Clinical and Bacteriological Evaluation of Cefoxitin Therapy in Children

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Cefoxitin, a parenteral cephamycin β -lactam antibiotic, was evaluated for safety and efficacy in children with bacterial infections other than meningitis. Twenty-six patients between 3 months and 7 years of age were treated with 80 to 160 mg/kg per day. The most common diagnoses were cellulitis (13 patients), pneumonia (5 patients), and bone and joint infection (4 patients). Nine patients were bacteremic. The most frequently recovered pathogens were *Staphylococcus aureus* (six patients), *Haemophilus influenzae* (four patients), and *Streptococcus pneumoniae* (three patients). All organisms were susceptible to cefoxitin. All 26 children were considered improved or cured. No severe adverse reactions were encountered. Phlebitis (4%), eosinophilia (12%), and elevated liver function tests (4%) were associated with therapy. Cefoxitin appears to be a safe, effective, and well-tolerated antibiotic when used in children with susceptible bacterial infections other than meningitis.

Cefoxitin, a cephamycin, beta-lactam antibiotic, has been effective and well tolerated in adults with infections due to susceptible bacteria (3-5). Its antimicrobial spectrum of activity, which includes gram-positive cocci and *Haemophilus influenzae*, makes it a potentially useful drug for the parenteral treatment of serious infections in children, which are most often due to these organisms (2). The therapy of serious *H. influenzae* type b infections has been complicated by the emergence of ampicillin resistance in this organism. Currently, chloramphenicol is added to or substituted for ampicillin in the initial treatment of such infections. In infections where staphylococci are also considered likely etiological agents such as cellulitis or osteomyelitis, another drug, resistant to penicillinase, is often added to the empiric regimen until culture results are available. Cefoxitin may provide a single-drug alternative to these regimens, possibly resulting in decreased cost or less potential drug interference.

To explore this possibility, we evaluated the efficacy and tolerance of cefoxitin in an open clinical trial in 26 children.

METHODS

Children eligible for study were those between the ages of 3 months and 12 years whose parents voluntarily consented to participation. Patients with a history of hypersensitivity to cephalosporins were ineligible. Patients were considered for inclusion in the study if they had clinical or bacteriological evidence

of an infection other than meningitis due to bacteria known or expected to be susceptible to cefoxitin. Patients were excluded if they had received presumably effective antibiotics during the 3 days preceding admission.

Cefoxitin was administered either intravenously through a scalp vein needle which was changed at approximately 48-h intervals or intramuscularly, generally in the muscle of the anterior thigh. Dosage was 80, 120, or 160 mg/kg per day depending upon whether the infection was categorized as mild, moderate, or severe. The drug was given at 6-h intervals. The intravenous preparation was infused in 15 min. The children were examined daily by one of the investigators with emphasis on resolution of signs and symptoms and detection of possible clinical adverse effects. Laboratory studies obtained immediately before, during, and immediately after cefoxitin therapy included complete blood count, direct Coombs test, urinalysis, creatinine, bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, and lactic dehydrogenase.

Etiological diagnosis was sought in all patients with multiple blood cultures and, when appropriate, cultures of urine, nasotracheal secretions, or aspirates from infected sites.

Pathogens recovered from patients were tested for susceptibility to cefoxitin by broth dilution and/or the Kirby-Bauer technique (1).

RESULTS

Twenty-six children were studied (Table 1). All were between 3 months and 7 years of age. Twelve were male. A specific bacterial etiology was identified in 19 (73%). Nine (35%) patients

TABLE 1. *Diagnoses and etiological agents of 26 children treated with cefoxitin*

Diagnosis	No. of cases	Etiological agent
Cellulitis	6	<i>H. influenzae</i> (1), ^a <i>S. aureus</i> (2), <i>S. pyogenes</i> (1)
Buccal cellulitis	3	<i>H. influenzae</i> (2)
Periorbital cellulitis	4	<i>H. influenzae</i> (1), <i>S. aureus</i> (1)
Osteomyelitis	2	<i>S. epidermidis</i> ^b (1), alpha-hemolytic streptococcus ^c
Septic arthritis	2	<i>S. pneumoniae</i> (1), <i>H. influenzae</i> (1)
Pneumonia	5	<i>S. pneumoniae</i> (2), <i>S. aureus</i> (2)
Abscess	2	<i>S. aureus</i> (1)
Suppurative thyroiditis	1	<i>S. pneumoniae</i>
Urinary tract infection	1	<i>E. coli</i>

^a Number in parentheses indicates number of isolates.

^b Recovered from needle aspiration of clavicle with radiological evidence of osteomyelitis.

^c Recovered from blood cultures from patient with fever, elevated sedimentation rate, and pus aspirated from left trochanter.

had bacteremia, five with *H. influenzae* and one each with *Staphylococcus aureus*, alpha-hemolytic streptococcus, *Streptococcus pneumoniae*, and group A beta-hemolytic streptococcus. Etiological bacteria were not recovered from five patients who had cellulitis with a typical clinical presentation and physical findings. Three had periorbital or buccal cellulitis, and the others had apparent bacterial infection of the skin and soft tissues of the legs. Of the two other patients without an identified bacterial etiology, one had a retropharyngeal abscess and the other had pneumonia. Both had fever, leukocytosis with a left shift, and radiographs consistent with bacterial infection.

