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Comparison of Ceftriaxone and Ampicillin Plus Chloramphenicol for the Therapy of Acute Bacterial Meningitis

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Ceftriaxone, a new third-generation cephalosporin, appears to be promising for the therapy of acute bacterial meningitis. The 90% MBCs of ceftriaxone against 54 recent cerebrospinal fluid isolates of *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* were ≤0.06 to 0.25 μg/ml. We examined the efficacy and safety of ceftriaxone therapy of meningitis in Bahia, Brazil. The study was conducted in two phases; in phase A, ceftriaxone was coadministered with ampicillin. The mean cerebrospinal fluid concentrations of ceftriaxone 24 h after an intravenous dose of 80 mg/kg were 4.2 and 2.3 μg/ml on days 4 to 6 and 10 to 12 of therapy, respectively. These concentrations were 8- to more than 100-fold greater than the 90% MBCs against the relevant pathogens. In phase B, ceftriaxone (administered once daily at a dose of 80 mg/kg after an initial dose of 100 mg/kg) was compared with conventional dosages of ampicillin and chloramphenicol in a prospective randomized trial of 36 children and adults with meningitis. The groups were comparable based on clinical, laboratory, and etiological parameters. Ceftriaxone given once daily produced results equivalent to those obtained with ampicillin plus chloramphenicol, as judged by cure rate, case fatality ratio, resolution with sequelae, type and severity of sequelae, time to sterility of cerebrospinal fluid, and potentially drug-related adverse effects. The cerebrospinal fluid bactericidal titers obtained 16 to 24 h after ceftriaxone dosing were usually 1:512 to >1:2,048 even late in the treatment course, compared with values of 1:8 to 1:32 in patients receiving ampicillin plus chloramphenicol. Ceftriaxone clearly deserves further evaluation for the therapy of meningitis; the optimal dose, dosing frequency (every 12 h or every 24 h), and duration of therapy remain to be determined.

Bacterial meningitis remains a relatively common disease worldwide. The recent emergence of pneumococci resistant to penicillin or chloramphenicol or both (18, 27), the emergence of *Haemophilus influenzae* strains resistant to ampicillin or chloramphenicol or both (16, 32, 44, 45), the continued high mortality due to gram-negative bacillary meningitis despite therapy with aminoglycosides or chloramphenicol or both (7), and the potential toxicity of chloramphenicol have all prompted the search for alternative agents for the therapy of meningitis.

Ceftriaxone (RO13-9904) is a new third-generation cephalosporin with excellent in vitro activity against all major meningeal pathogens (1, 14, 17, 28, 39; Scheld, Rocha, Sande, and Bryan, Am. J. Med., in press), except *Listeria monocytogenes*. In addition, ceftriaxone was the most rapidly bactericidal agent within the cerebrospinal fluid (CSF) in vivo when it was compared with moxalactam, cefotaxime, ampicillin, and netilmicin in experimental animal models of meningitis induced by *Escherichia coli*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, or *H. influenzae* (9, 11, 24, 34; Scheld et al., in press). Although the ceftriaxone concentrations in CSF are only a small fraction (≅3 to 9%) of the concurrent serum concentrations, the bactericidal activity of this agent in CSF routinely exceeds the 90% MBC (MBC_{90}) for the most common meningeal pathogens (5, 13, 20, 21, 26, 35; Scheld et al., in press).

Encouraging results have been obtained by using ceftriaxone for therapy of meningitis in open clinical trials (3, 4). Ceftriaxone administered every 12 h proved to be equivalent to ampicillin and chloramphenicol for the therapy of meningitis in children in recent prospective randomized studies (8, 12, 40). Because of the long serum elimination half-life (4.2 to 6.5 h in infants and children and 5.8 to 8.8 h in adults [5, 13, 26, 30, 35, 38, 41]), ceftriaxone may prove to be effective for therapy of bacterial meningitis when it is administered only once daily. In addition, the concentration-dependent protein binding of ceftriaxone (35, 42) produces increased serum concentrations of free drug at higher dosages. Thus, less frequent administration of higher doses may enhance entry of free ceftriaxone into the CSF.

The purposes of this study were to determine the CSF concentrations of ceftriaxone 24 h after a dose of 80 mg/kg and, if these concentrations proved to be greater than 10-fold above the MBC of the major meningeal pathogens, to compare ceftriaxone with ampicillin plus chloramphenicol for therapy of bacterial meningitis in a prospective randomized clinical trial in Salvador, Bahia, Brazil.

MATERIALS AND METHODS

Selection of patients. Informed consent was obtained from the parents or appropriate relatives of all patients. The guidelines for human experimentation of the University of Virginia School of Medicine and Universidade Federal da Bahia were followed in the conduct of this clinical study.

