

Study of Use of Cefdinir versus Cephalexin for Treatment of Skin Infections in Pediatric Patients

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Three hundred ninety-four patients, aged 6 months to 12 years, entered a multicenter, randomized, controlled, investigator-blind study comparing cefdinir, 7 mg/kg of body weight twice a day, with cephalexin, 10 mg/kg four times a day, each given for 10 days. The most common infections treated were impetigo and secondary infection of preexisting dermatitis. The most common pathogens isolated were *Staphylococcus aureus* and *Streptococcus pyogenes*. Two hundred thirty-one patients were microbiologically evaluable. Microbiologic eradication rates were 164 of 165 pathogens (99.4%) in the cefdinir group and 152 of 156 pathogens (97.4%) in the cephalexin group ($P = 0.14$). Clinical cure rates were 116 of 118 patients (98.3%) in the cefdinir group and 106 of 113 patients (93.8%) in the cephalexin group ($P = 0.056$). Sixteen percent of cefdinir patients and 11% of cephalexin patients experienced adverse events ($P = 0.11$), the most common being diarrhea, which affected 8% of the cefdinir group and 4% of the cephalexin group. Cefdinir appears to be an effective and well-tolerated agent for the treatment of uncomplicated skin and skin structure infections in pediatric patients.

Uncomplicated skin and skin structure infections, including impetigo, cellulitis, and other pyodermas such as folliculitis, are frequent among children and represent one of the most common reasons (up to 18%) for visits to pediatric outpatient clinics (14). The most common pathogens involved in outpatient infections are the gram-positive organisms *Staphylococcus aureus* and *Streptococcus pyogenes*. Although these infections usually respond to a number of antimicrobial regimens, the activity of many commonly used agents against staphylococci is less than optimal. A recent survey showed that MICs at which 90% of the isolates are inhibited (MIC₉₀s) of cephalexin, cefaclor, and erythromycin, three frequently used antimicrobial agents, were 16, 8, and 16 µg/ml, respectively, for beta-lactamase-producing, methicillin-susceptible *S. aureus* (4). Although the rate of *S. pyogenes* resistance to erythromycin in the United States is currently approximately 2% (1), resistance rates in other parts of the world are high: e.g., MIC₉₀s of >128 µg/ml have been reported from Taiwan (7). More active agents against the common pathogens causing uncomplicated skin and skin structure infections would be desirable.

Cefdinir (CI-983, FK-482) is a new orally available, extended-spectrum cephalosporin with good in vitro activity against gram-positive pathogens. MIC₉₀s for methicillin-susceptible *S. aureus* are in the range of 0.25 µg/ml; it is also very active against streptococci, such as *S. pyogenes*, with MIC₉₀s in the

range of 0.06 µg/ml (2, 10). Peak levels of 2.6 and 3.6 µg/ml in plasma are achieved with doses of 7 and 14 mg/kg, respectively, and the half-life in plasma is approximately 1.5 h (5). Penetration into skin, as gauged by a skin blister fluid model, is 92 to 108% (11). Cefdinir is thus a promising agent for the treatment of uncomplicated skin and skin structure infections, where these pathogens are frequently encountered. Preliminary data from small Japanese trials have suggested its efficacy against these infections (8). The present study was performed to evaluate the usefulness of cefdinir in the treatment of uncomplicated skin infections in children.

(Data from this study were presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., 1995.)

