

## Pharmacokinetics and Cerebrospinal Fluid Bactericidal Activity of Ceftriaxone in the Treatment of Pediatric Patients with Bacterial Meningitis

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Single-dose pharmacokinetics of ceftriaxone were determined in 19 patients with proven bacterial meningitis. The dosage was 50 mg of ceftriaxone per kg. The plasma concentration time curve declined in a biexponential manner. The mean peak plasma concentration was 207  $\mu\text{g/ml}$ , and the elimination half-life was 4 h. In 12 patients, multiple-dose pharmacokinetics were determined after a loading dose of 75 mg of ceftriaxone per kg, followed by 50-mg/kg doses every 8 h in 5 patients or every 12 h in 7 patients. The mean peak plasma concentration was 230  $\mu\text{g/ml}$  after the first dose and 263  $\mu\text{g/ml}$  after the last dose. Of 12 patients, 5 had trough values that were larger after multiple doses than after a single dose. Mean penetration of ceftriaxone into cerebrospinal fluid was 3.1%. The median cerebrospinal fluid bactericidal titer against the patients pathogens was  $>1:1,024$  and  $<1:2,048$ . The drug was well tolerated without adverse effects.

The most common causes of bacterial meningitis in infants and children younger than 5 years of age are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Because of the increasing incidence of  $\beta$ -lactamase-producing strains of *H. influenzae* (1, 6, 14) and the appearance of *S. pneumoniae* strains which are resistant to penicillin (2-5, 8), the initial treatment of bacterial meningitis currently consists of ampicillin and chloramphenicol. However, strains of *H. influenzae* resistant to both ampicillin and chloramphenicol have been recently reported (12, 24). These changes in susceptibilities of the principal meningitis pathogens have prompted the search for alternative antibiotics.

Ceftriaxone (Ro 13-9904) is a cephalosporin derivative with broad antimicrobial activity, including the organisms that cause bacterial meningitis (10, 20). In experimentally induced meningitis in rabbits, ceftriaxone exhibited greater bactericidal activity and a larger reduction in the concentrations of *H. influenzae* and *S. pneumoniae* in the cerebrospinal fluid (CSF) than did moxalactam, cefoperazone, cefuroxime, or chloramphenicol (15).

For these reasons, we studied the pharmacokinetics and bactericidal activity of ceftriaxone in infants and children with bacterial meningitis.

### MATERIALS AND METHODS

**Population characteristics.** Thirty-two infants and children with bacterial meningitis admitted to Children's Medical Center or Parkland Memorial Hospital, Dallas, from February to November 1981 were included in the study. Their ages ranged from 2 to 42 months (mean, 12.1 months), their weights ranged from 5.1 to 21.1 kg (mean, 9.6 kg), and their heights ranged from 53 to 110.5 cm (mean, 77.8  $\pm$  13 cm).

There were 20 boys and 12 girls. No patient had a history of hypersensitivity or other adverse reactions to  $\beta$ -lactam antibiotics. Ceftriaxone was only administered to patients who had normal serum glutamic oxalacetic transaminase, blood urea nitrogen, and serum creatinine values. These values were repeated after therapy in patients given multiple doses of ceftriaxone.

In all cases, a bacterial strain was recovered from cultures of CSF before therapy: *H. influenzae* type b (23  $\beta$ -lactamase-negative and 3  $\beta$ -lactamase-positive strains), *N. meningitidis* group B (4 strains) and *S. pneumoniae* (2 strains).

Informed written consent was obtained from the parents before the patients were enrolled in the study.

