ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1984, p. 273–275
0066-4804/84/020273-03$02.00/0

Vol. 25, No. 2

Cefuroxime Treatment of Bacterial Meningitis in Infants and Children

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Received 20 May 1983/Accepted 14 November 1983

Recently, ampicillin- and chloramphenicol-resistant strains of *Haemophilus influenzae* type b and multiply-resistant *Salmonella* strains have appeared in some areas of the world. Therefore, alternative drug therapy for infections caused by these organisms is being sought. We used cefuroxime to successfully treat five children with *H. influenzae* type b meningitis and two children with *Salmonella* meningitis. Four *H. influenzae* type b isolates and one *Salmonella* isolate were resistant to ampicillin, chloramphenicol, and co-trimoxazole. Each of the patients received 200 to 250 mg of cefuroxime per kg per day in four divided doses for 14 to 21 days. The concentrations of cefuroxime in cerebrospinal fluid at 2 h after intravenous 50-mg/kg doses were 6.4 ± 1.7 (mean ± standard deviation) and 3.6 ± 2.2 μg/ml on days 2 and 14 of treatment, respectively. The level of drug in cerebrospinal fluid was 1.34 ± 1.3 μg/ml in children without meningitis. The mean cefuroxime concentration in subdural fluid samples from each of three patients was 12.6, 15, and 25.2 μg/ml. Cefuroxime is recommended as an alternative drug for the treatment of *H. influenzae* type b meningitis, but additional information is necessary before cefuroxime can be recommended for therapy of *Salmonella* meningitis.

Haemophilus influenzae type b (HIB) is the most common cause of bacterial meningitis in children. Conventional antibiotic therapy for this disease is ampicillin plus chloramphenicol. Approximately 20% of HIB strains in the United States are currently resistant to ampicillin (5, 6, 13). Chloramphenicol, the alternative drug, has potential bone marrow toxicity, and resistance of HIB strains to this drug has been reported recently (7, 8, 10, 15, 19). In Bangkok, *Salmonella* strains, a relatively common cause of meningitis in early infancy, have also been found to be resistant to ampicillin, chloramphenicol, co-trimoxazole, and all available aminoglycosides.

Cefuroxime is a second-generation cephalosporin which is resistant to inactivation by many beta-lactamases. It is active in vitro against HIB strains, *Streptococcus pneumoniae*, and *Neisseria meningitidis* (9), the three most common causes of bacterial meningitis in infants and children. It is also active against many gram-negative enteric bacilli, including *Salmonella* strains (9). Successful treatment of bacterial meningitis in children with cefuroxime was recently reported (14, 17). The causative agents in these studies included HIB, *S. pneumoniae*, and *N. meningitidis*, but there were no ampicillin- and chloramphenicol-resistant HIB or *Salmonella* strains.

We report here our experience with cefuroxime for the treatment of bacterial meningitis in seven infants and children, among whom were four patients with ampicillin- and chloramphenicol-resistant HIB infections and one infant with a multiply-resistant *Salmonella* sp. infection. We measured the concentration of cefuroxime in cerebrospinal fluid (CSF) samples from 15 children who had meningitis and 10 children who did not have meningitis.

MATERIALS AND METHODS

Patients. The patients in this study included 15 children who had bacterial meningitis and 10 without meningitis for whom lumbar puncture was indicated. Their ages ranged from 25 days to 12 years. All received 50 mg of cefuroxime per kg by intravenous infusion for 3 to 5 min at 2 h before the CSF and serum specimens were obtained for measurement of cefuroxime levels.

Of the 15 patients with meningitis, 6 were treated with 200 and 1 with 250 mg of cefuroxime per kg per day in four divided doses for 14 to 21 days. For six patients, cefuroxime was added to or substituted for penicillin after two to three doses of penicillin had been given or during the latter part of therapy. The causative organisms in these patients included beta-hemolytic streptococci (not group A or D by presumptive tests) and *S. pneumoniae*. CSF and serum specimens were obtained from these patients after at least four doses of cefuroxime had been given. Cefuroxime was discontinued after 2 days of treatment in two patients because the etiological agents were hospital-acquired *Pseudomonas cepacia* and *Pseudomonas aeruginosa* strains that were resistant to cefuroxime.

The CSF and serum specimens were obtained for cefuroxime measurement on day 2 of treatment for 11 patients and on day 14 for 8 patients. Four daily specimens of subdural fluid were obtained from each of the three patients who had HIB meningitis.

Ten patients without meningitis were given one dose of 50 mg of cefuroxime per kg for the study. Their diagnoses included septicemia, convulsion, mastoiditis, post encephalitis, and pseudotumor cerebri.

