Penetration of Cefamandole into Spinal Fluid

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Twelve patients, aged 6 months to 62 years, with proven bacterial meningitis, were given a single intravenous dose of cefamandole (33 mg/kg) 75 to 140 min before a routine lumbar puncture. Infecting organisms included Haemophilus influenzae (eight cases), Streptococcus pneumoniae (two cases), and Neisseria meningitidis and β-hemolytic streptococcus (one each). Cerebrospinal fluid (CSF) was analyzed by microbiological assay for cefamandole. The median concentration was 0.60 μg/ml, ranging from undetectable to 7.4 μg/ml. CSF cefamandole concentrations correlated with CSF protein: in six patients with CSF protein less than 100 μg/dl, the range of drug concentration was 0 to 0.62 μg/ml; and in six patients with CSF protein above 100 mg/dl, the range was 0.57 to 7.4 μg/ml. No significant correlation was noted between severity of illness, type of organism involved, or patient age and concentration of drug achieved.

Cefamandole nafate, 7-D-mandelamido-3-[[1-methyl-1H-tetrazole-5-y1]-thio[methyl]-3 cepham-4-carboxylic acid, formate (ester), sodium salt, is a semisynthetic cephalosporin antibiotic with broad antibacterial spectrum (4, 14, 15), and is 70 to 80% protein bound (7, 8). It is notably active against β-lactamase-producing Haemophilus influenzae type b (9). Therefore, a pilot study was conducted to evaluate achievable antibiotic levels in cerebrospinal fluid (CSF) after the intravenous administration of a single dose of cefamandole to patients with bacterial meningitis.

MATERIALS AND METHODS

Patients. Twelve patients admitted to the Los Angeles County-University of Southern California Medical Center with bacterial meningitis were selected for study. The diagnosis was confirmed by a positive CSF culture on all patients. Informed written consent was obtained from patients or their parents or responsible guardians. The patients included two adults (62 and 46 years), one adolescent (13 years), and nine children (6 months to 3.5 years with a median age of 10 months). Patients 4 and 5 had Streptococcus pneumoniae isolated from CSF; patient 12 had a β-hemolytic streptococcus; patient 10 had Neisseria meningitidis. All other patients had H. influenzae type b isolated (Table 1).

The severity of meningitis upon admission was graded according to the criteria of Mathies (13). All patients were treated with ampicillin intravenously, 200 mg/kg per day in six divided doses. One dose of cefamandole, 33 mg/kg, was substituted for ampicillin before a routine lumbar puncture within the first 72 h of treatment in all patients, except no. 12, whose dose was given on day 7 of treatment. Infusion times varied from 10 to 25 min. Two serum samples were obtained for cefamandole concentration (micrograms per milliliter): the first at 35 to 135 min, the second at 5 to 9 h. CSF was obtained for cefamandole assay at 75 to 140 min postinfusion, a time interval yielding the highest CSF concentrations of ampicillin and carbenicillin (16).

Antibiotic assay. A modification of the standard microbiological assay of Bennett et al. (2) was used. Test plates were prepared with polystyrene petri dishes (Van-Lab) (150 by 15 mm). The assay agar used nutrient agar (pH 6.8, Difco, in 40-ml portions, seeded with 0.3 ml of a Bacillus subtilis spore suspension prepared by the addition of one vial of spores (Difco) to 50 ml of 0.1 M phosphate buffer (pH 7.4). Two thousand units of penicillinase (Difco) was added concomitantly with the spore inoculum. Standard curves, utilizing cefamandole lithium, with CSF or serum as diluent, were run simultaneously by the inclusion of three control wells (0.8, 6.25, and 50 μg/ml). Sera and CSF that were not analyzed immediately were stored at −20°C; no specimen was stored longer than 7 days before analysis.

Susceptibility testing. Minimal inhibitory concentrations (MICs) were determined for cefamandole lithium by standard twofold serial dilution methods: Levinthal broth was used for H. influenzae; tryptic soy broth was used for streptococcus. An inoculum of approximately 10^6 organisms was prepared from overnight growth. Minimal bactericidal concentrations (MBCs) were determined by plating broth, with a 3-mm loop, from tubes without growth after 24 h of incubation. Chocolate agar plus supplement B was used for H. influenzae; sheep blood agar was used for streptococcus. MBC was defined as the lowest antibiotic concentration which allowed growth of no greater than 10 colonies after
18 h of incubation. All *H. influenzae* isolates were tested for β-lactamase production by the method of Thornsberry (19).