MATERIALS AND METHODS

Pediatric patients aged 6 months to 12 years who met the following criteria were eligible for study entry: clinical diagnosis of uncomplicated mild to moderate skin or skin structure infection warranting systemic antimicrobial therapy, with pain, tenderness, erythema, swelling, induration, crusting, fluctuation, and/or drainage. Each of these conditions was quantified (absent, mild, moderate, or severe) at the admission visit and at each return visit. Standard definitions of infections (impetigo, cellulitis, wound infection, abscess, paronychia, folliculitis, etc.) were used (13). Patients were prohibited from entering the study if they had a history of hypersensitivity to beta-lactams, previous therapy for the current infection, significant renal (a creatinine level >1.5 times the upper limit of normal) or hepatic (bilirubin or serum glutamic oxalacetic transaminase and/or serum glutamic pyruvic transaminase level >2 times the upper limit of normal) dysfunction, a pathogen known to be resistant to either cefdinir or cephalexin, or prior participation in any other cefdinir clinical study. Cultures were obtained by aspiration of an abscess or swabbing of a draining lesion. Patients were then randomized to receive either cefdinir suspension (Parke-Davis Pharmaceuticals, Ann Arbor, Mich.), 7 mg/kg of body weight twice a day, or cephalexin suspension (Warner-Chilcott, Morris Plains, N.J.), 10 mg/kg four times a day, each to be given for 10 days. Since true blinding of the suspension formulations could not be achieved, caregivers were advised not to discuss the dosing regimen or any other information about the medication itself with the evaluating investigator. Patients were scheduled to return for two posttherapy visits. The first, the test-of-cure (TOC) visit, was to take place 7 to 14 days after completion of therapy; the second, the long-term follow-up (LTFU) visit, was to occur 21 to 35 days after completion of therapy. At each of these visits, the presenting signs and symptoms were reassessed and cultures of the original lesion were obtained. Cultures were performed by broth microdilution at a central laboratory (Pharmaceutical Laboratory Services, Baltimore, Md.). MIC determinations were performed accord-

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TABLE 1. In vitro susceptibility testing results

Pathogen	No. of isolates	MIC ($\mu\text{g/ml}$) of:					
		Cefdinir ^a			Cephalexin ^b		
		Range	50%	90%	Range	50%	90%
<i>Staphylococcus aureus</i>	284	0.06–2.0	0.25	0.5	1.0–64	2.0	4.0
<i>Streptococcus pyogenes</i>	111	<0.008–0.12	0.008	0.03	<0.12–4.0	0.25	2.0
<i>Streptococcus agalactiae</i>	17	0.015–0.25	0.03	0.12	0.5–16	2.0	4.0
<i>Enterobacter agglomerans</i>	12	0.06–1.0	0.25	0.25	8.0–8.0	8.0	8.0

^a Tentative breakpoints: susceptible, ≤ 1.0 $\mu\text{g/ml}$; intermediate, 2.0 $\mu\text{g/ml}$; resistant, ≥ 4.0 $\mu\text{g/ml}$.

^b National Committee for Clinical Laboratory Standards breakpoints: susceptible, ≤ 8 $\mu\text{g/ml}$; intermediate, 16 $\mu\text{g/ml}$; resistant, ≥ 32 $\mu\text{g/ml}$.

ing to standards published by the National Committee for Clinical Laboratory Standards (9). Coagulase-negative staphylococci were not considered pathogens. All other isolates were considered potential pathogens and were included in the analysis. For cefdinir, the following tentative breakpoints were used: susceptible, ≤ 1 $\mu\text{g/ml}$; intermediate, 2 $\mu\text{g/ml}$; resistant, ≥ 4 $\mu\text{g/ml}$. Microbiologic outcome was defined as eradication (negative culture for the original pathogen or the absence of material to culture because of improvement, which was presumed to be eradication) or persistence (positive culture for the original pathogen) at the TOC visit, or sooner in the case of clinical failure. Clinical outcomes were determined by the investigator and defined as cure (absence or satisfactory remission of all admission signs and symptoms) or failure (no significant remission of admission signs and symptoms or further antibacterial therapy required). An outcome of "improved" was not used, and patients were considered nonassessable only if no follow-up information was available. For any patient whom the investigator classified as unable to be evaluated, but who had follow-up data, data were forced into a cure or failure outcome on the basis of a predefined algorithm. Equivalence of outcomes was assessed by using a two-tailed 95% confidence interval (CI) approach (12). Treatment outcomes were to be defined as equivalent if the CI was within $\pm 10\%$. A sample size of 120 evaluable patients in each arm was planned to achieve an 80% power to prove equivalence, assuming an overall efficacy rate of 85%. A confirmatory Cochran-Mantel-Haenszel (CMH) test was performed for treatment differences (12).