**Susceptibility studies.** In vitro susceptibilities of the bacterial isolates to ampicillin and ceftriaxone were determined with a microtiter broth dilution technique. The bacterial inoculum was from  $1.0 \times 10^4$  to  $5.9 \times 10^5$  colony-forming units. Twofold dilutions of antibiotics from 1.0 to 0.001  $\mu\text{g/ml}$  were tested for ceftriaxone and from 8 to 0.008  $\mu\text{g/ml}$  for ampicillin. Mueller-Hinton broth containing 1% supplement C (Difco Labora-

TABLE 1. Susceptibilities to ampicillin and ceftriaxone of bacteria recovered from CSF cultures of 32 patients

Strain	No. tested	Concn ( $\mu\text{g/ml}$ ) <sup>a</sup>			
		Ampicillin		Ceftriaxone	
		MIC	MBC	MIC	MBC
<i>H. influenzae</i> $\beta$ -lactamase negative	23	0.0625–0.25 (0.125)	0.156–0.5 (0.125)	0.001–0.008 (0.001)	0.001–0.008 (0.002)
<i>H. influenzae</i> $\beta$ -lactamase positive	3	0.312–4.0 (0.625)	5– $\geq$ 8	0.001 (0.001)	0.002 (0.002)
<i>N. meningitidis</i>	4	0.01 (0.015)	0.01–0.08 (0.02)	$\leq$ 0.002 (0.002)	$\leq$ 0.002 (0.002)
<i>S. pneumoniae</i>	2	0.01 and 0.08	0.01 and 0.08	0.001 and 0.016	0.001 and 0.016

<sup>a</sup> Range and (median) values. MIC, Minimal inhibitory concentration; MBC, minimal bactericidal activity.

ories) was used for isolates of *H. influenzae* and *N. meningitidis*, and Todd-Hewitt broth was used for isolates of *S. pneumoniae*.

The minimal inhibitory concentration was defined as the smallest concentration of drug which inhibited visible growth of the organism after 16 to 18 h of incubation at 37°C. The minimal bactericidal concentration was determined by quantitative subculture onto chocolate agar for *H. influenzae* or onto blood agar plates for *N. meningitidis* and *S. pneumoniae* and was defined as the smallest concentration of antibiotic which killed 99.9% or more of the original inoculum.

**Antibacterial titers in CSF.** CSF bacteriostatic titers against the patients' pathogens were determined in microtiter plates by using twofold dilutions of CSF in either Mueller-Hinton broth with 1% supplement C for isolates of *H. influenzae* or *N. meningitidis* or Todd-Hewitt broth for isolates of *S. pneumoniae*. An inoculum of approximately  $10^5$  colony-forming units was used. Bactericidal activity was determined by quantitative subculture of broth onto chocolate agar or blood agar as described above.

**Administration of ceftriaxone.** A single dose of 50 mg/kg was given as a 10- to 15-min intravenous infusion of a solution containing 40 to 50 mg of ceftriaxone per ml. One patient received a dose of 75 mg/kg. Ceftriaxone was given on day 1 through day 3 of meningitis therapy in addition to conventional treatment with ampicillin, chloramphenicol, or both.

Multiple doses of ceftriaxone were administered to 12 patients with a loading dose of 75 mg/kg followed by 50 mg/kg doses given either every 8 h (5 patients) or every 12 h (7 patients). Ceftriaxone was given for 4 to 5 days, whereas ampicillin was administered for the entire 10-day period. Samples from the patient receiving chloramphenicol were analyzed for ceftriaxone by using a *Morganella morganii* strain resistant to chloramphenicol.

Plasma samples were obtained before, at completion of the 10- to 15-min infusion and at 0.5, 1, 2, 4, and 6 h after the infusion. In those patients who received multiple doses, a sample was collected at 8 or at 12 h after the dose on first and last day of the study. In some patients, samples were obtained 24 and 48 h after therapy was stopped. Plasma samples were collected either by a heparin lock or by finger stick.

A CSF sample was obtained by a randomization

schedule at 0.5, 2, 4, or 6 h postinfusion of single doses and at 8 or 12 h in those patients who received multiple doses. In the latter patients, a CSF sample was also obtained on the last day of ceftriaxone therapy; the interval after the dose was the same for both samples in each patient.

**Ceftriaxone assay.** Samples were stored at  $-20^\circ\text{C}$  until assayed within 4 days of collection. Plasma and CSF were assayed by the agar diffusion micromethod (22), using *Escherichia coli* Ro 1346 (provided by Hoffmann-LaRoche, Inc.) or *M. morganii* as the test strain.

