Evaluation of Cefuroxime Axetil and Cefadroxil Suspensions for Treatment of Pediatric Skin Infections

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A randomized, single-blind, multicenter study was conducted to evaluate the safety and efficacy of cefuroxime axetil and cefadroxil suspensions for the treatment of skin or skin structure infections in 287 children. Each drug was given at a dosage of 30 mg/kg of body weight per day in two divided doses. *Staphylococcus aureus* and *Streptococcus pyogenes*, or a combination of the two, were the primary pathogens isolated from infected skin lesions. A satisfactory bacteriologic response (cure or presumed cure) was obtained in 97.1 and 94.3% of children in the cefuroxime axetil and cefadroxil groups, respectively (P > 0.05). Satisfactory clinical responses (cure or improvement) were more likely to occur in cefuroxime axetil recipients than in cefadroxil recipients (97.8 versus 90.3%; P < 0.05). Both regimens were equally well tolerated, with adverse events occurring in 7.9 and 6.1% of cefuroxime axetil and cefadroxil recipients, respectively. There were more patients who refused to take cefuroxime axetil (7 of 189) than there were who refused to take cefadroxil (0 of 98), but the difference was not statistically significant (P = 0.1). In this study, cefuroxime axetil was at least as effective as cefadroxil in resolving skin and skin structure infections in children.

Cefuroxime is an expanded-spectrum cephalosporin with improved β-lactamase stability and a broad spectrum of activity against clinically important gram-positive and gram-negative pathogens. The lowest concentrations that inhibited the growth of 90% of the *Staphylococcus aureus* and *Streptococcus pyogenes* strains tested were 1 to 2 and <0.125 μg/ml, respectively (2).

Cefuroxime axetil, the acetyloxyethyl ester of cefuroxime, is a prodrug that is suitable for oral administration. After oral ingestion, cefuroxime axetil is deesterified in the intestinal mucosa and appears as cefuroxime in the blood. Peak concentrations in serum increase in proportion to dose and are 3.3 and 5.1 μg/ml after oral doses of a cefuroxime axetil suspension of 10 and 15 mg/kg of body weight, respectively (12). These results are comparable to those achieved in adults following administration of a 250-mg cefuroxime axetil tablet (7). Thus, achievable concentrations in serum exceed the MICs for common cutaneous pathogens (2). The tablet formulation of cefuroxime axetil has previously been found to be effective in the treatment of skin or skin structure infections in adults (4, 5).

The purpose of the study described here was to evaluate the efficacy and safety of a new liquid suspension of cefuroxime axetil in children with skin or skin structure infections. Cefadroxil suspension was selected as the active control because it has been proven to be effective in the treatment of skin or skin structure infections and is suitable for twice-daily administration.

**MATERIALS AND METHODS**

**Eligibility criteria.** Children (ages 3 months to 12 years) with skin or skin structure infections requiring antibiotic treatment were eligible to participate in the study. Patients were excluded if any of the following were present: infection requiring incision and drainage, hypersensitivity to cephalosporin or penicillin, previous systemic antibacterial drug treatment (within 7 days), history of gastrointestinal disorder that could alter drug absorption (within 3 months), unstable concomitant disease, immunosuppression, or previous enrollment in this study. Patients were to be withdrawn after enrollment if, upon culture and susceptibility testing, no pathogen was isolated or the pathogen was not susceptible to the study drugs (e.g., methicillin-resistant *S. aureus*). Patients were discontinued from the study if any of the following occurred: adverse event necessitating discontinuation of drug therapy, treatment failure or recurrence of infection, patient refusal of further doses, or failure to return for follow-up.