Patients were treated at Hospital Couto Maia, which serves as a referral center for patients with meningitis for almost the entire state of Bahia, Brazil. The laboratory aspects of the study were performed at Hospital das Clinicas

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of the Federal University of Bahia in Salvador or at the University of Virginia in Charlottesville. Patients with historical, clinical, and laboratory findings consistent with acute bacterial meningitis were admitted to the study. Patients who were less than 2 months old or pregnant or who had a history of allergy to β-lactam antibiotics or recurrent meningitis were excluded from entrance. In phase B we evaluated patients who (i) survived ≥6 h after hospitalization, (ii) had CSF culture or Gram stain proof of bacterial meningitis, or (iii) had ≥10,000 leukocytes per mm^3 of CSF (predominantly polymorphonuclear leukocytes), a protein concentration of ≥250 mg/dl, and a glucose concentration ≤20 mg/dl. Patients who had a history of prior antibiotic usage and whose cultures were negative were excluded.

Drug administration. This study was conducted in two phases and was similar to a previous study conducted in Brazil (15). Phase A was designed to evaluate the pharmacokinetics of ceftriaxone and to determine the CSF concentration achieved 24 h after a dose of 80 mg/kg at two time points during the disease course. Phase B was a comparative randomized trial. Patients in phase A received ampicillin (300 mg/kg per day intravenously in six divided doses) plus ceftriaxone given as a loading dose of 75 mg/kg followed by 50 mg/kg every 12 h. However, on days 4 to 6 and again on days 10 to 12 of therapy, a single 80-mg/kg dose of ceftriaxone was given, followed by collection of CSF and serum 24 h later. Ampicillin treatment was continued at the above dose throughout therapy, and ceftriaxone was given at a dose of 50 mg/kg every 12 h except on the 2 days when the 80-mg/kg dose was administered. After inactivation of the ampicillin by the addition of 10% penicillinase (Difco Laboratories, Detroit, Mich.), the CSF ceftriaxone concentrations were determined by the bioassay method described below. Since these ceftriaxone concentrations achieved in CSF 24 h after dosing far exceeded the MBC_{90} values of the major meningeal pathogens, a prospective randomized trial was initiated.

Phase B was an open prospective randomized trial in which we compared a group receiving ceftriaxone (administered as a loading dose of 100 mg/kg, followed by 80-mg/kg doses every 24 h) with a group receiving ampicillin (given as a 75-mg/kg loading dose, followed by 50 mg/kg every 4 h) plus chloramphenicol (given as a 50-mg/kg loading dose, followed by 25 mg/kg every 6 h). All doses were intravenous. All patients except those with meningococcal disease were treated for at least 10 days; patients with meningococcal disease were given 7 days of therapy. Patients were enrolled and assigned randomly (by a random number table) to either the group receiving ampicillin plus chloramphenicol or the group receiving ceftriaxone alone.

Clinical and laboratory evaluation. The clinical condition and severity of the meningitis of patients upon admission were graded as mild (alert or somnolent), moderate (disorientation or stupor), or severe (frank coma). Patients were monitored daily for signs of meningeal irritation, neurological changes, fever response, and allergic reactions. A lumbar puncture was repeated 24 to 48 h after admission, on day 10 to 12 of therapy, and at other times as clinically indicated. Follow-up of the patients was attempted 1 to 2 weeks after discharge. Both groups were monitored for adverse effects by determining pre- and posttreatment complete blood and platelet counts and biochemistries (liver enzymes, including transaminases and alkaline phosphatase, total and indirect bilirubin, blood urea nitrogen, creatinine) and by urinalysis.

Bacteriological studies. MICs and MBCs were determined for all meningeal pathogen isolates from Hospital Couta Maia, which were transported on slants of chocolate agar enriched with 5% IsoVitaleX. Standard macrotube dilution methods (National Committee for Clinical Laboratory Standards) were used. *H. influenzae* and meningococci were grown in Mueller-Hinton broth supplemented with 5% Fieldes (Difco) enrichment. Pneumococci were grown in tryptic soy broth supplemented with 5% defibrinated sheep blood.