To be evaluable, a patient must have had admission clinical signs and symptoms compatible with the diagnosis of uncomplicated skin and skin structure infection, had a pathogen identified by culture which was susceptible or intermediately susceptible to both cefdinir and cephalexin, taken at least 70% of assigned medication and returned on schedule for the TOC visit (except for failures), and taken no other antimicrobial agents. Compliance was assessed by questioning the parent or guardian, by checking a medication diary, and by quantifying returned medication. An intent-to-treat analysis was also planned.

Patients were observed between the TOC and LTFU visits for reappearance of the original infectious process, which was defined as recurrence. Recurrence could include both relapse (infection caused by the original pathogen) and reinfection (infection caused by a new pathogen).

All patients receiving the study drug were evaluated for safety. Safety was assessed by questioning the patient and parent or guardian about the occurrence of adverse events, by looking for changes on physical examination, and by routine laboratory screening (complete blood count with differential, blood urea nitrogen, creatinine, hepatic enzymes, and urinalysis) performed at study admission and repeated after completion of therapy at the TOC visit. Adverse events were classified by severity as mild (no effect on daily activities), moderate (minor effect on daily activities), or severe (major effect on daily activities). CMH testing was used to detect treatment differences in adverse event rates, with a P value of <0.05 defined as significant.

This study was approved by the Institutional Review Board at each study site. Written informed consent was obtained from each patient's parent or guardian.

RESULTS

Between July 1992 and August 1993, 18 investigators enrolled 394 patients into the study, 217 boys and 177 girls. Fifty-one percent of the patients were white, 13% were black, and the rest were Asian, Hispanic, or "other." The median age was 5.3 years (range, 0.5 to 13.1 years), and the most common diagnoses were impetigo (57%), infected dermatitis (9%), wound infection (8%), and cellulitis (7%). The two treatment groups

were comparable in respect to sex, age, and race distribution and in the types of infections present.

A total of 517 pathogens were isolated. Gram-positive pathogens predominated, the most frequent being *S. aureus* (284 isolates) and *S. pyogenes* (111 isolates). *Enterobacter agglomerans* was the most frequently identified gram-negative pathogen. Susceptibility data for the most common pathogens are summarized in Table 1. None of the most commonly encountered pathogens were resistant to cefdinir, though occasional isolates of *S. aureus* demonstrated only intermediate susceptibility. In total, 40 isolates were resistant to cefdinir and 56 were resistant to cephalexin ($P < 0.001$ by CMH testing). For both study drugs, the most frequent resistant isolates were *Enterococcus spp.* and *Acinetobacter calcoaceticus* bv. *anitratus*.

A total of 231 patients were evaluable. The most common reasons why patients were not evaluable were as follows: the pathogen was resistant to either study medication, no pathogen was isolated at study admission, or the patient was noncompliant. The numbers of patients excluded for each of these reasons were similar in both groups. Microbiologic outcomes, broken down by pathogen, for these patients at the TOC visit are shown in Table 2. Overall, 164 of 165 (99.4%) pathogens in the cefdinir group were eradicated or presumed eradicated, as were 152 of 156 (97.4%) in the cephalexin group. These rates were statistically equivalent; the 95% CI test yielded a result of -0.8% to 4.7%, and the CMH test gave a P value of 0.135.

Clinical outcomes in evaluable patients, broken down by type of infection, are shown in Table 3. Approximately two-thirds of the patients had impetigo. In the cefdinir group, 116 of 118 (98.3%) were cured, and 106 of 113 (93.8%) in the cephalexin group were cured. Statistical testing showed the 95% CI ranges to be -0.5% to 9.5%, showing that the two treatment groups were equivalent. The CMH test yielded a P value of 0.056, indicating that the differences were marginally significant.

The cefdinir patients with intermediately susceptible pathogens appeared to do as well as those with fully susceptible isolates, both microbiologically and clinically.