**Study design.** This was an evaluator-blinded, multicenter study. Patients were randomly chosen to receive either cefuroxime axetil suspension (Cefit; Glaxo Inc., Research Triangle Park, N.C.) or cefadroxil suspension (Duricef; Mead Johnson Pharmaceuticals, Evansville, Ind.) in a 2:1 ratio according to a predetermined randomization schedule. Both drugs were administered orally at a dosage of 30 mg/kg/day in two divided doses every 12 h (maximum dose, 1 g/day) for 10 days. Cefuroxime axetil was given after morning and evening meals, because postprandial administration of cefuroxime axetil (in the tablet form) has been shown to enhance absorption (3). Cefadroxil was given without regard to meals, as recommended by the manufacturer. Compliance was assessed by assay of antibiotic activity in urine during treatment and by the volume of drug

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returned upon completion of the treatment period. The absence of detectable antibacterial activity in a during-treatment urine sample excluded a patient from the efficacy analyses. Written informed consent was obtained from all patients' parents or legal guardians. This protocol was approved by the institutional review boards of the respective investigators' institutions.

**Efficacy assessment.** Response to treatment was assessed bacteriologically and clinically. Although 10 days was the standard length of therapy for most infections in children, for purposes of efficacy assessments, 5 days (10 doses) was predetermined as the minimum length of treatment necessary to effect clinical improvement and eradication of the causative organism(s) from superficial skin infections.

Specimens from the involved skin lesion(s) were obtained for bacterial culture and susceptibility testing at the initial visit and, if culturable, by needle aspiration or sterile swab of a lesion(s). Crusted material was partially unroofed. The culture material obtained was processed at an accredited laboratory according to that laboratory's standard protocol for wound or surface specimen culture. Standard disk or dilution methods were used for susceptibility testing; the current criteria of the National Committee for Clinical Laboratory Standards were used to interpret the results (10). Bacteriological outcome was determined at the completion of the study or when the patient's condition dictated the need for alternate antibiotic therapy. Bacterial responses were rated as cure (initial pathogen eradicated), failure (identification of the original pathogen in a follow-up culture), or relapse (eradication with subsequent isolation of the original pathogen). Presumptive bacterial responses were made on the basis of the clinical response when follow-up cultures were not obtainable because of healing of the lesion(s) (e.g., presumed cure). For statistical analysis, bacteriological outcomes were grouped as satisfactory (cure or presumed cure) or unsatisfactory (failure or relapse).

Patients underwent at least three clinical evaluations at the following intervals: at the start of therapy (initial visit), at 4 to 6 days after the initiation of therapy (during treatment), and at 5 to 7 days after the completion of therapy (posttreatment). If complete healing did not occur at 5 to 7 days, an additional visit was required at 14 to 20 days posttreatment. Clinical response was rated as cure (resolution of clinical signs and symptoms of infection), improvement (resolution of signs and symptoms with incomplete lesion healing; further antibacterial therapy required), failure (no improvement after ≥5 days of treatment or discontinuation of treatment because of adverse event; alternate antibacterial therapy required), or recurrence (initial diminution of signs and symptoms but recurrence by the posttreatment visit; further or alternate antibacterial therapy required). For statistical analysis, a satisfactory clinical response was defined as cure or improvement; an unsatisfactory clinical response was defined as failure or recurrence.

**Safety assessment.** All patients were monitored for adverse events. Each patient's parent or guardian was interviewed at each visit to determine the presence of adverse events. In order to avoid bias in eliciting adverse events, the initial questioning was restricted to "Is your child having any problems?" In addition, physical findings that were detected by the physician observer but that were not present at the initial visit were recorded as adverse events and were assessed as to their possible relationship to treatment. For the purpose of monitoring laboratory safety, blood was collected for complete blood count with differential, platelet count, prothrombin time, and the direct Coomb's test and for evaluation of hepatic enzymes, blood urea nitrogen, and serum creatinine. Urine was obtained for evaluation of albumin and glucose and a microscopic examination. These tests were performed at the initial and posttreatment visits.