RESULTS

Serum concentrations of cefamandole ranged from 2.6 to 40 μg/ml, with a median of 31.25 μg/ml in 12 patients, at 35 to 135 min after administration (Table 1), and from undetectable to 7.4 μg/ml, with a median of 1.17 μg/ml, in 10 patients, at 5 to 9 h after administration (Table 1). The wide range in serum cefamandole concentrations may be explained by the fact that the rate of antibiotic infusion and the time of serum collection postinfusion were not kept constant. All patients had normal renal function, as indicated by serum urea nitrogen, which was less than 18 mg/dl, or serum creatinine, which was less than 1.1 mg/dl.

CSF concentrations of cefamandole ranged from undetectable in one patient to 7.4 μg/ml, with a median of 0.60 μg/ml, at 75 to 140 min after administration. No correlation was apparent between the concentration attained and type of organism or severity of disease upon admission. Greater CSF concentrations were observed in CSF with higher protein concentrations. In six patients with CSF protein less than 100 mg/dl, concentrations ranged from undetectable to 0.62 μg/ml, with a median of 0.36 μg/ml. In six patients with CSF protein above 100 mg/dl, concentrations ranged from 0.54 to 7.4 μg/ml, with a median of 2.83 μg/ml. (Table 1).

All *H. influenzae* type b isolates were negative for β-lactamase production. Susceptibility studies to cefamandole on five of these yielded an MIC of 0.4 μg/ml and an MBC of 0.4 μg/ml on each organism. The single β-hemolytic streptococcus had an MIC of 0.1 μg/ml and an MBC of 0.8 μg/ml.

Two patients manifested unusual symptoms in association with administration of the drug. One adult developed agitation and a generalized urticarial rash within 15 min. All symptoms resolved within 3 h, after the administration of 50 mg of diphenhydramine intravenously. One child had an increase in temperature from 100°F to 102°F (ca. 37.8 to 38.9°C) at 1 h and 45 min after administration of the drug. This was associated with generalized shaking, but there was no change in other vital signs and no loss of consciousness.

DISCUSSION

The spectrum of cefamandole includes the three organisms responsible for most bacterial meningitis in children and adults. *S. pneumoniae* is highly susceptible; reported MICs have ranged from 97% inhibited at less than or equal to 0.4 μg/ml (4, 14) to 100% inhibited at less than or equal to 0.2 μg/ml (5, 15). *N. meningitidis* has MICs less than or equal to 0.25 μg/ml (12). Reported MICs for *H. influenzae* type b have ranged from 90% susceptible to less than or equal to 2.5 μg/ml (4, 14) to 100% susceptible to 2.0 μg/ml, including ampicillin-resistant strains producing β-lactamase (9).

Concentrations achieved in CSF during treatment of bacterial meningitis have been reported for several antibiotics (18). An antibiotic that fails to achieve measurable CSF concentrations in the presence of meningitis is generally ineffective in treating central nervous system infections. However, neither proof of CSF penetration nor actual concentrations...
measured, by themselves, assures the efficacy of an antibiotic (6).

Penicillin and ampicillin generally attain CSF concentrations between 0.5 and 10 μg/ml during treatment of meningitis (1, 18, 20, 22), but single random samples may have no detectable concentrations despite clinical evidence of therapeutic efficacy (16, 22). On a daily dosage of 200 mg/kg given in six doses of 33 mg/kg, ampicillin achieved a median concentration of 0.45 μg/ml, with a range of 0.1 to 2.3 μg/ml in 15 patients with CSF protein less than 75 mg/dl. At a similar dosage, in 14 patients with CSF protein greater than 75 mg/dl, ampicillin achieved a median concentration of 2.20 μg/ml, with a range of 0.37 to 30 μg/ml (16). Cephalosporins have also demonstrated penetration of CSF in the presence of meningeal inflammation. Cephalothin (3, 10, 17, 21) and cephaloridine (11) each have attained CSF median concentrations in the range of 0.1 to 6 μg/ml. Yet, despite adequate drug dosage and measured antibiotic concentrations exceeding the MIC of the infecting organism, these cephalosporins have, on occasion, been associated with persistence of bacteria in CSF and poor clinical response (3, 6).

Chloramphenicol is, at present, the most reliable effective antibiotic for infections with H. influenzae type b. The documented occurrence of aplastic anemia after the administration of chloramphenicol, although rare, has caused concern about its use. The results of this pilot study show that cefamandole does penetrate inflamed meninges. It is possible that this agent may be useful in the therapy of meningitis, but further in vitro and careful in vivo research is required before cefamandole can be considered as a therapeutic agent for central nervous system infections.

LITERATURE CITED