Not included in the above data are those from eight patients who were not evaluable only because their pathogens, most

TABLE 2. Microbiologic eradication rates

Organism	Cefdinir		Cephalexin	
	No. eradicated/no. treated	%	No. eradicated/no. treated	%
<i>Enterococcus durans</i>	1/1	100.0	0/0	0.0
<i>Enterococcus faecalis</i>	0/0	0.0	1/1	100.0
<i>Enterococcus hirae</i>	1/1	100.0	0/0	0.0
<i>Staphylococcus aureus</i>	96/97	99.0	95/98	96.9
<i>Streptococcus agalactiae</i>	4/4	100.0	6/6	100.0
<i>Streptococcus pneumoniae</i>	2/2	100.0	1/1	100.0
<i>Streptococcus pyogenes</i>	42/42	100.0	41/42	97.6
<i>Streptococcus group C</i>	1/1	100.0	0/0	0.0
<i>Acinetobacter lwoffii</i>	2/2	100.0	1/1	100.0
<i>Enterobacter agglomerans</i>	5/5	100.0	5/5	100.0
<i>Enterobacter cloacae</i>	2/2	100.0	0/0	0.0
<i>Escherichia coli</i>	1/1	100.0	1/1	100.0
<i>Haemophilus influenzae</i>	2/2	100.0	0/0	0.0
<i>Klebsiella oxytoca</i>	1/1	100.0	0/0	0.0
<i>Klebsiella pneumoniae</i>	3/3	100.0	0/0	0.0
<i>Moraxella sp.</i>	1/1	100.0	1/1	100.0
Total	164/165	99.4	152/156	97.4

TABLE 3. Clinical cure rates

Diagnosis	Cefdinir		Cephalexin	
	No. cured/ no. treated	%	No. cured/ no. treated	%
Impetigo	72/74	97.3	73/76	96.1
Infected dermatitis	15/15	100.0	5/6	83.3
Wound infection	9/9	100.0	8/8	100.0
Cellulitis	7/7	100.0	4/5	80.0
Paronychia	3/3	100.0	6/7	85.7
Abscess	2/2	100.0	4/4	100.0
Other	8/8	100.0	6/7	85.7
Total	116/118	98.3	106/113	93.8

often *S. aureus* or *Enterococcus faecalis*, were resistant to cephalexin (but susceptible to cefdinir). All of these pathogens were eradicated, and all of these patients were assessed as clinically cured at the TOC visit.

An intention-to-treat analysis was also performed. This analysis counted as failures all patients who had negative admission cultures or for whom follow-up information was not available. This analysis did not reveal any statistically significant differences between the two treatment groups in clinical outcome, with cure rates of 179 of 196 patients (91.3%) for cefdinir and 181 of 198 patients (91.4%) for cephalexin. Microbiologic eradication rates were 238 of 249 pathogens (95.6%) in the cefdinir group and 243 of 267 pathogens (91.0%) in the cephalaxin group ($P < 0.05$).

By the time of the LTFU visit, 2 of 104 (1.9%) available cefdinir patients and 4 of 97 (4.1%) cephalaxin patients had recurrences of their original infections.

Adverse events are summarized in Table 4. Thirty-two (16%) cefdinir patients and 22 (11%) cephalaxin patients experienced at least one adverse event during therapy ($P = 0.11$); these figures represent all adverse events, regardless of the investigator's opinion of their relationship to a study drug. Diarrhea was the most common adverse event in the cefdinir group (15 patients, 7.7%), and new infection was the most common event in the cephalaxin group (7 patients, 3.5%). Neither of these differences was statistically significant. Rates of adverse events did not appear to differ by sex or race. Reports of diarrhea decreased with increasing age: they were highest in the 6-month- to 2-year-old group and lowest in the 6- to 12-year-old group. The overwhelming majority of adverse events were mild or moderate; two patients (1%) in the cefdinir group and one patient (0.5%) in the cephalaxin group experienced severe adverse events. In both treatment groups, the incidence of adverse events was highest during the first 4 days of treatment.

Three cefdinir patients (1.5%) discontinued the study drug because of adverse events: rash, diarrhea, and bronchitis in one patient each. No cephalaxin patients discontinued the study medication because of adverse events. The difference in discontinuation rates was not statistically significant.

Analysis of laboratory value changes showed a trend in both treatment groups toward lowering of the peripheral leukocyte count and percent polymorphonuclear leukocytes, consistent with resolution of infection. Increases in eosinophil levels and liver function test results were observed rarely in both treatment groups. It could not be determined if these were caused by the study medication.

