

Clinical Efficacy and Safety of Cefmenoxime in Children

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Received 14 December 1984/Accepted 24 July 1985

Cefmenoxime, an investigational semisynthetic cephalosporin, was evaluated in 18 pediatric patients with a variety of infections. There were seven patients with urinary tract infections, two with wound infections, two with osteomyelitis, two with abscess infections, one with cervical adenitis, one with hidradenitis, one with pneumonia and sepsis, one with periorbital cellulitis, and one with ventriculitis. A total of 16 (88%) patients had a satisfactory clinical response demonstrated by improvement in clinical signs and symptoms. A total of 12 (67%) patients demonstrated eradication of their infecting organisms. Of the pathogens isolated in these patients, 16 isolates were susceptible to cefmenoxime. One patient developed a generalized urticarial rash that resolved within 24 h after cessation of cefmenoxime therapy. Mean peak level in serum after intravenous infusion was 55 µg/ml.

Cefmenoxime is a semisynthetic cephalosporin that displays a broad spectrum of activity against many gram-positive and gram-negative bacteria (1, 6). Recent studies in adults have demonstrated the clinical efficacy of cefmenoxime in a wide variety of infections, including urinary tract infections, pneumonia, and septicemia (3, 5). The current study was initiated to determine the clinical pharmacokinetics of cefmenoxime and to evaluate its clinical efficacy and safety in the treatment of bacterial infections in children.

MATERIALS AND METHODS

Patient selection. The patients were hospitalized at the Kings County Hospital and Downstate Medical Centers, Brooklyn, N. Y., and Children's Hospital Medical Center of Akron, Akron, Ohio. Children between the ages of 1 and 15 years were enrolled if they had suspected or confirmed bacterial infections and had no effective prestudy antimicrobial therapy. Children with meningitis, known hypersensitivity to beta-lactam antibiotics, or known renal insufficiency (creatinine, ≥ 2.5 mg/dl) were excluded. Written informed consent was obtained from the parent or legal guardian. Appropriate pretreatment radiologic studies were performed. Cultures were obtained within 48 h before the initiation of therapy; repeat cultures were obtained as clinically indicated, usually 2 to 4 days after therapy was started. If a wound remained unhealed or if purulent drainage persisted, cultures were obtained 24 to 48 h posttherapy. To diagnose urinary tract infection, a clean-catch specimen producing $\geq 100,000$ colonies per ml or a suprapubic aspiration containing $\geq 5,000$ colonies per ml was considered positive. Repeat urine cultures were obtained 2 to 4 days after the start of therapy. Patients were evaluated for adverse drug reactions and response to therapy by monitoring daily vital signs, by clinical evaluation 48 to 72 h after the onset of therapy, and by laboratory studies at weekly intervals.

Dosage and administration. Cefmenoxime was administered at a dose of 75 to 150 mg/kg of body weight per day by either bolus (for 3 to 5 min) or 30-min intravenous (i.v.) infusion, every 6 h. The duration of treatment was deter-

mined individually for each specific infection. No other antibiotics were administered concomitantly; in some cases, however, additional oral antibiotics followed completion of the course of cefmenoxime therapy.

Cefmenoxime levels. Patients receiving 30-min infusions had blood drawn for determination of trough and peak cefmenoxime levels in serum 30 min before and immediately after the infusion, respectively. Blood samples were obtained by venipuncture through a heparin lock. Samples were collected in tubes without anticoagulant. Serum was separated after centrifugation at $500 \times g$ for 5 min and was kept frozen at -70°C until assayed. Drug levels were determined by the agar well diffusion technique (2) in Trypticase soy agar (BBL Microbiology Systems, Cockeysville, Md.) with *Escherichia coli* ATCC 25922. Cefmenoxime standards were prepared in normal human serum and ranged from 1 to 64 µg of cefmenoxime per ml.

Susceptibility studies. Kirby-Bauer disk diffusion tests with a 30-µg disk were performed for all bacterial isolates. MICs by tube dilution (7) were also observed for the isolates obtained from patients enrolled at Kings County Hospital and Downstate Medical Center.