The protocol for study was approved by the Research Committee of the Department of Pediatrics, Ramathibodi Hospital. Verbal informed consent for cefuroxime injection was obtained from the parents or guardians of the patients.

Causative bacteria. The causative bacteria in the seven patients who were treated with cefuroxime only were HIB strains in five and *Salmonella krefeld* and *Salmonella typhimurium* in one each. For four patients from the same orphanage, three isolates of ampicillin- and chloramphenicol-resistant HIB strains were recovered from cultures of CSF, whereas cultures of the fourth isolate were sterile because the specimen was left overnight before being cultured, but HIB antigen was detected in the CSF by counter-

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immunoelectrophoresis. This case of meningitis was presumed to be resistant to ampicillin and chloramphenicol because of the failure of these two drugs to cure the patient and the epidemiological setting in which the disease occurred (15). One HIB isolate was ampicillin and chloramphenicol susceptible. *S. krefeld* was resistant to ampicillin, chloramphenicol, co-trimoxazole, tetracycline, streptomycin, gentamicin, and amikacin. *S. typhimurium* was susceptible to these drugs. The four HIB strains had MICs and MBCs of 0.5 μg of cefuroxime per ml, whereas the two *Salmonella* strains had MICs and MBCs of 4 μg/ml.

Susceptibility studies. The susceptibilities to antibiotics of the pathogens isolated from the CSF samples were initially determined by the Kirby-Bauer method (3). Resistance to ampicillin and chloramphenicol was subsequently confirmed, and MICs and MBCs of cefuroxime were determined by the macro-broth dilution method with an inoculum of 10^5 CFU. Mueller-Hinton broth was used for *Salmonella* isolates, and Mueller-Hinton broth supplemented with 5% (vol/vol) Fildes peptic digest of blood (2) was used for HIB isolates. The procedures were performed as previously described (4). The resistant HIB strain had MICs of >32 μg/ml for both ampicillin and chloramphenicol.

Cefuroxime assay. CSF and serum specimens were stored at −20°C until assayed (within 24 h). Cefuroxime concentrations were measured by the agar diffusion technique with *Bacillus subtilis* 1904E and MB32SDR (Glaxo Research Ltd.) with the test organisms (Cefuroxime Laboratory Manual, Glaxo). Penicillin activity in some specimens was eliminated by using penicillinase (Bacto-Penase; Difco Laboratories) at a 1:125 dilution in buffer to dilute the specimens. This concentration was proven to destroy penicillin activity without affecting cefuroxime activity.

RESULTS

Treatment of bacterial meningitis. Seven patients who had meningitis caused by HIB or *Salmonella* strains were cured with cefuroxime therapy. Their ages ranged from 25 days to 7 months. Of the five patients with HIB meningitis, three did not receive prior therapy, whereas two had been unsuccessfully treated with ampicillin and chloramphenicol before cefuroxime therapy. The illness of the latter two patients was complicated by ventriculitis and hydrocephalus before cefuroxime treatment. Of the four patients with previous positive CSF cultures, cultures of CSF samples obtained after 24 h of treatment were sterile for two, and the other two had rare organisms in cultures of CSF samples obtained at 24 h and sterile cultures for 72-h samples. All patients improved rapidly. Two patients were afebrile after 6 days of treatment, and cefuroxime treatment was discontinued after 14 days. By contrast, three patients with subdural empyema did not become afebrile for 10 to 12 days, and their total course of treatment was 21 days. The three patients who were treated 1 to 3 days after onset of fever were considered normal 15 months to 2 years after recuperation from meningitis, whereas both children who were initially treated ineffectively with ampicillin and chloramphenicol for 2 weeks were severely brain damaged.

Of the two patients infected with *Salmonella* strains, one was a 2.5-month-old girl whose CSF and blood cultures grew a multiply-resistant strain of *S. krefeld*. Therapy with cefuroxime was started after she had already developed ventriculitis. She improved gradually with a regimen of cefuroxime given intravenously (200 mg/kg per day) and intraventricularly (5 mg daily for 4 days). Fever disappeared and ventricular fluid was sterile after 72 h of treatment. Intravenous therapy was continued for 21 days, and she had an uneventful recovery and was considered normal at age 2.5 years.

The other patient was a 25-day-old girl with *S. typhimurium* meningitis. Initial treatment consisted of cefuroxime, gentamicin, and co-trimoxazole. Gentamicin and co-trimoxazole were discontinued after 2.5 days when the isolate was shown to be susceptible to cefuroxime. A culture of CSF taken on that day still grew a few *S. typhimurium* colonies. She became afebrile and was considered clinically normal on day 4 of treatment, at which time the CSF culture was sterile. Therapy with 250 mg of cefuroxime per kg per day was continued for 21 days.