Because ceftriaxone is 95% protein bound (20), plasma samples and laboratory standards were prepared in 100% pooled human plasma. CSF samples were diluted in 1% phosphate buffer, pH 6.0, and compared with standards prepared in buffer. Ampicillin was inactivated by addition of penicillinase (Penase, Difco Laboratories) to the samples.

**Pharmacokinetic analysis.** Plasma curves were analyzed by the NONLIN least-squares computer program (21; C. M. Metzler, G. L. Elfring, and A. J. McEwen, *Biometrics* 30:562, 1974). The plasma concentration time curves were biexponential and were best fitted to a two-compartment pharmacokinetic model (7, 13, 17).

## RESULTS

Susceptibilities of the bacterial isolates from CSF cultures of the 32 patients to ceftriaxone are shown in Table 1.

The median minimal bactericidal concentration of ceftriaxone (0.002  $\mu\text{g/ml}$ ) was one-sixtieth of that of ampicillin (0.125  $\mu\text{g/ml}$ ) for  $\beta$ -lactamase-negative *H. influenzae* strains. A ceftriaxone concentration of  $\leq 0.002$   $\mu\text{g/ml}$  killed the three  $\beta$ -lactamase-positive *H. influenzae* strains compared with an ampicillin concentration of 5 to  $\geq 8$   $\mu\text{g/ml}$ . Against the few *N. meningitidis* and *S. pneumoniae* strains tested, ceftriaxone was 5- to 20-fold more active than ampicillin.

**Single-dose pharmacokinetics.** Plasma concentrations of ceftriaxone at completion of the 10- to 15-min infusion were from 120 to 375  $\mu\text{g/ml}$

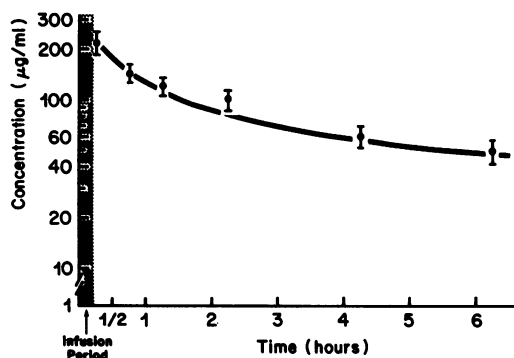


FIG. 1. Plasma concentration time curve and pharmacokinetics for 20 patients given a single dose of 50 mg of ceftriaxone per kg.

(mean, 207  $\mu\text{g/ml}$ ) in 19 patients (Fig. 1). The patient who was given a 75-mg/kg dose had a peak plasma concentration of 300  $\mu\text{g/ml}$  and a concentration at 6 h of 54  $\mu\text{g/ml}$ .

The plasma concentration time curve was biexponential and best fitted to a two-compartment pharmacokinetic model (7, 13, 17) (correlation coefficient, 0.998). There was an initial rapid fall in concentrations representing the  $\alpha$ -phase or distribution phase ( $t_{1/2\alpha}$ ) of 0.25 h, followed by the  $\beta$ -phase or elimination phase ( $t_{1/2\beta}$ ) of 4 h. The calculated plasma clearance rate was 38.4 ml/min per 1.73  $\text{m}^2$  and the apparent volume of distribution was 350 ml/kg. Because plasma specimens were collected over only approximately one half-life, these pharmacokinetic calculations may not be accurate.

The mean CSF concentrations in 19 infants and children are shown in Table 2. The half-life of ceftriaxone in CSF could not be calculated because the largest concentration was observed in the specimen taken at 6 h. The mean penetration of ceftriaxone into CSF was 3.1%, expressed as a ratio of calculated areas under the curve in CSF to plasma times 100. A CSF concentration of 4.6  $\mu\text{g/ml}$  was measured at 40 min in one patient who received a 75-mg/kg

dose. There was no correlation between the concentration of ceftriaxone in the CSF and CSF cell count. However, there was an association, although not statistically significant ( $P = 0.08$ , Pearson correlation coefficients), between the ceftriaxone concentration and the protein content in CSF.