Members of the *Enterobacteriaceae* were grown in tryptic soy broth. MBCs were determined by plating 0.001-ml portions from one turbid and three clear tubes from the MIC assays after 18 to 24 h of incubation. *Haemophilus* and *Neisseria* strains were subcultured to chocolate agar supplemented with 5% IsoVitaleX and pneumococci were plated onto blood agar plates and incubated in 10% CO_2 at 37°C. Members of the *Enterobacteriaceae* were plated onto tryptic soy agar. The MBC was read after 24 h of incubation as the concentration of antibiotic that killed 97.0% of an inoculum of 10^5 bacteria (e.g., ≤3 CFU/ 0.001 ml plated). Identical results (or, at most, one dilution higher) were obtained when we repeated the MBC determinations in Charlottesville, when 99.9% killing was used as the MBC endpoint. Bactericidal titers were determined for patient CSF samples by using broth (see above) as the diluent and 10^5 CFU/ml as the inoculum size. After 18 to 24 h of growth, subcultures were transferred to plates as described above, and the bactericidal titer was determined as the dilution that killed 97.0% of the inoculum. CSF obtained while patients were on antibiotics was cultured directly and diluted 1:100 and 1:1,000 before culturing to dilute the antibiotic concentration below the MBC for the pathogens. Failure to perform this dilution step has been shown to result in false-negative CSF cultures while patients are receiving therapy (12). All isolates of *H. influenzae* were tested for β-lactamase activity by using a rapid colorimetric assay involving chromogenic cephalosporin disks (Calbiochem-Behring, San Diego, Calif.).

Antibiotic assay. Simultaneous specimens of CSF and serum for assays of ceftriaxone concentrations were obtained from all patients on different days of therapy and at different intervals after antibiotic administration. All samples were transported on ice and stored at −40°C before assay (within two weeks). The samples were deproteinized by adding acetonitrile (Sigma Chemical Co., St. Louis, Mo.) before assay. A standard agar well diffusion method was used (13), with *E. coli* 1346 (provided by Hoffman-LaRoche, Nutley, N.J.) as the indicator organism in antibiotic medium no. 1 (Difco) agar base. Standards for assays of serum and CSF concentrations for phase A were prepared in pooled human serum and 0.85% NaCl, respectively. Ampicillin in the specimens was inactivated by adding 10% penicillinase. Proof of complete inactivation of ampicillin in the specimens was accomplished by preparing parallel standards of ceftriaxone and ceftriaxone plus 30 μg of ampicillin per ml plus penicillinase. The standard curves were identical. All specimens were tested in triplicate. Standards for serum and CSF for phase B were prepared in pooled human serum and CSF, respectively.

RESULTS

A total of 13 patients were enrolled in phase A, and these patients received ampicillin plus ceftriaxone. Nine patients were less than 1 year old, three patients were between 2 and 5 years old, and one patient was 29 years old. The results of bacterial isolation were as follows: *H. influenzae*, eight patients; *S. pneumoniae*, 1 patient; purulent sterile CSF, 4 patients. The mean CSF level of ceftriaxone on days 4 to 6 of

TABLE 1. Reasons for patient exclusion in phase B

Reason for exclusion	No. in control group (ampicillin plus chloramphenicol)	No. in ceftriaxone group
Death ≤6 h after admission	0	2
Incorrect dosing schedule	1	1
Nonbacterial etiology	1	3
Suppressive antibiotic therapy before enrollment	1	5[a]
Patient less than 2 months old	1	1

[a] $P > 0.4$, as determined by the Fischer exact test.

therapy (24 h after dosing) was 4.2 ± 1.9 μg/ml (range, 1 to 5.4 μg/ml; $n = 7$). In contrast, on days 10 to 12 of therapy the mean concentration was 2.3 ± 0.9 μg/ml (range, 1.0 to 3.7 μg/ml; $n = 7$). A ventricular fluid level of 12.5 μg/ml 24 h after the dose was noted on day 4 of treatment in one patient. Because these concentrations all exceeded (≥10-fold) the MBCs for the three most common bacterial pathogens 24 h after dosing, we proceeded with phase B, the comparative trial.

A total of 52 patients were originally enrolled in phase B, the controlled comparative trial in which we evaluated ceftriaxone alone (given every 24 h) and ampicillin plus chloramphenicol: 16 patients were excluded, as shown in Table 1. There were 18 patients in each group. The pretreatment characteristics of the patients in each group are shown in Table 2. The groups were very comparable on the basis of clinical and laboratory criteria. The mean duration of meningeal symptoms was ≅4 days in both groups, reflecting the delays in hospitalization often encountered in this area of Brazil. We feel that the statistical difference in the frequency of positive blood cultures between the groups has little significance. Blood cultures are not routinely drawn from patients with meningitis at Hospital Couta Maia. Several cultures were contaminated, whereas others may have been drawn after antibiotic treatment was initiated. The etiological agents are shown in Table 3. It should be noted that the ceftriaxone group included two patients with meningitis due to members of the *Enterobacteriaceae* (one of which had failed 48 h of therapy with ampicillin plus chloramphenicol). None of the *H. influenzae* isolates produced beta-lactamase.