**Statistical analysis.** Two-sided statistical tests were used. Demographic data were summarized by using a van Elteren statistic (13) (patient age and weight), a Mantel-Haenszel statistic (9) controlling for investigational center (sex and ethnic origin), or a Fisher exact test (8) (allergy, significant medical history, and abnormal physical finding) to examine the comparabilities of treatment groups. Summary statistics were performed on bacteriological and clinical assessments; the Mantel-Haenszel test was used to evaluate differences between treatment groups. The incidence rates of adverse events were compared between treatment groups by using a Fisher exact test. A P value of 0.05 or less was considered statistically significant.

### RESULTS

A total of 287 patients from 11 centers were enrolled in the study (Table 1). Forty-nine patients were excluded from the analyses because of the following prespecified protocol violations: inability to isolate a pathogen from the pretreat-
ment culture (for the cefuroxime axetil and cefadroxil treatment groups, 17 and 10 patients, respectively), negative urine bioassay (8 and 1 patient, respectively), absence of susceptibility testing on pretreatment pathogen (6 and 4 patients, respectively), resistant pathogen (2 and 0 patients, respectively), and concurrent antimicrobial therapy (0 and 1 patient, respectively). The two resistant pathogens were methicillin-resistant *S. aureus*. One cefuroxime axetil-treated patient from whom no pathogen was isolated in the pretreatment culture was withdrawn from the study because of the patient's refusal to take the study medication. Two additional patients who were withdrawn from the study because of refusal to take the study medication were excluded from the analysis because of prior negative urine bioassays. The remaining six patients with negative urine bioassays were either lost to follow-up (n = 3) or completed the study but did not return medication bottles to provide other evidence of compliance (n = 3). The cefadroxil-treated patient completed the study but did not return medication bottles to provide other evidence of compliance. In total, three cefuroxime axetil-treated patients who refused to take the study medication were excluded from analysis because of the prespecified protocol violations described above; data for these patients are not given below in the bacteriological and clinical outcome sections. All patients with protocol violations were included in an intent-to-treat analysis, the results of which appear later in this report. There were no differences (P > 0.05) between the two treatment groups in the proportion of patients with any particular reason for exclusion from analysis.

After excluding the 49 patients, 156 patients in the cefuroxime axetil treatment group and 82 patients in the cefadroxil treatment group were available for bacteriological and clinical efficacy analyses. These remaining patients were evenly distributed on the basis of age, weight, and sex but not ethnic origin. The majority of cefadroxil recipients were Caucasian, whereas cefuroxime axetil recipients were nearly evenly divided between Caucasian and black ethnic origins (P < 0.007). The primary diagnosis in both groups was impetigo; this was followed in descending order of frequency by cellulitis, injury-induced wound infection, and paronychia. The mean dose received (approximately 28 mg/kg/day) and the duration of treatment (10 days) were nearly identical for the two treatment groups.

**Bacteriological outcome.** In the cefuroxime axetil-treated patients, 198 of 206 pathogens isolated were either *S. aureus* (n = 129; 63%) or *S. pyogenes* (n = 69; 33%). Both *S. aureus* and *S. pyogenes* were isolated as copathogens from 47 of 156 patients in this group. In the cefadroxil group, 104 of 110 pathogens were *S. aureus* (71; 65%) or *S. pyogenes* (33; 30%). Both microorganisms were isolated from 23 of 82 patients in this group.

Thirty patients were bacteriologically uneventful because of failure to return for follow-up, drug treatment for less than 5 days (less than 10 doses), or clinical recurrence without a documented bacteriological outcome (Table 2). Of the seven cefuroxime axetil-treated patients classified by the investigator as receiving less than 5 days of study drug, four withdrew from the study because of refusal to take the study medication, one withdrew before any doses were given, and two withdrew because of an inability to complete the study requirements for personal reasons. Of the cefadroxil-treated patients who received less than 5 days of study drug, one withdrew for personal reasons and one withdrew because of an adverse event. Of the remaining patients, satisfactory responses occurred in 97.1 and 94.3% of cefuroxime axetil and cefadroxil recipients, respectively (P = 0.242). In the cefuroxime axetil group, all unsatisfactory responses were associated with infections caused by *S. aureus* (three failures, one relapse). Likewise, unsatisfactory responses in the cefadroxil group were associated with infections caused by *S. aureus* (four treatment failures). Two of these patients had polymicrobial infections that were also caused by *S. pyogenes* or non-group A, β-hemolytic streptococci.

