Penetration of Cefoxitin into Cerebrospinal Fluid of Infants and Children with Bacterial Meningitis

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Three consecutive doses of 75 mg of cefoxitin per kg were given intravenously every 6 h (225 mg/kg), in addition to penicillin or ampicillin, to 24 patients on days 4 and 5 and 9 and 10 of therapy for meningitis. Haemophilus influenzae b was isolated from cerebrospinal fluid (CSF) of 21 patients, Streptococcus pneumoniae from 2 patients, and Neisseria meningitidis from 1 patient. The median minimal inhibitory and bactericidal concentrations of cefoxitin for 16 isolates of H. influenzae b were 0.312 and 0.625 μg/ml, respectively. Sixteen isolates of H. influenzae b and S. pneumoniae were killed by 2.5 μg of cefoxitin per ml. Mean levels in CSF peaked at 1 h at 6 and 4.9 μg/ml on days 5 and 10, respectively. CSF levels on days 5 and 10 were ≥ twice the median minimal inhibitory and bactericidal concentration in 20 and 18 patients, respectively. However, bacterial levels in CSF were ≥2.5 μg/ml in only 11 of 23 patients on days 5 and 10. No significant adverse effects were found. These data indicate that at this dosage, cefoxitin may not reach levels in the CSF required for killing all susceptible strains of H. influenzae b and S. pneumoniae.

Cefoxitin is a semisynthetic cefamycin, active in vitro against common meningal pathogens such as Neisseria meningitidis, Streptococcus pneumoniae, and ampicillin-susceptible and -resistant strains of Haemophilus influenzae type b (1, 2, 6, 8, 14, 17). The results of clinical trials in adults (6, 12, 13) and children (2, 8) have shown that this drug is safe and effective against infections with S. pneumoniae and H. influenzae b outside the central nervous system. Thus, cefoxitin has the potential for single-drug therapy for infants and children with suspected bacterial meningitis provided it effectively penetrates into the cerebrospinal fluid (CSF).

Available data are limited on the penetration of cefoxitin into the CSF (3, 7, 11). Galvao and co-workers (3) gave three 2-g doses of cefoxitin, in addition to ampicillin or penicillin, to 25 adult patients with purulent meningitis. The mean peak level 4 h after the third dose was 6.9 μg of cefoxitin per ml. Humbert and co-workers (7) reported CSF levels in patients with bacterial meningitis ranging from 2.9 to 4.7 μg/ml, depending upon the day of treatment and the time after the last dose of cefoxitin. Liu et al. (11) measured levels ranging from 1.25 to 5.0 μg/ml after multiple 2-g doses of cefoxitin in five adult patients who had no evidence of meningeal inflammation.

These data indicate that multiple doses of cefoxitin enter the CSF of adults in levels which are above the minimal inhibitory concentration (MIC) of most pediatric pathogens. However, no data are available showing CSF penetration in infants and children with meningitis. The present study was done to determine the ability of cefoxitin to enter the CSF of pediatric patients.

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MATERIALS AND METHODS

Patients from Grady Memorial Hospital or the Henrietta Egleston Hospital for Children were enrolled into the study between October 1979 and March 1981. Informed consent was obtained in all cases. Patients were initially treated with ampicillin IV (50 mg/kg) and chloramphenicol IV (25 mg/kg) every 6 h. Therapy was completed with ampicillin if β-lactamase negative H. influenzae type b was isolated or with penicillin if S. pneumoniae or N. meningitidis was cultured.

On days 4 and 5 and again on days 9 and 10 three doses of 75 mg of cefoxitin IV per kg were given every 6 h (225 mg/kg) by a 15-min rapid infusion, in addition to ampicillin or penicillin therapy. Lumbar punctures were performed by random assignment on days 5 and 10 at 0.5, 1, 2, or 4 h after the third cefoxitin dose. Serum samples were also obtained on days 5 and 10 after the third doses at the indicated times.

Samples of CSF and serum were treated with 40,000 U of penicillinase (Neutrapen; Difco Laboratories) for 15 min at 37°C before they were assayed in triplicate.
for cefoxitin content by the microbioassay technique of Simon and Yin (16), using E. coli strain MB 3804 as the test organism. Pilot experiments showed that cefoxitin levels in CSF or serum were not affected by the penicillinase treatment. Levels as low as 0.3 μg of cefoxitin per ml were reliably detected. Samples were stored at −70°C and assayed within 3 days of collection.

Serum concentrations were plotted against time by using a semilogarithmic scale, and half-life was calculated when levels were declining exponentially during the elimination phase. The formula used was ln 2/K, where K is the elimination rate constant represented by the slope of the regression line determined by the method of least squares (4). The volumes of distribution and plasma clearances were calculated by the method of Gurpide and Mann (5).

CSF samples were cultured on 5% sheep blood agar and on chocolate agar and thioglycolate broth. Isolates were identified by standard techniques (10). H. influenzae b isolates were tested for β-lactamase production by the rapid method of Jorgensen et al. (9). The MICs of cefoxitin for bacterial pathogens were determined by broth dilution, using Mueller-Hinton broth (Difco) with 2% supplement C (Difco). Twofold concentrations of cefoxitin from 20 to 0.019 μg/ml were prepared in 1-ml samples, and an inoculum of approximately 10⁵ organisms was added. The MIC was the smallest concentration of cefoxitin preventing visible growth after incubation at 37°C for 18 h. Minimal bactericidal concentrations (MBC) were determined by subculturing all clear tubes onto chocolate agar.