DISCUSSION

This study demonstrated that cefdinir is comparable to cephalaxin for the treatment of uncomplicated skin infections in children. It appeared to be at least as effective as cephalaxin in producing a clinical cure, and it was as effective as cephalaxin in eradicating pathogens causing these infections.

The clinical effectiveness of cefdinir may be related to its increased *in vitro* activity. Even though some resistance to cefdinir is present in the community, it was active against more pathogens isolated from patients entering this study than was cephalaxin. Eight patients with cephalaxin-resistant pathogens were treated successfully with cefdinir.

Most evaluable patients, approximately two-thirds, had impetigo. Although cefdinir appeared to be effective for the treatment of other types of infections, such as cellulitis, wound infection, and infected dermatitis, the small numbers of patients with these diagnoses make it difficult to generalize the results with complete assurance. Similarly, although the plasma levels of cefdinir in children are similar to those achieved in adults, and the MICs for pathogens are the same, different disease processes and the presence of underlying conditions may affect the outcome of treatment in the two groups. The results observed in this study are similar to those seen with other oral cephalosporin agents for the treatment of uncomplicated skin and skin structure infections. A study comparing loracarbef with cefaclor in pediatric patients with skin infections showed favorable response rates in loracarbef patients of 97.3% at 72 h after the completion of therapy and 95.6% at 10 to 14 days posttherapy (6). In a study comparing cefprozil with cefaclor in pediatric patients with infections due to *S. aureus* or *S. pyogenes*, all patients in both study arms responded favorably (3). In both of the studies cited, impetigo was the most common type of infection evaluated, as was the case in the present study.

In the present study, both study medications were well tol-

TABLE 4. Adverse-event rates

Adverse event	Cefdinir		Cephalexin	
	No. of patients (n = 196)	%	No. of patients (n = 198)	%
Diarrhea	15	7.7	8	4.0
Rash	4	2.0	1	0.5
Infection	2	1.0	7	3.5
Increased cough	2	1.0	1	0.5
Vomiting	2	1.0	1	0.5
Lung disorder	2	1.0	1	0.5
Eczema	2	1.0	0	0.0
Pharyngitis	1	0.5	1	0.5
Accidental injury	1	0.5	0	0.0
Asthenia	1	0.5	0	0.0
Fever	1	0.5	0	0.0
Headache	1	0.5	0	0.0
Dyspepsia	1	0.5	0	0.0
Cutaneous candidiasis	1	0.5	0	0.0
Incoordination	1	0.5	0	0.0
Nervousness	1	0.5	0	0.0
Bronchitis	1	0.5	0	0.0
Rhinitis	1	0.5	0	0.0
Conjunctivitis	1	0.5	0	0.0
Ear disorder	1	0.5	0	0.0
Nail disorder	1	0.5	0	0.0
Constipation	0	0.0	1	0.5
Gastroenteritis	0	0.0	1	0.5
Insomnia	0	0.0	1	0.5

erated. Although the incidence of all adverse events was greater in the cefdinir group, the difference was not statistically significant. Almost all were mild to moderate. Discontinuation of cefdinir because of an adverse event was uncommon. The most common adverse event seen in patients receiving either medication was diarrhea.

In selecting an antimicrobial for treatment of an individual patient, the practitioner must consider multiple variables, weighing both effectiveness and tolerance. The present study demonstrates that cefdinir is more likely than cephalexin to be active in vitro against pediatric skin pathogens and is effective in producing both microbiologic and clinical responses in patients. Cefdinir was used successfully to treat infections caused by cephalexin-resistant pathogens. On the other hand, adverse events were more frequent in cefdinir-treated patients. We did not conduct a cost-benefit analysis to determine if the cost of the drug (unavailable for cefdinir at present), the potential added cost of treatment failures, or the possible increased expenses associated with side effects favored one treatment arm or the other in terms of total cost of therapy. Studies comparing newer, more potent therapies with older, perhaps better-tolerated treatments need to be carried out to determine strategies appropriate for managed-care settings.

In summary, cefdinir appears to be a safe and effective drug for the treatment of mild to moderate skin and skin structure infections in pediatric patients.

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