Patient evaluation. Clinical response was defined as satisfactory (no evidence of infection), improved (incomplete resolution of infection), relapse (improvement followed by deterioration), and failure (no response). Bacteriological response was defined as eradication (absence of original pathogen 48 to 72 h posttreatment), persistence (presence of original pathogen 48 to 72 h posttreatment), and not applicable (no cultural material available to demonstrate eradication, as in the case of resolving pneumonia, surgically drained abscess, or osteomyelitis).

RESULTS

A total of 28 children (14 boys and 14 girls) ranging in age from 1 to 16 years (mean, 8.5 years) were enrolled. The diagnoses and number of cases of each were as follows: pneumonia, 3; cervical adenitis, 3; soft-tissue infection and cellulitis, 5; urinary tract infection, 10; osteomyelitis, 2; periorbital cellulitis, 2; hidradenitis, 1; superinfected intralobar pulmonary sequestration, 1; and ventriculitis, 1.

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TABLE 1. Disease and treatment characteristics of 18 children evaluated in a clinical study of cefmenoxime

Patient	Age (yr)	Infection	Organism	MIC ($\mu\text{g/ml}$) or KB ^a	Source	Clinical response	Bacteriologic response
1	2	Ventriculitis	<i>Flavobacterium</i> sp. IIB	≥ 64	Ventricular fluid	Unable to evaluate	Persistence
2	3.5	Pneumonia	<i>Streptococcus pneumoniae</i>	$\leq .03$	Blood	Satisfactory	Eradication
3	2.5	Cervical adenitis	<i>Streptococcus pyogenes</i>	$\leq .03$	Aspirate of node	Satisfactory	Not applicable
4	15	Hidradenitis	<i>Serratia marcescens</i>	$\leq .03$	Abscess	Satisfactory	Eradication
5	11	Abscess	<i>Staphylococcus aureus</i>	4	Abscess	Satisfactory	Eradication
6	15	Abscess	<i>Staphylococcus aureus</i>	2	Abscess	Satisfactory	Not applicable
7	12.5	Osteomyelitis	<i>Staphylococcus aureus</i>	2	Bone, blood	Satisfactory	Eradication
8	1	Osteomyelitis	<i>Staphylococcus aureus</i>	2	Bone	Satisfactory	Not applicable
9	2	Periorbital cellulitis	<i>Haemophilus influenzae</i> type b	S	Eye	Satisfactory	Eradication
10	10	Surgical wound infection	<i>Escherichia coli</i> , enterococci	R	Wound	Satisfactory	Failure
11	2	Wound infection	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	S S	Wound	Satisfactory	Persistence
12	5	Urinary tract infection	<i>Morganella morganii</i>	S	Urine	Satisfactory	Eradication
13	9	Urinary tract infection	<i>Escherichia coli</i>	S	Urine	Satisfactory	Eradication
14	10	Urinary tract infection	<i>Proteus mirabilis</i>	S	Urine	Satisfactory	Superinfection
15	6	Urinary tract infection	<i>Escherichia coli</i>	S	Urine	Satisfactory	Superinfection
16	3	Acute pyelonephritis	<i>Haemophilus influenzae</i>	I	Urine	Failure	Persistence
17	1	Urinary tract infection	<i>Escherichia coli</i>	S	Urine	Satisfactory	Eradication
18	5	Urinary tract infection	<i>Escherichia coli</i>	S	Urine	Satisfactory	Eradication

^a KB, Kirby-Bauer, disk diffusion. Diameters: S, susceptible (≥ 19 mm); I, intermediate (17 to 18 mm); R, resistant (≤ 16 mm).

The medium duration of therapy was 5 days (range, 5 to 18 days).

Of these 28 patients, 18 had organisms isolated that were evaluable for efficacy. The clinical and bacteriologic characteristics of these patients are summarized in Table 1.