The statistical tests used were chi-square analysis and the two-tailed Student's t test, comparing the means of two small samples from normal populations (15).

All patients were observed for rashes, liver tenderness, jaundice, and phlebitis before and after cefoxitin administration. The complete and differential blood counts, a platelet count, a urinalysis, and the blood urea nitrogen, creatinine, and serum glutamic oxaloacetic transaminase (SGOT) levels were determined before and after each course of cefoxitin.

RESULTS

Of the 24 patients, 10 were female. Their ages ranged from 4 to 57 months (mean, 14.1 months). Thirteen were less than 12 months of age. S. pneumoniae and N. meningitidis were isolated from CSF of two and one patients, respectively. H. influenzae type b, β-lactamase negative, was recovered from CSF of 21 patients.

The median MIC of 16 isolates of H. influenzae type b was 0.312 μg/ml (range, 0.03 to 2.5 μg/ml). The median MBC was 0.612 μg/ml (range, 0.03 to 5 μg/ml). Both isolates of S. pneumoniae were inhibited and killed by 1.25 μg of cefoxitin per ml. Sixteen of 18 isolates (89%) were tested and killed by ≥2.5 μg/ml.

Concentrations of cefoxitin in serum and CSF were determined on days 5 and 10 of therapy for 23 patients (Fig. 1). One patient had no detectable cefoxitin in his CSF obtained 0.5 h after the end of infusion on day 10. Mean CSF levels were greatest 1 h after the third dose on both days. CSF levels on day 5 remained above the median MIC and MBC of the H. influenzae b isolates for 22 patients. On day 10, CSF levels of two patients were less than the median MBC. However, only 11 patients had levels on both days ≥2.5 μg/ml, which killed approximately 90% of isolates in vitro. By the paired t-test (two-tailed), CSF levels on day 5 did not differ significantly from those on day 10 (P > 0.15).

Maximum CSF penetration, as judged by the ratio of CSF to serum levels, occurred 4 h after the dose on both days (Fig. 2). No significant difference (P = 0.19) was found when the ratios of the CSF level to the concomitant serum level on day 5 were compared with those on day 10.

The plasma clearance was significantly greater on day 10 than on day 5 (P < 0.01), but serum half-lives and volumes of distribution did not significantly differ on the 2 days (Table 1).

Sixteen patients had no adverse effects. One patient had a maculopapular skin rash during the first course of therapy, which did not recur after the second course; this patient also had a transient elevation of SGOT to 159 U/ml. Six other patients had transiently elevated SGOT levels ranging from 68 to 354 U/ml (normal, 0 to 40 U/ml). The SGOT levels decreased despite the continued administration of cefoxitin, and no patient had jaundice. One infant had a transient eosinophilia. The drug was not discontinued in
any patient because of an adverse effect. No patient had phlebitis.

DISCUSSION

In this study, the CSF levels were greater than the median MBC in the majority of patients in our study. However, several isolates required substantially more cefoxitin for a bactericidal effect. Levels ≥2.5 μg/ml, which would kill approximately 90% of isolates, were achieved in only 11 of 23 patients on days 5 and 10 of therapy. Thus, these data suggest that CSF penetration at this dosage may not be adequate to kill all bacterial isolates in vivo.

The dosage used in this study of 75 mg of cefoxitin per kg every 6 hours was larger than those previously reported (2, 8). However, the half-lives and volumes of distribution were comparable with those previously reported (2) for a smaller dosage (37.5 mg/kg) every 6 hours. Although one-third of the patients had "side-effects", these were mainly transient elevations in SGOT levels, which resolved despite continued administration of cefoxitin. No patient had a serious reaction which resulted in discontinuing the drug.

These data indicate that CSF penetration of multiple doses of cefoxitin in infants and children with bacterial meningitis is comparable to that previously reported in adult patients (3, 7, 11). Although the dosage used had no significant adverse effects, these levels in CSF may not be capable of killing all bacterial pathogens. Thus, these data do not support the evaluation of cefoxitin in a clinical trial as single-drug therapy for pediatric patients with meningitis.

LITERATURE CITED


### TABLE 1. Pharmacokinetics of multiple doses of cefoxitin

<table>
<thead>
<tr>
<th>Day of therapy</th>
<th>Serum half-life (min)</th>
<th>Plasma clearance (ml/min)</th>
<th>Vol of distribution (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>47.7 ± 16</td>
<td>90.8 ± 8.2</td>
<td>5.858 ± 3.548</td>
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<tr>
<td>10</td>
<td>42.0 ± 4</td>
<td>122 ± 9.0</td>
<td>7.177 ± 4.872</td>
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<tr>
<td>Paired t-test</td>
<td>NS</td>
<td>P &lt; 0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

* a Mean ± one standard deviation.

* b NS, Not significant.