Response to therapy. Patients could be evaluated if survival exceeded 6 h after admission. There were three deaths in the control group and four in the ceftriaxone group. In the control group, a 14-year-old girl with pneumococcal meningitis was admitted comatose after 2 days of high fever. She developed respiratory arrest 6 h later and required assisted ventilation. She died after 7 days, but a CSF sample obtained on hospital day 3 was sterile. Another death occurred in a 12-month-old female with meningitis due to *H. influenzae*. She had a cardiorespiratory arrest 10 h after admission and died on hospital day 3. The CSF culture remained positive for 38 h after the initiation of treatment despite MBCs for ampicillin and chloramphenicol of <0.06 and 0.125 μg/ml, respectively. A third death occurred in a 12-month-old female with *H. influenzae* meningitis 20 h after admission; the organism was subsequently lost.

The deaths in the ceftriaxone group included a poorly nourished 5-month-old female with a history of fontanelle swelling for 14 days before admission, which had followed trauma to the skull and a broken leg. *H. influenzae* was cultured from the CSF. The course of this patient was complicated by an enlarging subdural empyema which required needle aspiration and neurosurgical drainage. All CSF and empyema cultures were negative by day 3 of therapy, with ceftriaxone levels as high as 50 μg/ml in the empyema fluid. However, the patient never improved neurologically and died on day 12 of hospitalization. No autopsy was allowed. The other deaths in the ceftriaxone group all occurred in less than 24 h. One 3-month-old female with *S. pneumoniae* meningitis died of septic shock with deep jaundice, hepatomegaly, and hypotension. CSF cultures were positive at the time of death despite a CSF bactericidal titer of ≥1:2,048 and adequate antibiotic levels in the CSF. The third death was a 7-month-old male who died of a cardiorespiratory arrest 16 h after admission with *H. influenzae* disease, and the fourth was an 8-month-old female from whom no isolate was identified.

Sequelae. The neurological complications consisted of decreased hearing (assessed by physical exam) in two patients in each group. Two of these four patients had an associated otitis media at the onset of meningitis. One patient in the control group developed seizures on day 8 of therapy and generalized motor dysfunction and was found to have diffuse cortical atrophy by computed tomography. A 4-month-old patient with *H. influenzae* meningitis developed persistent generalized hypotonia. One patient in the ceftriaxone group had not regained full speech and motor ability 1 month after discharge.

Fever and meningeal signs. The patients in the control group who could be evaluated were febrile (>37.8°C) for 4.47 ± 4.19 days (mean ± standard deviation); however, five patients were never febrile. Ceftriaxone patients averaged

TABLE 2. Characteristics of patients in phase B (a prospective, randomized trial)

Group	No. of males	No. of females	No. in the following age groups:[a]				No. having seizures before admission[b]	No. with hemoglobin level of <10 g/100 ml	No. with CSF glucose level of ≤20 mg/100 ml	No. with initial CSF leukocyte count of:				No. having positive blood cultures/ no. evaluated[c]	Mean duration of illness before therapy (days)
			2 month-2 years	2–6 years	6–17 years	>17 years				>10,000	5,000–10,000	1,000–5,000	≤1,000		
Ceftriaxone	8	10	12	1	3	2	9	12	10	6	1	8	3	0/7	4.1
Ampicillin + chloramphenicol	7	11	13	2	3	0	4	11	13	9	2	6	1	5/8	3.7

[a] The patients in the group treated with ceftriaxone ranged in age from 3 months to 59 years; the patients in the group treated with ampicillin plus chloramphenicol ranged in age from 4 months to 14 years.

[b] $\chi^2 = 3.003$; $P > 0.05$.

[c] $P = 0.018$, as determined by the Fischer exact test.

TABLE 3. Etiology of meningitis for patients in phase B

Organism	No. of patients treated with:	
	Ceftriaxone	Ampicillin + chloramphenicol
H. influenzae	7	9
S. pneumoniae	2	3
N. meningitidis	1	2
Salmonella sp. (group B)	1	0
Klebsiella sp.[a]	1	0
None (culture negative)[b]	6	4

[a] Moved to ceftriaxone group after bacteriological failure on ampicillin and chloramphenicol.

[b] Includes positive Gram stain proof of bacterial etiology (three in the ceftriaxone group, three in the control group), CSF with >10,000 leukocytes per mm^3 (>50% polymorphonuclear leukocytes), >250 mg of protein per dl and ≤20 mg of glucose per dl.

5.28 ± 4.4 days of fever, with only two never having a febrile response. The numbers of days of nuchal rigidity or other signs of meningeal irritation were similar in the two groups (5.8 ± 1.6 and 6.0 ± 2.3 days for the control and ceftriaxone groups, respectively).

Adverse effects. No serious adverse reactions potentially related to the study drugs occurred in either group. One patient in the ceftriaxone group developed a decrease in hemoglobin concentration exceeding 2 g during therapy, compared with five patients in the control group. Five of these six patients had infections with *H. influenzae*, which is often associated with the development of anemia. One ceftriaxone-treated patient developed transient mild neutropenia (1,435 polymorphonuclear leukocytes per/mm^3), and two patients in the control group developed moderate but transient neutropenia (930 and 600 polymorphonuclear leukocytes per/mm^3). No changes in hepatic or renal function tests thought to be drug related were noted in either group. Two patients who were not in the randomized study developed a pruritic maculopapular rash after more than 10 days of ceftriaxone treatment. Diarrhea occurred in two patients in each group but was transient and mild and did not require discontinuation of therapy. Therefore, ceftriaxone was well tolerated.