A satisfactory clinical response was seen in 16 of the 18 (88%) children with positive bacterial cultures (Table 1). One child who did not respond developed ventriculitis caused by *Flavobacterium* sp. IIB, which was resistant to cefmenoxime (MIC, ≥ 64 $\mu\text{g/ml}$). Another child who failed to respond had a urinary tract infection caused by *Pseudomonas aeruginosa*, which was also resistant to cefmenoxime. Four patients had *Staphylococcus aureus* isolated, including two children with osteomyelitis and soft-tissue abscesses. The MICs for the isolates ranged from 2 to 4 μg of cefmenoxime per ml. All four patients had a satisfactory clinical response, and bacteriologic cure was demonstrated in two of them; all four patients also had surgical drainage of their infections. Additional isolates included six *E. coli* (four urinary tract infections and two wound infections, including one from which *S. aureus* was also recovered), one *Proteus mirabilis* (urinary tract infection), one *Morganella morganii* (urinary tract infection), one *Streptococcus pneumoniae* (pneumonia and sepsis), one *Serratia marcescens* (hidradenitis), one *Streptococcus pyogenes* (cervical adenitis), and one *Haemophilus influenzae* type b (periorbital cellulitis). Eradication was confirmed in 10 of these patients. The two children with wound infections involving *E. coli* showed clinical resolution of inflammation and purulent discharge, but at the completion of therapy a culture from the incision continued to grow

E. coli. The youngster with a urinary tract infection secondary to *Proteus mirabilis* showed eradication of the organism, but the emergence of *P. aeruginosa* was seen in the follow-up urine cultures. All of the initial isolates were susceptible to cefmenoxime.

The remaining 10 patients, from whom we did not isolate any organisms, all appeared to respond satisfactorily with cefmenoxime. These patients included two children with cervical adenitis (who had surgical drainage), two children with pneumonia, one child with periorbital cellulitis, three children with urinary tract infection, two children with soft-tissue infection, and one child with superinfected intralobar pulmonary sequestration.

Cefmenoxime was administered without any significant toxicity. One child developed a generalized urticarial rash after 18 days of treatment, which resolved within 24 h of cessation of therapy. No side effects or laboratory abnormalities occurred in any patient. The mean peak and trough cefmenoxime concentrations were 55.0 ± 33.6 $\mu\text{g/ml}$ (range, 15 to 130 $\mu\text{g/ml}$; $n = 12$) and 1.1 ± 2.1 $\mu\text{g/ml}$ (range, 0 to 6.2 $\mu\text{g/ml}$; $n = 13$), respectively, after the 30-min i.v. infusion.

DISCUSSION

Cefmenoxime compares favorably in vitro with the recently released broad-spectrum cephalosporins cefotaxime, moxalactam, and cefoperazone for gram-negative bacteria (6). Cefmenoxime has greater in vitro activity against gram-positive bacteria than does moxalactam, especially against *S. pneumoniae*, *S. pyogenes*, and *S. aureus* (1).

In two recent clinical studies of cefmenoxime for the

therapy of bacterial infections in adults, Gombert et al. (3) reported a satisfactory clinical response in 94% of the patients enrolled, and LeFrock et al. (5) reported an overall clinical success rate of 96% and a bacteriologic cure rate of 88%. Clinical and bacteriologic failure was associated with infection with *Bacteroides fragilis* and *P. aeruginosa*, against which cefmenoxime has only moderate or no activity. Superinfection with *P. aeruginosa* also complicated the course of one of our patients. The most common adverse effects observed by Gombert et al. (3) were transient eosinophilia and thrombocytosis. LeFrock et al. (5) found 24 transient reactions in 23 patients, including eosinophilia, diarrhea, rash, leukopenia, elevated liver enzymes, and phlebitis. These reactions were not observed in any of our patients, except for the one child who developed a rash.

The mean peak concentration of cefmenoxime in serum in our patients after one 75- to 150-mg/kg dose was 55 µg/ml after the 30-min i.v. infusion. In a study of single-dose pharmacokinetics of cefmenoxime in adults (4), the mean calculated peak levels after 60-min i.v. infusions of 500, 1,000, and 200 mg were 22.8, 41.6, and 94.5 µg/ml, respectively. Gombert et al. (3) found peak concentrations of 47 µg/ml after a 1-g dose and 95 µg/ml after a 2-g dose. The trough levels were 9 µg/ml. The pharmacokinetics were best described by a two-compartment open model with a beta-phase half-life of 55 min.

The results of this preliminary study demonstrated that cefmenoxime is a safe and efficacious antibiotic in the

treatment of urinary tract infections, soft-tissue infections, and osteomyelitis in children.

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