

Pharmacokinetics of Ceftriaxone in Pediatric Patients With Meningitis

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Pharmacokinetics of ceftriaxone after a single dose of 50 or 75 mg/kg were determined in 30 pediatric patients with bacterial meningitis. Data for doses of 50 and 75 mg/kg, respectively, were as follows (mean \pm standard deviation): maximum plasma concentrations, 230 ± 64 and 295 ± 76 $\mu\text{g/ml}$; elimination rate constant, 0.14 ± 0.06 and 0.14 ± 0.04 h^{-1} ; harmonic elimination half-life, 5.8 ± 2.8 and 5.4 ± 2.1 h; plasma clearance, 51 ± 24 and 55 ± 18 ml/h per kg; volume of distribution, 382 ± 129 and 387 ± 56 ml/kg; mean concentration in cerebrospinal fluid 1 to 6 h after infusion, 5.4 and 6.4 $\mu\text{g/ml}$. A dosage schedule of 50 mg/kg every 12 h for bacterial meningitis caused by susceptible organisms is suggested for pediatric patients over 7 days of age.

Newer β -lactam antibiotics have been considered as an alternative to the current therapy for bacterial meningitis. There are features unique to these agents which make them particularly attractive, primarily their excellent penetration into cerebrospinal fluid (CSF), a broad spectrum of bactericidal activity including most enteric organisms and β -lactamase-producing *Haemophilus influenzae*, and relatively rare toxicity. Ceftriaxone offers additional advantages over other β -lactam antibiotics in its activity against group B streptococci and relatively long half-life.

The present study was designed to examine ceftriaxone pharmacokinetics after a single intravenous dose. Safety and tolerance were also evaluated.

MATERIALS AND METHODS

Patients and study design. The study population included five full-term neonates, 8 to 21 days, and 25 infants, aged 6 weeks to 2 years, who were receiving conventional therapy for documented bacterial meningitis at Arkansas Children's Hospital, Little Rock. Written informed consent was obtained from the parents of all participants. Between days 2 and 5 of therapy, when infection was judged to be under adequate control, and without alteration of the antimicrobial regimen, a single dose of ceftriaxone was administered intravenously over a 10-min period. The study was randomized so that half of the patients received 50 mg/kg and half received 75 mg/kg for this one infusion. Plasma samples were obtained just before infusion and at 15, 30, and 60 min and 2, 4, 6, and 10 h after infusion. A lumbar puncture was performed 1 to 6 h

after drug administration, and a sample of CSF was obtained for analysis of ceftriaxone concentration.

Susceptibility studies. Mean inhibitory concentrations (MICs) of ceftriaxone for each pathogen were determined by standard microtiter broth dilution (6). An inoculum of 10^5 organisms per ml in logarithmic growth phase was introduced into wells containing appropriate nutrients for that organism and serial dilutions of ceftriaxone.

Ceftriaxone concentrations. Plasma and CSF concentrations of ceftriaxone were analyzed by high-pressure liquid chromatographic techniques (9). To monitor ceftriaxone levels on a daily basis for patients receiving this investigational antibiotic, microbiological methodology was employed; briefly, this was a standard agar well diffusion assay in which susceptible *Escherichia coli* is used after dilution of the specimen with pooled plasma (1).

Pharmacokinetic determinations. The elimination rate constant, β , was determined from the regression line of the log plasma concentrations versus time by the NONLIN computer program (8). Serum half-life, $t_{1/2}$, was calculated from the equation: $t_{1/2} = 0.693/\beta$. Successive trapezoidal approximations and extrapolation were used to calculate the area under the serum concentration-time curve from time zero to infinity. Plasma clearance (Cl_p) was derived from the equation: $Cl_p = \text{dose}/\text{area under the serum concentration-time curve}$. The volume of distribution, V_d , was determined from the equation: $V_d = \text{dose}/(Cl_p \times \beta)$ (10).

Clinical and laboratory studies. Patients were carefully monitored for adverse reactions during infusion by one of the investigators and followed during the duration of hospitalization. In addition, laboratory parameters for bone marrow, renal, or hepatic toxicity were obtained preinfusion and at 2 and 4 days. These included CBC, blood urea nitrogen, creatinine, urinal-

TABLE 1. Organisms recovered from 30 patients with bacterial meningitis

Organism	No. of patients	Susceptibility to ceftriaxone ($\mu\text{g/ml}$)
<i>Haemophilus</i>		
β -Lactamase (-)	10	≤ 0.06
β -Lactamase (+)	3	≤ 0.06 –0.125
<i>Streptococcus pneumoniae</i>	3	≤ 0.06 –0.25
<i>Neisseria meningitidis</i>	4	≤ 0.03
<i>Escherichia coli</i>	3	≤ 0.03 –0.25
Group B streptococci	2	≤ 0.06
<i>Staphylococcus aureus</i>	2	2.0–4.0
<i>Listeria monocytogenes</i>	2	64
<i>Bacillus</i> sp.	1	8

ysis, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase.