One of the seven cefuroxime-treated patients had high fever followed by a generalized maculopapular rash on day 18 of treatment, which disappeared within 24 h, after discontinuation of cefuroxime treatment.

Cefuroxime penetration into CSF and subdural fluid. The concentrations of cefuroxime in CSF and serum at 2 h after a 50-mg/kg dose given by rapid intravenous infusion are shown in Table 1. All CSF specimens had less than 100 erythrocytes per ml. The cefuroxime concentrations in the CSF of the two patients who were severely brain damaged were 14.6 and 17.6 μg/ml on day 2 and 8.7 and 9.6 μg/ml on day 14. These concentrations were exceptionally high due to greater than usual brain damage, so the figures were not included for statistical calculation.

Cefuroxime concentrations in subdural fluid were measured in 12 specimens, 4 from each of three patients who had HIB meningitis. The cefuroxime concentration in each of these patients was 12.6, 15, and 25.2 μg/ml.

DISCUSSION

The data from the present study are consistent with those of previous studies showing good correlation between the concentration of cefuroxime in the CSF and the degree of meningeal inflammation (12, 14). The cefuroxime concentration in the CSF at 2 h after the dose on day 2 of treatment was comparable to that reported by Pfenninger et al. (14) using the same dosage 7.0 ± 1.0 μg/ml. These levels exceed

TABLE 1. Concentrations of cefuroxime in the CSF and serum of infants and children with bacterial meningitis

Patient group	No. of patients	Cefuroxime concn (μg/ml) (mean ± SD [range]) in:		Concn of cefuroxime in CSF/concn of cefuroxime in serum
		CSF	Serum	
With meningitis[a]				
Day 2 of treatment	9	6.4 ± 1.7 (4.3–9.3)	35.5 ± 9.5 (25.2–53.2)	18.2 ± 3 (15.0–22.2)
Day 14 of treatment	6	3.6 ± 2.2 (0.94–7)	32.0 ± 23.3 (6.8–68)	12.1 ± 2.5 (9.9–16.2)
Without meningitis	10	1.34 ± 1.3 (0.22–1.75)	32.5 ± 14.7 (14.4–60)	3.8 ± 2.4 (1.1–9.9)

[a] Excluding two patients who developed severe brain damage before cefuroxime treatment was started (see the text).

the MICs for HIB, *S. pneumoniae*, and *N. meningitidis* by at least 10-fold but are similar to MICs for *Salmonella* strains. The concentrations in CSF on day 14 of treatment in this study (range, 0.94 to 7.0 μg/ml) were also larger than the MICs for HIB, *S. pneumoniae*, and *N. meningitidis* but not for *Salmonella* strains. The concentrations and penetration of cefuroxime in the CSF of patients without meningitis were one-third to one-sixth of those in purulent CSF. Del Rio et al. (6) reported concentrations of cefuroxime in CSF at 0.5 to 4 h after a single dose of 50 mg/kg was given to children with purulent meningitis of 3.03 ± 2.5 μg/ml (mean ± standard deviation).

Among the second-generation cephalosporins, cefuroxime and cefamandole have comparable in vitro activity against HIB meningitis and better activity than cefoxitin has (9). Treatment failures of HIB meningitis with cefamandole (150 to 200 mg/kg per day) have been reported (1, 16) and are believed to be due to the instability of cefamandole to the *Haemophilus* beta-lactamase (1, 16, 18). McCracken and coworkers (11) showed that cefuroxime was relatively ineffective in experimental meningitis compared with chloramphenicol, cefoperazone, ceftriaxone, or moxalactam. On the other hand, controlled studies demonstrated that cefuroxime was comparable to ampicillin and chloramphenicol in treating childhood meningitis caused by the three most common organisms (14, 17). There have been no reports of failure in the therapy of meningitis with appropriate dosages of cefuroxime. In addition we report the effectiveness of cefuroxime for treatment of meningitis caused by ampicillin- and chloramphenicol-resistant HIB and *Salmonella* strains.

In conclusion, we recommend a dosage of 200 mg of cefuroxime per kg per day given intravenously in four divided doses for therapy of HIB meningitis. Although the two patients with *Salmonella* meningitis were successfully treated with 200 mg/kg per day plus 5 mg given intraventricularly for 4 days in one case and 250 mg/kg per day in the other, the most appropriate regimen for salmonella meningitis has not been considered.

ACKNOWLEDGMENTS

The susceptibility testing of the bacteria and the cefuroxime assay were performed by Suwanna Boonrumlucktanom. Our thanks to the house staffs and nurses of the Pediatric Department, Ramathibodi Hospital, for collecting blood and CSF specimens.

