP strains are rare, cefotaxime at daily doses of 200 to 300 mg/kg or ceftriaxone at a dosage of 100 mg/kg/day should be adequate empiric therapy. Where intermediately CRSP strains are known to occur, albeit infrequently, it seems reasonable to recommend the upper range of cefotaxime dosages. In areas where CRSP (intermediately or fully resistant) occur with some frequency (e.g., $\geq 5\%$), empiric therapy with the combination of a

cephalosporin and vancomycin is recommended. The importance of susceptibility testing of strains from all patients with pneumococcal meningitis is emphasized. It is also recommended that CSF be recultured 36 to 48 h after starting therapy in patients infected with strains with suspected or confirmed penicillin or cephalosporin resistance or when susceptibility has not yet been determined.

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