Clinical and Laboratory Investigation of Cefamandole in Infections of Infants and Children

PARVIN H. AZIMI†

Departments of Pediatrics and Medical Microbiology, College of Medicine, The Ohio State University, Columbus, Ohio 43210

Received for publication 25 November 1977

Forty-seven infants and children with a variety of infections including bacteremia, ethmoiditis, and periorbital cellulitis, soft tissue infection, pneumonia, and lymphadenitis were treated with intravenous cefamandole. The infections were due to *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. The clinical response was prompt, and, with the exception of two cases who developed skin rash, significant side effects were not noted. In vitro cefamandole was very effective in inhibiting the growth of *H. influenzae*, including ampicillin-resistant isolates.

Cefamandole is a new cephalosporin derivative available in parenteral form as cefamandole nafate. It is active against a wide range of bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes* group A, *Streptococcus pneumoniae*, and members of *Enterobacteriaceae*. Cefamandole has greater activity against *Haemophilus influenzae* than currently available cephalosporins.

The purpose of this study is to report the in vivo effect of cefamandole in treatment of a variety of infections of infants and children. In addition, we are reporting on the in vitro sensitivity to cefamandole, chloramphenicol, and ampicillin of 136 isolates of *H. influenzae* cultured from blood or cerebrospinal fluid of children with sepsis or meningitis.

MATERIALS AND METHODS

Patients. Children over 3 months of age who were admitted to Columbus Children's Hospital and were suspected of having infection caused by bacteria susceptible to cefamandole were entered into the study protocol. Patients with central nervous system infection, those with prior antibiotic therapy, and those who were thought to need more than one antibiotic were excluded from the study.

Forty-seven patients, ranging in age from 4 months to 17 years, were treated with cefamandole; 33 patients were 5 years of age or younger. Infections treated included cellulitis, ethmoid or pansinusitis with periorbital cellulitis, pneumonia, cervical adenitis, epiglottitis, septic joint, peritonsillar abscess, and mastoiditis. The children received 100 mg of cefamandole per kg per day intravenously every 6 h. Forty of the 47 patients received the drug for 5 to 7 days, five received

10 to 17 days of treatment, and two were withdrawn due to side effects. Before administration of cefamandole, cultures of the blood in all patients and exudates, when applicable, were obtained.

Susceptibility tests. When a pathogen was isolated, susceptibility tests were done by both disk diffusion and broth dilution methods, using standard procedures (1). Strains of *H. influenzae* were tested against cefamandole, ampicillin, and chloramphenicol by using a microdilution method with Autotiter IV (Ames Co.). The inoculum consisted of a 10^{-3} dilution of an overnight culture of *H. influenzae* in Mueller-Hinton broth with 5% Field enrichment (Difco) adjusted to McFarland standard 0.5. Antibiotics were diluted in the above broth. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of antibiotic in which no growth was observed after 12 to 18 h of incubation.

Blood levels. Blood levels were determined in 53 samples from 18 study patients. Concentrations of cefamandole were determined by the cup-plate method (2), using *Bacillus subtilis* spore suspension as the test organism.

Toxicity studies. A number of tests were done before initiation and on termination of cefamandole therapy. These included complete blood count, urinalysis, blood urea nitrogen, serum creatinine, bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and direct Coombs tests.

RESULTS

Laboratory studies: susceptibility of *H. influenzae* to cefamandole. All 136 isolates of *H. influenzae* from blood and cerebrospinal fluid were inhibited by 0.5 μ g of cefamandole or less per ml. Figure 1 compares the susceptibility of these organisms to ampicillin, cefamandole, and chloramphenicol. One hundred and twelve isolates were inhibited by 0.12 μ g of ampicillin per

† Present address: Infectious Diseases, Children's Hospital Medical Center, Oakland, CA 94609.

ml. Four isolates were resistant to ampicillin with MICs $>8 \mu\text{g/ml}$. All isolates were inhibited by $2 \mu\text{g}$ or less of chloramphenicol per ml. In general, ampicillin MICs were lower than cefamandole, and cefamandole MICs were lower than chloramphenicol. The four isolates resistant to ampicillin were susceptible to both cefamandole and chloramphenicol.

Clinical studies. Clinical response in the group with periorbital cellulitis was prompt with reduction of fever, edema, and erythema 24 to 48 h after onset of therapy in 20 cases. Treatment was continued for 7 days in these patients. Cefamandole was discontinued in a 9-month-old infant from this group who developed a generalized erythematous rash 3 h after the first dose. Of these 20, 10 had bacteremia, 6 with *H. influenzae*, 1 with *S. pneumoniae*, 1 with *S. pyogenes*

group A, 2 with *S. aureus* (Table 1). Sixteen patients were treated for cellulitis. Cultures yielded one or two major bacterial pathogens in nine patients, *S. pyogenes* group A and *S. aureus* (Table 1). No exudate was available for culture in the remaining seven cases. These patients were treated for 5 days. Clinical response was prompt in all, except for a 2-year-old patient who developed a generalized erythematous and pruritic rash after dose five, and use of cefamandole was discontinued in him.