The inhibitory and bactericidal titers in CSF against the patients' pathogens were determined in specimens from 20 infants. The CSF bactericidal titers were from 1:64 to  $\geq 1:2,048$  (median titer,  $>1:1,024$  to  $<1:2,048$ ; mode,  $\geq 1:2,048$ ). With the exception of three samples in which there was a one-dilution difference, the bacteriostatic and bactericidal titers were identical. The titers were significantly correlated with the concentrations of ceftriaxone in CSF ( $P = 0.017$ , Pearson correlation coefficient).

**Multiple-dose pharmacokinetics.** Multiple doses of ceftriaxone were administered to 12 infants and children with meningitis. Plasma concentration time curves were constructed from assayed samples obtained after the first and last doses (Fig. 2 and 3). In all patients, the initial 75-mg/kg dose was followed by 50-mg/kg doses given intravenously every 8 or 12 h. Peak (end of infusion) concentrations in plasma were from 145 to 400  $\mu\text{g/ml}$  (mean,  $230 \pm 70.2 \mu\text{g/ml}$ ) after the first dose and from 150 to 410  $\mu\text{g/ml}$  (mean,  $263 \pm 79.8 \mu\text{g/ml}$ ) after the last dose. In 8 of 10 patients, peak concentrations were larger after multiple doses than after the first dose. After the first dose, the ceftriaxone concentrations at 12 h were from 23 to 46  $\mu\text{g/ml}$  (mean,  $33.9 \pm 8.5 \mu\text{g/ml}$ ), whereas the predose (approximately 12 h after the previous dose) values after multiple doses administered every 12 h were from 13 to 52.5  $\mu\text{g/ml}$  (mean,  $32.3 \pm 18.7 \mu\text{g/ml}$ ). Two of five patients had slightly larger plasma concentrations after multiple than after single doses of the drug. When ceftriaxone was given every 8 h, trough concentrations were from 45 to 75  $\mu\text{g/ml}$  (mean,  $54.4 \pm 12.6 \mu\text{g/ml}$ ) after the first dose and from 46 to 85  $\mu\text{g/ml}$  (mean,  $70.5 \pm 14.7 \mu\text{g/ml}$ ) after multiple doses.

TABLE 2. Ceftriaxone concentration in CSF

Ceftriaxone dose	Concn ( $\mu\text{g/ml}$ ) at indicated time after dose					
	0.5 h	1 h	2 h	4 h	6 h	12 h
Single dose (50 mg/kg)	0.26–3.3 <sup>a</sup> (2.1 $\pm$ 1.6)	1.2–3.0 (2.2 $\pm$ 0.08)	3.2 (3.2 $\pm$ 0)	1.4–4.3 (2.5 $\pm$ 1.2)	2.8–7.2 (4.2 $\pm$ 2.1)	
Multiple doses						
Dose 1 (75 mg/kg)	1.8, 3.7	4.2	1.2, 6.0	3.6, 4.3	7.2	1.8, 4.4
Last dose (50 mg/kg)	5.2, 10.4	5.2	3.0, 8.85	1.45, 4.8	4.8	0.94, 2.4

<sup>a</sup> Range and (mean  $\pm$  1 standard deviation) provided when three or more samples were analyzed.

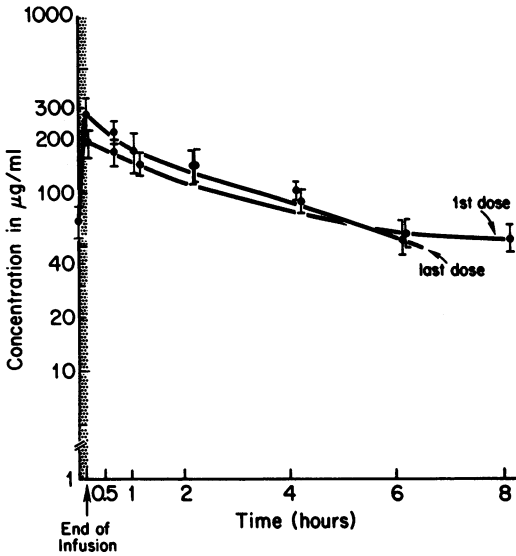


FIG. 2. Plasma concentration time curves of patients with bacterial meningitis who received multiple doses of ceftriaxone. A loading dose of 75 mg/kg was followed by 50 mg/kg every 8 h.