Laboratory evaluation. Nearly all of the CSF cultures (83 to 85%) were rendered sterile rapidly (within 24 h of initiation of therapy), except for two cases in each group. Therapy with ampicillin plus chloramphenicol did not eradicate a *Klebsiella* isolate from the CSF after 48 h, nor was this treatment effective in one *H. influenzae* case that was fatal after 36 h. Ceftriaxone steadily cleared the CSF of *Salmonella* sp. (group B), from very heavy growth (≥10^7 CFU/ml) initially to only 300 CFU/ml after six doses with bactericidal titers of 1:32 to 1:64; the culture was sterile thereafter. Ceftriaxone therapy for 22 h, despite producing a CSF bactericidal titer of 1:2,048, failed to sterilize the CSF of a 3-month-old patient with *S. pneumoniae* meningitis. Serial dilution of the CSF to diminish the concentration of antibiotic in the CSF yielded no additional positive cultures but was useful in quantitating the bacteria.

The CSF bactericidal titers during ceftriaxone therapy between 16 and 24 h after a dose ranged from 1:64 to ≥1:2,048 for organisms that were not members of the *Enterobacteriaceae* and from 1:4 to 1:256 for *Klebsiella* sp. and *Salmonella* sp.; however, comparable bactericidal titers in the control group ranged from 1:8 to 1:256 for *H. influenzae* and meningococci (Tables 4 and 5). The CSF bactericidal titers in the ceftriaxone group were generally higher than those predicted from the ratio of the CSF ceftriaxone concentration to the MBC for the infecting strain. Similar dichotomous values have been noted in humans receiving ceftriaxone for meningitis (12), but the explanation for this phenomenon is unclear. The MBC_{90}s of ceftriaxone for recent CSF isolates, including *H. influenzae* (n = 33), *S. pneumoniae* (n = 9), *Neisseria meningitidis* (n = 7), and *Salmonella* group B (n = 5), were ≤0.06 to 0.25 μg/ml.

The ceftriaxone concentrations achieved in the CSF and serum after a loading dose of 100 mg/kg were high. The CSF concentrations attained after 2 h were 19.7 ± 10.6 μg/ml (mean ± standard deviation), and these concentrations were maintained for 24 h. The CSF concentrations were 10.5 ± 5.5 μg/ml 24 h after the initial loading dose (at least 90-fold higher than the MBC_{90} of ceftriaxone against the three major meningeal pathogens). The serum and CSF concentrations of ceftriaxone achieved at different times after intravenous doses of 80 mg/kg on days 2 to 4 and 8 to 12 of therapy are shown in Fig. 1 and 2, respectively. The CSF concentrations of ceftriaxone achieved with 80-mg/kg doses were less but very adequate (mean, 1.4 μg/ml 20 to 24 h after the dose on days 2 to 4 of treatment). The concentrations in CSF on days 8 to 12 of therapy remained >1.0 μg/ml (mean, 1.5 μg/ml 20 to 24 h after dosing) (Fig. 1 and 2). These concentrations were substantiated by the excellent CSF bactericidal titers attained (Table 4). Ventricular fluid concentrations of 100 and 18.9 μg/ml were attained in two patients 12 and 21 h after doses of 80 mg of ceftriaxone per kg. These concentrations suggest excellent entry into the ventricles for treatment of ventriculitis.

DISCUSSION

Our results demonstrate that ceftriaxone administered once daily was essentially equivalent to conventional therapy of ampicillin plus chloramphenicol given at standard

TABLE 4. Bactericidal titers in CSF during phase B therapy: ceftriaxone group

Organism	Ceftriaxone MBC (μg/ml)	Time (h) after:		Bactericidal titer on:	
		Dose 2	Dose 10	Day 2 of therapy	Day 10 of therapy
H. influenzae	≤0.06	19	19	1:512 (3.2)[a]	1:256 (1.6)
S. pneumoniae	≤0.06	18	24	1:256 (5.6)	1:256 (0.7)
H. influenzae	≤0.06	21	21	1:512 (1.8)	1:256 (3.5)
H. influenzae	≤0.06	16	16	≥1:2,048 (6.0)	≥1:2,048 (0.6)
Klebsiella sp.	0.5	22.5		1:16 (1.5)	1:4 (0.7)
S. pneumoniae	≤0.06	23 (1st dose)		≥1:2,048 (10.0)	
Salmonella sp. (group B)	≤0.06	12		1:256 (2.0)	1:32 (2.0)

