Concentrations of Ceftriaxone in Cerebrospinal Fluid of Children with Meningitis Receiving Dexamethasone Therapy

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The penetration of ceftriaxone into cerebrospinal fluid (CSF) was studied with 11 children (mean age: 2 years, 4 months; range: 4 months to 8 years) with meningitis, receiving dexamethasone (0.15 mg/kg of body weight intravenously four times daily) as adjunctive therapy. Ceftriaxone was given intravenously at doses of 50 mg/kg twice daily to patients <18 months old and 100 mg/kg once daily to patients ≥18 months old. CSF was collected after 1 day of treatment at the expected peak concentration of ceftriaxone in CSF. Concentrations of ceftriaxone in CSF ranged from 0.7 to 9.2 mg/liter, with a mean value of 4.0 (standard deviation [SD], 2.9) mg/liter. Values were significantly higher for patients with CSF glucose levels of <1 mmol/liter on admission to the hospital than for patients with CSF glucose levels of ≥1 mmol/liter (mean values of 7.1 [SD, 2.2] mg/liter versus 2.2 [SD, 1.1] mg/liter; P < 0.001). After 1 day of treatment, ceftriaxone concentrations in the CSF of children receiving dexamethasone are similar to the mean values reported for children not treated with dexamethasone.

Current management of bacterial meningitis in children more than 2 months old now includes dexamethasone administration (1, 9). The beneficial effects of dexamethasone therapy have been clearly shown in a recent double-blind trial for 101 infants and children with bacterial meningitis (12). Dexamethasone is believed to improve the outcome of meningitis by modulating cytokine production (10, 11) and thus decreasing the patient's inflammatory response to bacterial endotoxins or endotoxin-like substances (13, 16). However, because of its action on meningeal inflammation, dexamethasone might reduce the penetration of antibiotics into cerebrospinal fluid (CSF). Were this the case, dexamethasone administration might result in delayed CSF sterilization (3), which has been shown to correlate with the occurrence of neurological sequelae (7). Indeed, concentrations of most antibiotics in CSF are higher in patients with inflamed meninges than in those with normal meninges and higher in patients with bacterial meningitis than in patients with aseptic meningitis (2). In experimental models of meningitis, the administration of steroidal agents has been shown to result in a marked decrease in CSF antibiotic levels (14). In this study, we measured the CSF correlations of an expanded-spectrum cephalosporin, ceftriaxone, for children with bacterial meningitis receiving dexamethasone as adjunctive therapy.

Between March 1992 and March 1993, 11 patients (mean age: 2 years, 4 months; range: 4 months to 8 years) with meningitis were included in the study. The infecting organism was Haemophilus influenzae in four cases, Streptococcus pneumoniae in three cases, Streptococcus agalactiae in one case, Neisseria meningitidis in one case, and unknown in two cases. The bacterial strains were isolated from CSF and, for five patients, from blood. All patients had normal renal function. Ceftriaxone was given intravenously over 15 min at a dose of 50 mg/kg of body weight twice daily (to patients aged less than 18 months) or of 100 mg/kg once daily (to other patients) for the first 48 h and then at a dose of 50 mg/kg once daily (to all patients). The total duration of therapy was 7 to 10 days, depending on the nature of the infecting organism and the clinical response. Intravenous amikacin (7.5 mg/kg twice daily) was administered in combination with ceftriaxone for the first 48 h. Dexamethasone was given intravenously at a dose of 0.15 mg/kg four times daily for the first 4 days. Other measures included fluid restriction and the administration of anticonvulsant drugs, as necessary.

CSF and blood samples were taken after 1 day of treatment, i.e., probably under non-steady-state conditions. Follow-up lumbar puncture was performed after the second (on patients aged 18 months or over) or third (on patients aged less than 18 months) dose of ceftriaxone. For each of the 11 patients, CSF was collected exactly 4 h 30 min after completion of ceftriaxone infusion, at the expected peak concentration of ceftriaxone in CSF (8). Blood samples were taken immediately before (trough) and 5 min after (peak) completion of the intravenous injection of ceftriaxone. Ceftriaxone concentrations in serum and CSF were measured by high-performance liquid chromatography (HPLC) (15) with a normal phase technique and a Spherisorb C18 NH-bonded phase column (100 mm; 5-µm internal diameter; Waters-Millipore). The mobile phase was a combination of acetonitrile (50 ml), hexadecyltrimethylammonium bromide (0.4 g), titrisol buffer pH 7.0 (5 ml), and HPLC-grade water (45 ml). The internal standard was procneicid (Theraplex Laboratories, Rhône-Poulenc, Paris, France). The bonded-phase column was connected to a UV spectrophotometer (254 nm). The lower limit of detection was 0.5 mg/liter and the within-day and between-day reproducibilities were assayed over a range of 1 to 400 mg/liter, with coefficients of variation of 2 and 5%, respectively. The Mann-Whitney U test was used for statistical analysis.