RESULTS

Pathogens recovered from these 30 cases, along with their susceptibilities to ceftriaxone, as determined by MICs, are included in Table 1. Predictably, the organisms most frequently isolated from infants were *H. influenzae*. All recovered organisms except two isolates of *Listeria monocytogenes* and one *Bacillus* sp. were susceptible to ceftriaxone at concentrations well below the range of those achievable in CSF; these three resistant organisms were recovered from neonates. Two CSF isolates of *Staphylococcus aureus* from infants with ventriculoperitoneal shunts, previously placed for hydrocephalus, were susceptible at 2 and 4 $\mu\text{g/ml}$.

Results for the five neonates, all over 7 days of age, were not different from those for infants in the present study, so determinations were combined for analysis. Pharmacokinetic data are summarized in Table 2 and Fig. 1.

Most importantly, concentrations in CSF were usually 10 to 100 times greater than the MIC for recovered bacteria. The measured levels of ceftriaxone in the two infants with *S. aureus* were two- to threefold higher than the MIC for those organisms. Other exceptions included three resistant organisms already described.

Ceftriaxone administered intravenously over a 10-min period was well tolerated by infants and neonates, with no local or systemic reactions observed. There were no changes in laboratory parameters used to assess bone marrow, renal, or hepatic toxicity.

CSF drug concentrations are presented in Table 2 simply as the mean for all samples obtained; the wide variation in the time that CSF was obtained (1 to 6 h) prevents a full statistical analysis of penetration into CSF for these study subjects. The CSF-to-plasma concentration ratio ranged from 1.8 to 24.6% after a single dose. Results for individual patients are presented in Fig. 2. Mean values expressed as a percentage of plasma levels were as follows for the 50-mg/kg dose: 4.8% at 2 h, 11.8% at 3 h, 3.5% at 4 h, 14.6% at 5 h, and 10.0% at 6 h. For the 75-mg/kg dose, the percent penetration was 6.2% at 2 h, 7.7% at 3 h, 4.8% at 4 h, 3.5% at 5 h, and 12.9% at 6 h.

DISCUSSION

Previously published studies have demonstrated the in vitro activity of ceftriaxone against a wide variety of gram-positive and gram-negative bacteria (5, 7, 14). Pertinent to considerations of meningitis therapy are susceptibilities of the three major etiological agents causing disease in infants and those two most commonly associated with infection in neonates. The concentration (in micrograms per milliliter) of ceftriaxone inhibiting 90% of clinical isolates in vitro were as follows: *H. influenzae*, <0.004; *Neisseria meningitidis*, 0.004; *Streptococcus pneumoniae*, 0.03; *E. coli*, 0.12; and group B streptococci, 0.10.

Subsequent studies in a rabbit meningitis model (11) demonstrated penetration into the CSF at a concentration that was >7% of the

TABLE 2. Ceftriaxone pharmacokinetics for infants and children

Dose (mg/kg)	Pharmacokinetic data ^a					
	β (h^{-1})	$t_{1/2\beta}$ (h^{-1})	Cl_p (ml/h per kg)	V_d (ml/kg)	Maximum plasma concn ($\mu\text{g/ml}$)	CSF concn ($\mu\text{g/ml}$)
50	0.14 ± 0.06	5.8 ± 2.8	51 ± 24	382 ± 129	230 ± 64	5.4
75	0.14 ± 0.04	5.4 ± 2.1	55 ± 18	387 ± 56	295 ± 76	6.4

^a β , Elimination rate constant; $t_{1/2\beta}$, elimination half-life, Cl_p , plasma clearance; V_d , volume of distribution. Values are expressed as means \pm standard deviation.