[a] The numbers in parentheses are CSF ceftriaxone concentrations (in micrograms per milliliter).

accepted dosages for acute bacterial meningitis of diverse etiology in a small (n = 36) group of patients more than 2 months old. In our initial study (phase A) we used ceftriaxone in combination with ampicillin to determine CSF concentrations 24 h after an intravenous infusion of 80 mg/kg. Our results demonstrate that ceftriaxone maintains bactericidal concentrations within the CSF for prolonged periods, even late in the treatment course. The mean CSF concentrations of ceftriaxone attained in CSF after 24 h were 83- and 38-fold higher than the MBC_{90} values for the three most common meningeal pathogens on days 4 to 6 and 10 of 12 of therapy, respectively. Because of these results, the excellent in vitro activity against all meningeal pathogens except *Listeria* (1, 14, 17, 28, 39; Scheld et al., in press), and the favorable results in vivo in experimental animal models of meningitis (9, 11, 24, 34; Scheld et al., in press), a prospective randomized trial was undertaken to compare ceftriaxone with ampicillin plus chloramphenicol for therapy of bacterial meningitis.

We found no statistically significant differences in clinical, laboratory, or etiological characteristics between the two groups analyzed in phase B, the prospective randomized trial. The results of therapy were essentially identical in the two groups, as judged by cure rate, case fatality ratios, neurological sequelae, and possible drug-related toxicity. However, the CSF bactericidal titers achieved 16 to 24 h after intravenous infusion of 80 mg of ceftriaxone per kg (1:64 to ≥1:2,048) were substantially higher than values obtained (generally 1:8 to 1:32) at varying intervals after dosing with ampicillin plus chloramphenicol in the control group (Tables 4 and 5). Much higher bactericidal titers might be expected during ceftriaxone therapy if specimens were obtained in the first several hours after dosing on day 1 of treatment. Nevertheless, the rates of bacterial killing within purulent CSF, as judged by the percentage of CSF samples rendered sterile within 48 h of initiation of therapy, were similar (83 to 85%) in the two groups. Similar high bactericidal titers in CSF during ceftriaxone therapy and equivalent rates of bacterial killing (compared with ampicillin plus chloramphenicol) have been noted by other workers (8, 12, 40) (see below). The mortality rate in this study was high and does not include two patients who died of fulminant meningitis within 3 h of admission. The overall case fatality rates were 17 and 22% for patients treated with ampicillin plus chloramphenicol and patients treated with ceftriaxone, respectively. This high level of mortality reflects the poor general condition of these patients on admission with advanced disease and the local results in Bahia, Brazil. In a retrospective analysis of the outcome of 4,101 cases of bacterial meningitis at Hospital Couta Maia from 1973 to 1982, the overall mean mortality rates, by etiological agent, were as follows: *H. influenzae*, 36.5%; *S. pneumoniae*, 61%; and *N. meningitidis*, 14.4% (Bryan, da Silva, Tavares, Rocha, and Scheld, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 24th, abstr. no. 244, 1984). The results achieved in the present study are comparable.

The results of the present study are in general agreement with those reported by other workers (3, 4, 8, 12, 23, 40) who evaluated ceftriaxone for therapy of bacterial meningitis. Cadoz and colleagues were the first to describe (3, 4) the use of ceftriaxone for therapy of meningitis. These authors compared this agent with amoxicillin alone, but their analysis was retrospective and the patients were treated at dif-

TABLE 5. Bactericidal titers in CSF during phase B therapy: control group (group treated with ampicillin plus chloramphenicol)

Organism	MBC (μg/ml)		Day of therapy	CSF bactericidal titer
	Ampicillin	Chloramphenicol		
H. influenzae	0.25	2.0	10	1:16
H. influenzae	<0.06	0.25	8, 12	1:16, 1:8
H. influenzae	0.25	0.5	10	1:8
H. influenzae	0.25	0.25	3	1:32
H. influenzae	0.25	0.5	2	1:256
N. meningitidis	<0.06	2.0	2	1:8
H. influenzae	0.25	1.0	2	1:16
Klebsiella sp.	>64	>64	2	<1:2