This study was supported by a grant from Glaxo Research Ltd., Bangkok, Thailand.

LITERATURE CITED

1. **Azimi, P. H., and P. A. Chase.** 1981. The role of cefamandole in the treatment of Haemophilus influenzae infections in infants and children. J. Pediatr. **98**:995–1000.
2. **Barry, A. L.** 1976. Antimicrobic susceptibility of Haemophilus influenzae, p. 86. *In* A. L. Barry (ed.), The antimicrobial susceptibility test: principles and practice. Lea & Febiger, Philadelphia, Pa.
3. **Barry, A. L., and L. D. Sabath.** 1974. Special tests: bactericidal activity and activity of antimicrobics in combination, p. 431–435. *In* E. H. Lennette, E. H. Spaulding, and J. P. Truant (ed.), Manual of clinical microbiology, 2nd ed. American Society for Microbiology, Washington, D.C.
4. **Bauer, A. W., W. W. M. Kirby, J. C. Sherris, and M. Turck.** 1966. Antibiotic susceptibility testing by a standard single disc method. Am. J. Clin. Pathol. **45**:493–496.
5. **Center for Disease Control.** 1979. Bacterial meningitis and meningococcemia—United States, 1978. Morbid. Mortal. Weekly Rep. **23**:77–78.
6. **Del Rio, M. A., D. F. Chrane, S. Shelton, G. H. McCracken, Jr., and J. D. Nelson.** 1982. Pharmacokinetics of cefuroxime in infants and children with bacterial meningitis. Antimicrob. Agents Chemother. **22**:990–994.
7. **Kenny, J. F., C. D. Isburg, and R. H. Michaels.** 1980. Meningitis due to Haemophilus influenzae type b resistant to both ampicillin and chloramphenicol. Pediatrics **66**:14–16.
8. **Kinmoth, A., C. N. Storrs, and R. G. Michell.** 1978. Meningitis due to chloramphenicol-resistant Haemophilus influenzae type b. Br. Med. J. **1**:694.
9. **Kucers, A., and N. M. Bennett.** 1979. Cefamandole, cefoxitin, cefuroxime, cefazaflur, cefotaxime, SK & F 75073 and cefsulodin, p. 268–273. *In* The use of antibiotics, 3rd ed. William Heinemann Medical Books Ltd., London.
10. **Long, S. S., and S. E. Phillips.** 1976. Chloramphenicol-resistant Haemophilus influenzae. J. Pediatr. **90**:1030–1031.
11. **McCracken, G. H., Jr., J. D. Nelson, and L. Grimm.** 1982. Pharmacokinetics and bacteriological efficacy of cefoperazone, cefuroxime, ceftriaxone, and moxalactam in experimental *Streptococcus pneumoniae* and *Haemophilus influenzae* meningitis. Antimicrob. Agents Chemother. **21**:262–267.
12. **Müller, C., and A. Netland.** 1980. The penetration of cefuroxime into the cerebrospinal fluid through inflamed and non-inflamed meninges. J. Antimicrob. Chemother. **6**:279–283.
13. **Nelson, J. D.** 1980. The increasing frequency of beta-lactamase-producing Haemophilus influenzae B. J. Am. Med. Assoc. **244**:239.
14. **Pfenninger, J., U. B. Schaad, J. Lütschg, A. Nussbaumer, and U. Zellweger.** 1982. Cefuroxime in bacterial meningitis. Arch. Dis. Child. **57**:539–543.
15. **Simasthien, S., C. Duangmani, and P. Echeverria.** 1980. Haemophilus influenzae type b resistant to ampicillin and chloramphenicol in an orphanage in Thailand. Lancet **ii**:1214–1217.
16. **Steinberg, E. A., G. D. Overturf, J. Wilkins, L. J. Baraf, J. M. Streng, and J. M. Leedom.** 1978. Failure of cefamandole in treatment of meningitis due to Haemophilus influenzae type b. J. Infect. Dis. **137**(Suppl.):180–187.
17. **Swedish Study Group.** 1982. Cefuroxime versus ampicillin and chloramphenicol for the treatment of bacterial meningitis. Lancet **i**:295–299.
18. **Thirumoorthi, M. C., D. M. Kobos, and A. S. Dejani.** 1981. Susceptibility of *Haemophilus influehzae* to chloramphenicol and eight beta-lactam antibiotics. Antimicrob. Agents Chemother. **20**:208–213.
19. **Uchiyama, N., G. R. Greene, D. B. Kitts, and L. D. Thrupp.** 1980. Meningitis due to Haemophilus influenzae type b resistant to ampicillin and chloramphenicol. J. Pediatr. **97**:421–424.