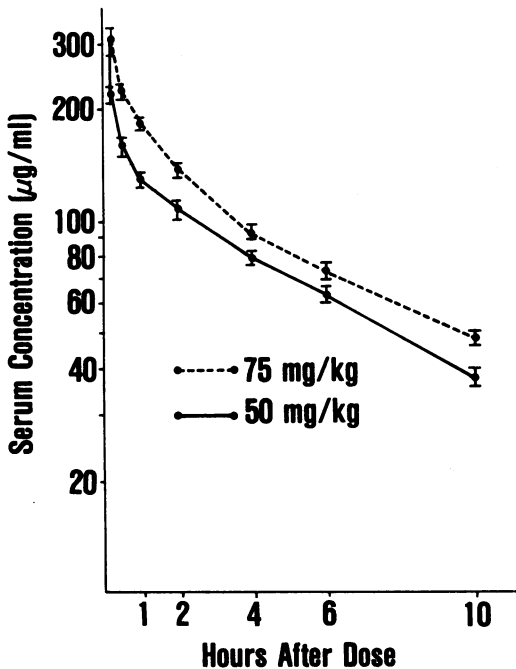


FIG. 1. Dose and mean plasma concentration-time curves \pm standard deviation after a single intravenous infusion of ceftriaxone.

concomitant serum levels. Compared with other β -lactam antibiotics, ceftriaxone exhibited the longest half-life and duration of bactericidal activity and was the most effective in reducing bacterial counts of *E. coli* and group B streptococcus type III test strains in CSF.

Initial pharmacokinetic data in normal adult volunteers indicated an elimination half-life of approximately 8 h (2, 13). Similar studies in five infants and five young children demonstrated a slightly lower half-life at 6.5 h (12).

Preliminary studies for the treatment of bacterial meningitis in neonates, infants, and children have been published (4). Clinical efficacy and tolerance studies in adults with serious bacterial infections have recently been published and have established ceftriaxone as an agent with a high degree of efficacy and a low incidence of toxicity (3, 7). These reports support its selection as single drug therapy for a variety of clinical presentations.

The present studies have focused on aspects of meningitis therapy in children primarily to establish dosage recommendations for future treatment protocols and to examine CSF drug levels relative to susceptibility of invading pathogens. A tentative dosage schedule of 100 mg/kg given in two intravenous infusions every 24 h is suggested. Preliminary results in a recently completed comparative clinical trial of cef-

triaxone versus standard therapy for bacterial meningitis have confirmed these recommendations (R. W. Steele and R. W. Bradsher, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Atlantic City, N.J., abstr. no. 317, 1982).

Most important for the treatment of meningitis are data concerning penetration of antibiotics into CSF. CSF levels 5 to 10% of concomitant plasma concentrations are comparable to those previously reported in animal models (11) and human studies (4). These CSF levels exceeded the MIC for common pathogens by at least 10-fold; this appears to be the most critical determining factor for success of therapy.

These and other studies indicate that ceftriaxone would not be effective for meningitis caused by *L. monocytogenes* or enterococci and must be considered of questionable value for the treatment of *Pseudomonas aeruginosa* and *S. aureus* meningitis. When any of these pathogens are initially suspected, ceftriaxone should be used in combination with other agents pending results of cultures and susceptibility tests.

Repeated measurement of antibiotic levels is important in monitoring the adequacy of antimicrobial therapy. In the present studies, a simple microbiological assay was comparable to high-pressure liquid chromatographic methodology for assaying serum and CSF concentrations of drug. Thus, more ready application in the usual clinical setting of a medical center is ensured.

In summary, we found that ceftriaxone penetrated into the CSF of infants and neonates to a

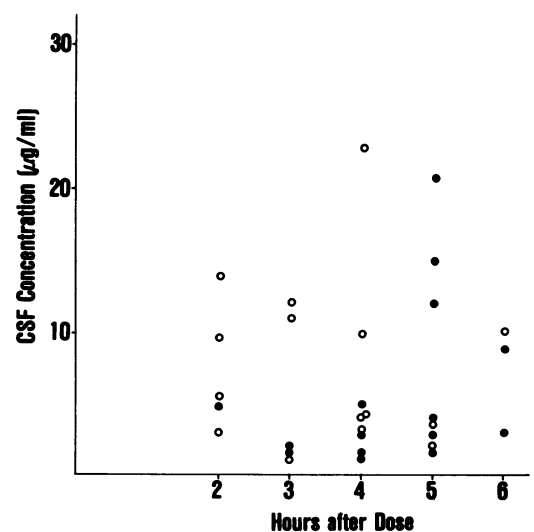


FIG. 2. CSF concentrations of ceftriaxone at various times after a single intravenous dose of 50 mg/kg (●) or 75 mg/kg (○) in 30 pediatric patients with bacterial meningitis.

degree that should provide adequate levels to treat the usual bacterial causes of meningitis. The measured plasma half-life was longer than those of other cephalosporins and investigational β -lactam antibiotics, ensuring a greater duration of bactericidal activity for individual doses. These initial pharmacokinetic data establish a tentative dosage schedule of 50 mg/kg every 12 h for the treatment of meningitis in pediatric patients over 7 days of age.

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