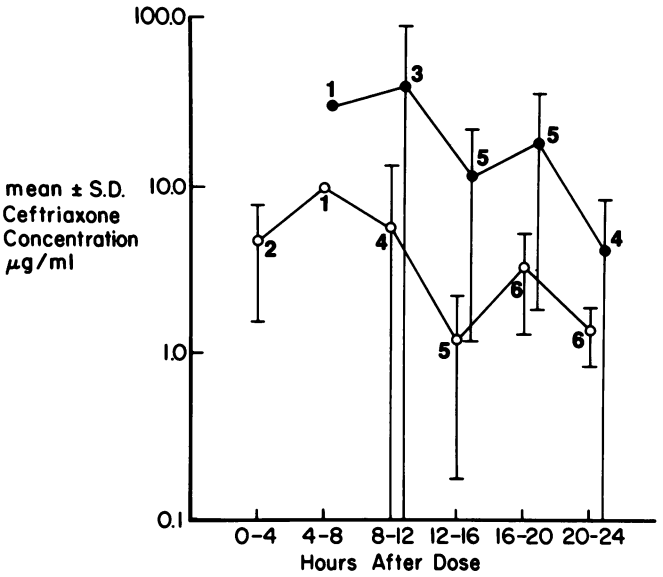

FIG. 1. Ceftriaxone concentrations in serum (●) and CSF (○) after 80-mg/kg intravenous doses on days 2 to 4 of therapy. The numbers beside the points are the numbers of samples used to calculate the values shown (mean ± standard deviation).

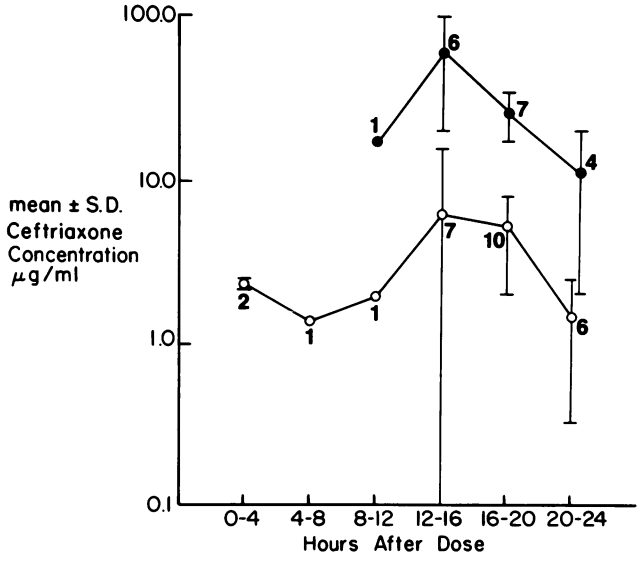

FIG. 2. Ceftriaxone concentrations in serum (●) and CSF (○) after 80-mg/kg intravenous doses on days 10 to 12 of therapy.

ferent periods in time. A large number of patients were treated (more than 300), and the mortality rate was high (4), similar to results obtained in other locales in the developing world and higher than our experience in Brazil. Nevertheless, the results achieved with ceftriaxone, which was generally administered twice daily, were equivalent (or better in cases of pneumococcal meningitis) to those obtained with amoxicillin (4). Importantly, some patients with meningococcal meningitis were cured by a single administration of ceftriaxone, and the mean duration of therapy was only 3 days in this group of patients (4).

Three other groups of workers have recently evaluated the comparative efficacy of ceftriaxone for the therapy of bacterial meningitis (8, 12, 40). All of these studies were performed in the United States, and they included a total of 153 cases. Unlike the present study, only pediatric age groups were enrolled, and very few patients were more than 2 years old. Each trial was randomized and prospective and compared ceftriaxone (50 mg/kg given twice daily intravenously or intramuscularly) with standard parenteral doses of ampicillin plus chloramphenicol. Thus, in four studies workers have compared ceftriaxone with standard, accepted regimens for the therapy of meningitis, an unusual occurrence since only two other prospective randomized trials evaluating a new agent for treatment of meningitis have been performed in the last 17 years (43; S. L. Kaplan, E. O. Mason, S. J. Kvernland, et al., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, abstr. no. 314, 1982). Ceftriaxone has been scrutinized carefully for this indication. In the other three studies (8, 12, 40) the authors described the results of twice daily dosing, and no CSF concentrations 24 h after dosing were determined, unlike the present study. Nevertheless, in all four trials ceftriaxone proved to be equivalent to (or slightly better than) ampicillin plus chloramphenicol, as judged by the following parameters: outcome (cure, death, resolution with sequelae); number of days of fever or signs of meningitis; type and severity of sequelae; resolution of abnormal CSF findings; time to sterility of CSF; differences in CSF bactericidal titers; tolerance; and adverse effects potentially related to the study drugs. However, the equivalent results must be interpreted with caution due to the rather small number of patients enrolled (less than <40) (8, 40), including the small number of patients in this study (n = 36), and the large potential β-error in this situation. The evidence certainly suggests that ceftriaxone given once or twice daily produces results similar to those obtained in patients receiving ampicillin plus chloramphenicol. Remarkably, only 3 of 153 patients died, and there were no deaths in two of the trials (12, 40); however, exclusions due to early deaths after admission are not mentioned. In two of the studies, the time to achieve sterility and negative Gram stains of CSF was shorter, but did not differ significantly, in the ceftriaxone group (12, 40). In the present study, 15% of the CSF samples were still positive 22 to 48 h after the initiation of therapy in both study groups. In addition, the CSF remained culture positive in one patient with group B *Salmonella* meningitis despite 6 days of ceftriaxone therapy and CSF bactericidal titers of 1:32 to 1:256. Such a prolonged period of positive CSF cultures has been noted in cases of *Salmonella* meningitis treated with other regimens (31, 43, 46) and remains unexplained, although an intracellular location or protected sanctuaries of the organisms may be responsible.