Ceftriaxone concentrations in serum and CSF according to the characteristics of CSF obtained on admission are indicated in Table 1. Peak and trough concentrations of ceftriaxone in serum ranged from 200 to 437 mg/liter (mean value: 301 mg/liter) and from 3.5 to 69 mg/liter (mean value: 26 mg/liter), respectively. Ceftriaxone was detected in the CSF of all

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patients, at concentrations between 0.7 and 9.2 mg/liter (mean value: 4.0 mg/liter). There was a negative correlation between concentrations of ceftriaxone in serum and CSF glucose levels. Ceftriaxone concentrations were significantly higher in patients with CSF glucose levels of < 1 mmol/liter than in those with CSF glucose levels of ≥ 1 mmol (mean values of 7.1 [standard deviation, 2.2] mg/liter versus 2.2 [standard deviation, 1.1] mg/liter, respectively; \( P < 0.001 \)). Ceftriaxone concentrations were higher in patients with CSF protein levels of > 1 g/liter than in those with CSF protein levels of ≤ 1 g/liter (mean values of 5.2 [standard deviation, 4.1] mg/liter versus 3.1 [standard deviation, 1.1] mg/liter), but the difference was not significant (\( P = 0.125 \)). Finally, concentrations of ceftriaxone in CSF did not correlate with CSF leukocyte counts.

These results show that the penetration of ceftriaxone into the CSF within the first 24 h of treatment is primarily dependent on the initial degree of meningeal inflammation, as assessed by the degree of hypoglycorrhachia on admission. Ceftriaxone concentration in our population were comparable to those reported for children with inflamed meninges not treated with dexamethasone (4, 5, 6). Thus, concentrations of ceftriaxone in CSF on day one of treatment are not substantially influenced by dexamethasone therapy. Ceftriaxone penetrates the blood-brain barrier sufficiently to achieve presumed therapeutic concentrations in CSF within the first 24 h of treatment in children receiving dexamethasone therapy.

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### REFERENCES


<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Infection organism</th>
<th>Serum concn (mg/liter)</th>
<th>CSF concn (mg/liter)</th>
<th>Leukocytes (10⁹/liter)</th>
<th>Protein (g/liter)</th>
<th>Glucose (mmol/liter)</th>
<th>CSF characteristicsa</th>
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<tr>
<td>1</td>
<td>5 mo/F</td>
<td>H.i.b.</td>
<td>244</td>
<td>39</td>
<td>4,700</td>
<td>1.60</td>
<td>&lt;0.55</td>
<td>&lt;10</td>
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<td>2</td>
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<td>43</td>
<td>720</td>
<td>1.20</td>
<td>&lt;0.55</td>
<td>&lt;10</td>
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<tr>
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<td>2 yr, 6 mo/M</td>
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<td>0.95</td>
<td>&lt;0.55</td>
<td>&lt;10</td>
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<tr>
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<td>170</td>
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<td>NDb</td>
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<td>ND</td>
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<td>11</td>
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<td>S.p.</td>
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<td>17</td>
<td>5,600</td>
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</table>

Total (mean ± SD) 301 (90) 26 (21) 4.0 (2.9) 2,764 (3,040) 1.06 (0.51) 1.86 (1.13) 33.6 (20.4)

a Bacteria were isolated from the CSF of all patients and from the blood of patients 2, 7, 8, 9, and 11. H.i.b, Haemophilus influenzae b; S.p., Streptococcus pneumoniae; S.a., Streptococcus agalactiae; N.m., Neisseria meningitidis.

b CSF obtained on admission, before antibiotic treatment.

Not determined.