A total of 11 patients with miscellaneous infections including epiglottitis, pneumonia, peritonsillar abscess, mastoiditis, otitis media, and septic arthritis were treated successfully for 4 to 14 days. Four patients had positive cultures (Table 1). *H. influenzae* was isolated from the middle ear aspirate of patient with otitis media, *S. aureus* from the middle ear aspirate of the case with mastoiditis, *S. pyogenes* group A from a needle aspirate of the cervical adenitis, and *H. influenzae* from blood in a case of epiglottitis.

Toxic effects. Cefamandole was discontinued in two patients who developed skin rash, one after the first dose and the second after the third dose of cefamandole. Both of these patients were treated with penicillin derivatives uneventfully. Eosinophilia, in the range of 350 to 1,353 per mm^3 , was seen in 17 cases. One patient had eosinophilia of 2,226 per mm^3 , which was reversed with completion and discontinuation of therapy. Mild elevation of liver transaminases occurred in seven cases.

Serum concentration of cefamandole. There were mean serum concentrations of 19 $\mu\text{g/ml}$ in 1 h and 4 $\mu\text{g/ml}$ in 2 h, concentrations

FIG. 1. MICs of three antibiotics for *H. influenzae* (micrograms per milliliter).

TABLE 1. Susceptibility of pathogens isolated from patients to cefamandole

Infection (no. of patients)	Pathogen (site)	Disk zone (mm)	MIC ($\mu\text{g/ml}$)
Periorbital cellulitis and ethmoiditis (6)	<i>H. influenzae</i> (blood)	25-42	0.03-0.05
Otitis media (1)	<i>H. influenzae</i> (middle ear aspirate)	22	0.25
Epiglottitis (1)	<i>H. influenzae</i> (blood)	28	1.0
Ethmoiditis and periorbital cellulitis (1)	<i>S. pneumoniae</i> (blood)	35	<0.03
Ethmoiditis and periorbital cellulitis (1)	<i>S. pyogenes</i> group A	30	0.06
Cervical adenitis (1)	<i>S. pyogenes</i> group A (exudate)	38	0.03
Cellulitis (1)	<i>S. pyogenes</i> group A (exudate)		0.03
Peritonsillar abscess (1)	<i>S. pyogenes</i> bacitracin resistant (exudate)	32	0.06
Cellulitis (5)	<i>S. pyogenes</i> group A	32-40	0.03-0.06
	<i>S. aureus</i> (exudate)	20-25	0.7-2
Ethmoiditis and periorbital cellulitis (2)	<i>S. aureus</i> (blood)	24	1.0
Mastoiditis (1)	<i>S. aureus</i> (middle ear aspirate)	23	
Cellulitis (2)	<i>S. aureus</i> (blood)	25	0.35
Cellulitis as a result of dog bite (1)	<i>Enterobacter</i> species (exudate)		25

that would be sufficient to inhibit susceptible organisms. Serum concentrations were below 1 $\mu\text{g/ml}$ in 6 h.

DISCUSSION

Cefamandole was effective in treatment of a variety of infections in children including bacteremia, ethmoiditis and periorbital cellulitis, soft tissue infection, pneumonia, and lymphadenitis. The organisms isolated from these infections included *S. aureus*, *S. pyogenes* group A, *S. pneumoniae*, and *H. influenzae*. In vitro, cefamandole was very effective in inhibiting the growth of *H. influenzae*. All 136 isolates from blood or CSF of children with sepsis or meningitis were inhibited by 0.5 μg of drug or less per ml, including the four isolates resistant to ampicillin.

In vivo, seven patients who had bacteremia in

association with periorbital cellulitis, ethmoiditis, and epiglottitis due to *H. influenzae* had prompt response to cefamandole. Despite these encouraging in vitro and in vivo results, experience with larger numbers of patients and evaluation of certain infections such as those of the central nervous system is needed.

With the emergence of ampicillin-resistant *H. influenzae*, cefamandole may prove to be an effective parenteral antibiotic for certain infections caused by this organism.

LITERATURE CITED

1. Ericsson, H. M., and J. C. Sherris. 1971. Antibiotic sensitivity testing report of an international collaborative study. Acta Pathol. Microbiol. Scand. Sect. B 217:65-87.
2. Grove, D. C., and W. A. Randall. 1955. Assay methods of antibiotics: a laboratory manual. Medical Encyclopedia, New York.