The CSF bactericidal titers reported in the four prospective randomized trials, including the present study, are remarkably similar (8, 12). Against the most common meningeal pathogens, the CSF bactericidal titers were generally 1:8 to 1:32 and 1:512 to >1:2,048 for ampicillin plus chloramphenicol and ceftriaxone, respectively. Despite the much higher bactericidal titers in CSF, the rate of bacterial killing in vivo, the time to sterility of CSF, and the outcome were not significantly improved during ceftriaxone therapy compared with therapy with ampicillin plus chloramphenicol. Experimental evidence (10, 37) and clinical evidence (6, 7, 23) strongly support the need for bactericidal activity in CSF for optimal therapy of meningitis. CSF antibiotic concentrations exceeding the MBC of the pathogen by ≥10-fold have been suggested for maximal rates of bacterial killing within purulent CSF in vivo (33, 37). The results of other studies (8, 12, 40) and our results support this concept since outcome and rate of response within CSF were equivalent, with median CSF bactericidal titers of 1:8 (ampicillin plus chloramphenicol) and 1:1,024 (ceftriaxone). Thus, increasing the CSF bactericidal titer manyfold in excess of 1:8 may not be reflected in improved response rates or eventual outcome.

As described above, ceftriaxone may prove to be useful in the therapy of bacterial meningitis. This agent displays many desirable characteristics for this indication compared with other cephalosporins. The accumulated experience with first- and second-generation cephalosporins for the therapy of meningitis has provided unimpressive results, with many failures (10, 19). Cefuroxime, a new second-generation agent, may prove to be an exception. Cefuroxime was equivalent to ampicillin plus chloramphenicol for the therapy of meningitis in a prospective, randomized multicenter cooperative trial conducted in Sweden (43). However, cefuroxime is less active than the third-generation agents in vitro against major meningeal pathogens, especially members of the *Enterobacteriaceae*. Moxalactam has the following two disadvantages compared with cefotaxime and ceftriaxone for the therapy of meningitis: (i) poor in vitro activity against pneumococci and group B streptococci, supported by poor results in animal models or humans with meningitis due to these organisms (24, 25, 34; Scheld, Eur. J. Clin. Microbiol., in press); and (ii) altered platelet aggregation and bleeding disturbances at the maximal dosages necessary for the therapy of central nervous system infections (29). The in vitro activities of ceftriaxone and cefotaxime are nearly identical (1, 14, 17, 28, 39; Scheld et al., in press), including the activities against the major meningeal pathogens, and both of these agents have proven efficacy in the therapy of meningitis in humans (2, 6, 8, 12, 29, 40). The clinical experience with ceftriaxone exceeds that with cefotaxime alone for this disease. In addition, the dosing interval for ceftriaxone (every 12 to 24 h) is an advantage compared with the regimen required for cefotaxime (every 4 to 6 h). Our results demonstrate the therapeutic efficacy of once daily ceftriaxone administration in the treatment of bacterial meningitis. Similar results were observed by Martin, who treated 24 patients once daily in Zurich, Switzerland (22). The mean CSF concentration attained 24 h after dosing in the study of Martin was 3.4 μg/ml, very similar to our results, and was 12- to >50-fold greater than the MBC_{90} of important meningeal pathogens (22). This advantage of every 24 h compared with every 12 h dosing may prove to be minor in industrialized nations but may be extremely important in the developing countries, pending further information on relative costs. However, once daily dosing demands strict monitoring of dose administration to ensure accurate and complete dose delivery. The very critical initial dose of any antibiotic regimen for such an emergent disease as meningi-

tis should be verified by a physician. Ceftriaxone may prove to be very useful in the following clinical settings (36): (i) patients with meningitis due to moderately or very penicillin-resistant pneumococci or *H. influenzae* strains, group B streptococci, or members of the *Enterobacteriaceae* that are resistant to ampicillin or chloramphenicol or both; (ii) patients with a penicillin allergy; and (iii) when chloramphenicol is not selected due to problems with unpredictable pharmacokinetics or to an inability to determine serum concentrations, resistance, or toxicity. The ultimate role of ceftriaxone for therapy of meningitis and the proper dose and dosing interval will become better defined as clinical experience accumulates in future studies.

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