The plasma concentrations 24 h after therapy was stopped ranged from  $<0.075$  to  $17.0 \mu\text{g/ml}$  (mean,  $6.6 \pm 6.5 \mu\text{g/ml}$ ). At 48 h after the last dose of ceftriaxone, plasma levels ranged from  $<0.075$  to  $1.5 \mu\text{g/ml}$  (mean,  $0.96 \pm 0.71 \mu\text{g/ml}$ ).

These plasma concentration time curves were not subjected to pharmacokinetic analysis because of the relatively few subjects studied,

resulting in considerable scatter of the data, and because plasma samples were obtained for only approximately one half-life. The elimination half-life was estimated in 10 of 20 data sets by fitting plasma concentrations of individual subjects observed between 2 h and 6, 8, or 12 h to a monoexponential equation by using the NONLIN program. The half-life values (3.7 to 6.1 h; mean, 4.7 h) after the first dose were similar to those (4.3 to 6.1 h; mean, 5.3 h) after multiple doses given every 8 or 12 h.

The mean concentrations in CSF when ceftriaxone was administered every 8 h ranged from  $1.8 \mu\text{g/ml}$  at 0.5 h to  $7.2 \mu\text{g/ml}$  at 6 h after the first dose and from  $5.2 \mu\text{g/ml}$  at 0.5 h to  $4.8 \mu\text{g/ml}$  at 6 h after multiple doses (Table 2). When ceftriaxone was given every 12 h, the mean CSF concentration in four patients 12 h after the first dose was  $2.8 \pm 1.1 \mu\text{g/ml}$  and  $1.6 \pm 0.73 \mu\text{g/ml}$  after multiple doses (Table 2).

The bactericidal titers in CSF after first and multiple doses were  $\geq 1:512$  against the pathogens causing meningitis. In 10 specimens, including 3 of 4 specimens obtained 12 h after the dose, the bactericidal titers were  $\geq 1:1,024$  (Table 3).

**Safety and tolerance.** The administration of ceftriaxone was well tolerated by all of the patients, and there were no adverse reactions.

## DISCUSSION

Stoekel et al. (23) showed by simple compartmental analysis that the area under the curve, total body clearance, and volume of

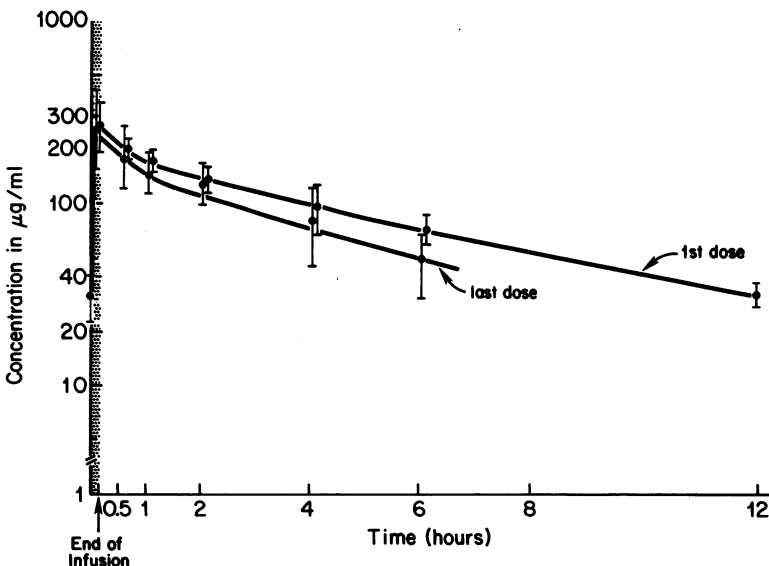


FIG. 3. Plasma concentration time curves and pharmacokinetic values for patients after the first dose and multiple doses of ceftriaxone administered every 12 h.