Twenty-one infections were considered moderate and five were severe. In all cases there was rapid and progressive improvement in visible lesions and clinical symptoms. Temperatures fell to less than 38°C rectally within 48 h in all but two patients. In one child, a 5-year-old girl with staphylococcal arthritis, pneumonia and bacteremia (listed in Table 1 as pneumonia), a fever persisted for 5 days even though multiple blood cultures obtained after 24 h of therapy were negative. Despite her fever, this child showed clinical improvement, with clearing of mental obtundation and restoration of motion in her affected joint. The other child, a 6-year-old girl with bacteremic pneumococcal pneumonia, had

a temperature of 38.4°C on day 4 of therapy but was otherwise afebrile after 48 h of treatment.

Most patients (77%) received cefoxitin therapy for 2 to 7 days, at which time their clinical status had improved sufficiently to continue therapy with an oral antibiotic generally on an outpatient basis. The oral agents used were ampicillin or amoxicillin (7 patients), phenoxymethyl penicillin (4 patients), and cephalexin (13 patients). Parenteral therapy was continued for longer periods (8 days to 3 weeks) in six patients, including children with bone or joint infections. No relapses, recurrences, or suprainfections occurred in the study patients. All twenty-six patients (100%) were considered improved or cured by cefoxitin.

The intravenous and intramuscular preparations of cefoxitin were both tolerated quite well. One case of phlebitis (4%) occurred in a child whose infusion site had been unchanged for more than 72 h. The inflammation at the site resolved within 24 h after removal of the scalp vein needle. Therapy continued with an orally administered cephalosporin. No other adverse clinical reactions were reported. No serious laboratory abnormalities were detected. Three children (12%) had mild eosinophilia (range: 4 to 11%) that appeared during or just after cefoxitin therapy. There was no clinical evidence of hypersensitivity in these or other treated children. One child (4%), a 3-month-old boy with pneumococcal arthritis of the wrist, had a mild (2×) elevation in bilirubin and serum glutamic oxaloacetic transaminase that was not readily explainable and may have been related to cefoxitin. It was first observed 1 day after the drug was discontinued after 7 days of intravenous and intramuscular therapy.

By using the criteria of disk zone size ≥ 18 mm and minimum inhibitory concentration ≤ 16 µg/ml, all of the organisms recovered were susceptible to cefoxitin by the disk diffusion or broth dilution method or both. An additional six clinical isolates of *H. influenzae* were tested, and all were susceptible to 1.6 µg/ml or less. All but one of the *Haemophilus* strains were susceptible to ampicillin. The minimum inhibitory concentrations for the 17 organisms available for study are shown in Table 2.

DISCUSSION

In this open study of cefoxitin in pediatric patients, the diagnosis was bacteriologically confirmed regularly in all categories except cellulitis. In this group, we assume that the responsible pathogens in the culture-negative patients were similar to those in the culture-positive children but that the insensitivity of the skin aspiration

TABLE 2. Minimum inhibitory concentration of cefoxitin for 17 clinical isolates

Organism (no.)	No. of strains inhibited by cefoxitin concn ($\mu\text{g/ml}$):					
	≤ 0.2	0.4	0.8	1.6	3.1	6.2
<i>S. aureus</i> (6)	1				5	
<i>S. epidermidis</i> (1)			1			
Alpha-hemolytic streptococcus (1)		1				
Group A beta-hemolytic streptococcus (1)				1		
<i>S. pneumoniae</i> (3)	1	2				
<i>H. influenzae</i> (4)				4		
<i>E. coli</i> (1)						1

technique and the absence of detectable bacteremia made bacteriological diagnosis more difficult.

The clinical response of virtually all patients regardless of site of infection or pathogen was excellent and rapid. Serious clinical adverse effects were not observed, and phlebitis, an anticipated problem, was not unduly frequent in this study where frequent rotation of intravenous sites was generally practiced. Clinically significant laboratory abnormalities were not encountered in study patients. No treatment courses were interrupted or discontinued because of clinical or laboratory adverse reactions.

The children involved in this study were generally in good health and not suffering from chronic diseases or taking immunosuppressive therapy. Their infections were community acquired, and the types and perhaps the susceptibility of the bacteria recovered from them reflect this. Gram-positive cocci and *H. influenzae* accounted for all but one documented infection. Predictably, these organisms were susceptible to cefoxitin (2). Interestingly, the single ampicillin-resistant *H. influenzae* (minimum inhibitory concentration, 16 $\mu\text{g/ml}$) was also sensitive to cefoxitin, a finding that has also been described previously (W. N. Khan, S. Ross, W. J. Rodriguez, A. Freeman, and G. Controni, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 17th, New York, N.Y., Abstr. no. 65, 1977).

Based on this limited open study in children, cefoxitin appears to be a safe, effective, and well-tolerated antibiotic when used in children with infections due to susceptible bacteria in sites other than cerebrospinal fluid.

The major advantage of cefoxitin over conventional empiric double- or triple-antibiotic therapy in situations where staphylococci and ampicillin-resistant *Haemophilus* strains are both likely pathogens would seem to be the convenience of single-drug therapy and the possible avoidance of toxicity and drug interactions associated with other presently available agents such as penicillinase-resistant penicillin and chloramphenicol.

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