TABLE 3. CSF concentrations and bactericidal titers of ceftriaxone 12 h after single and multiple doses

Patient no.	CSF concn ( $\mu\text{g/ml}$ )		Bactericidal titer	
	Dose 1	Steady state	Dose 1	Steady state
1	4.4	0.94	1:2,048	1:1,024
2	1.8	1.0	$\geq$ 1:2,048	$\geq$ 1:2,048
3	2.4	2.0	1:1,024	1:512
4	2.5	2.2	$\geq$ 1:4,096	1:2,048

distribution of ceftriaxone increased nonlinearly with dose, whereas serum half-life was independent of dose. The pharmacokinetics of this third-generation cephalosporin in adults (23) were strikingly different from those computed in infants and children in our study (Table 4) and in the study of Schaad and Stoeckel (19). The volume of distribution expressed in  $1.73 \text{ m}^2$  was approximately twice as large in the pediatric patients as in adults, which may explain the larger serum concentrations per unit dosage observed in adults. The half-life values in our pediatric patients were shorter than those in the pediatric patients in the study of Schaad and Stoeckel (19) and in adults in the study of Stoeckel et al. (23). This may be owing to the shorter period over which plasma specimens were obtained. Another important variable between our study and the studies by the Swiss investigators is that their patients were either normal healthy adults or children with viral infections or epilepsy, whereas our patients had bacterial meningitis. It is possible that inappropriate secretion of antidiuretic hormone in our meningitis patients caused initial retention of fluid, followed by diuresis which affected the extracellular fluid volume and elimination rate of ceftriaxone.

Our data indicate that the penetration of ceftriaxone into the CSF is similar to that of penicillin G in infants and children with meningitis (9) and is considerably smaller than that of other  $\beta$ -lactams such as ampicillin (25) or moxalactam (11, 18). These data in infants are similar to the penetration values for ceftriaxone observed in experimental *H. influenzae* or *S. pneumoniae* meningitis in rabbits (15). In that animal model, penetration of ceftriaxone into CSF was smaller than that of the other new  $\beta$ -lactam antibiotics. However, CSF bactericidal activity against *H. influenzae* and *S. pneumoniae* was substantially greater with ceftriaxone (15). The median bactericidal titer in our study patients was  $\geq$ 1:1,024 and  $\leq$ 1:2,048, which exceeds by manyfold the bactericidal titer of ampicillin against  $\beta$ -lactamase negative *H. influenzae*.

Ceftriaxone has been previously used for ther-

TABLE 4. Single-dose pharmacokinetics of ceftriaxone in pediatric patients and in adults

Parameter	Stoeckel et al. (23) (6 adults)	Schaad and Stoeckel (19) (10 infants and children)	Present study (20 infants and children)
Dose	1,500 mg	50 mg/kg	50 mg/kg
Mean wt (kg)	70	11.6	9.9
Body surface area ( $\text{m}^2$ )	1.73	0.52	0.45
Mean plasma half-life (h)	7.8	6.6	4
Mean volume of distribution (liters per $1.73 \text{ m}^2$ )	8.62	15.7	13.3
Plasma clearance rate (ml/min per $1.73 \text{ m}^2$ )	13	27.9	38.4

apy of meningitis in a noncontrolled study of 62 patients from Senegal (M. Cadoz, F. Denis, D. Peyramon, I. Dipmar, Program Abstr. Int. Congr. Chemother. 12th, Florence, Italy, abstr. no. 989, 1981). In 16 cases, sterilization was achieved within 2 h of a single dose of from 25 to 70 mg of ceftriaxone per kg. Eighteen patients died, but only one death of a patient with meningitis caused by *P. aeruginosa* (minimal inhibitory concentration,  $\geq$ 128  $\mu\text{g/ml}$ ) was attributed to drug failure.

On the basis of the information from experimental meningitis and of our pharmacokinetic data in pediatric patients with meningitis, we have initiated a study of the efficacy and safety of ceftriaxone in infants and children with meningitis. The regimen selected is of an initial 75-mg/kg dose, followed by 50-mg/kg doses given intravenously every 12 h. We have shown that this schedule produces peak and trough CSF bactericidal titers of  $\geq$ 1:512 against the three principal pathogens causing meningitis.

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