When all patients were included in an intent-to-treat analysis (i.e., patients previously excluded because of prespecified protocol violations and patients classified as bacteriologically uneventful), a satisfactory response was defined as cure or improvement, and an unsatisfactory response was all other responses (including uneventful). In these evaluable patients, satisfactory responses occurred in 70.9 and 68.4% of cefuroxime axetil and cefadroxil recipients, respectively (P = 0.625) (Table 3).

**Clinical outcome.** Twenty-eight patients were clinically uneventful because of failure to return for follow-up, drug treatment for less than 5 days (less than 10 doses), or withdrawal from the study for reasons other than an adverse event (Table 4). Six cefuroxime axetil recipients were classified by the investigator as receiving drug for less than 5 days. These patients were described above in the bacteriologic analysis of the cefuroxime axetil group.

<table>
<thead>
<tr>
<th>TABLE 2. Bacteriological outcome</th>
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<tbody>
<tr>
<td><strong>Result</strong></td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
</tr>
<tr>
<td>Satisfactory</td>
</tr>
<tr>
<td>Cure</td>
</tr>
<tr>
<td>Presumed cure</td>
</tr>
<tr>
<td>Unsatisfactory</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Relapse</td>
</tr>
<tr>
<td>Subtotal (bacteriologically evaluable)</td>
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* Percentage of bacteriologically evaluable patients.

* P = 0.242, by comparing satisfactory versus unsatisfactory responses.

<table>
<thead>
<tr>
<th>TABLE 3. Bacteriological outcome (intent to treat)</th>
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</thead>
<tbody>
<tr>
<td><strong>Result</strong></td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
</tr>
<tr>
<td>Satisfactory</td>
</tr>
<tr>
<td>Unsatisfactory</td>
</tr>
<tr>
<td>All patients</td>
</tr>
</tbody>
</table>

* Satisfactory was defined as cure, presumed cure, or cure with infection. Unsatisfactory was defined as all other responses (including uneventful).

* P = 0.625, by comparing satisfactory versus unsatisfactory responses.
logical outcome section. In addition, the one patient who was unevaluable because of reasons other than an adverse event was the patient who was withdrawn from the study prior to receiving any study drug (classified as receiving drug for less than 5 days in the bacteriological outcome assessment). No cefadroxil-treated patients were classified as clinically unevaluable by the investigator because they had received study drug for less than 5 days. The two patients in this category under bacteriological outcome were considered clinical failures because of an adverse event or were withdrawn from the study for reasons other than an adverse event (i.e., personal reasons). For the remaining patients, satisfactory clinical response rates were higher in cefuroxime axetil than in cefadroxil recipients (97.8 versus 90.3%; \( P = 0.009 \)).

When the patients that were excluded from the “clinical outcome” analysis were reassessed as having unevaluable outcomes, i.e., an intent-to-treat analysis, the difference in response rates in favor of cefuroxime axetil (81.5 versus 78.6%) was no longer statistically significant (\( P = 0.5 \)) (Table 5). This can be explained by the addition of more patients who were previously excluded from the cefuroxime axetil group because of poor compliance. However, 86.7 and 88.8% of cefuroxime axetil and cefadroxil recipients, respectively, completed at least 80% of the prescribed therapies.

### TABLE 5. Clinical outcome (intent to treat)

<table>
<thead>
<tr>
<th>Result</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefuroxime axetil</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>154 (81.5)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>35 (18.5)</td>
</tr>
<tr>
<td>All patients</td>
<td>189</td>
</tr>
</tbody>
</table>

* Satisfactory was defined as cure or improved. Unsatisfactory was defined as all other responses (including unevaluable).

\( P = 0.504 \), by comparing satisfactory versus unsatisfactory responses.

In the evaluable population, after controlling for differences in ethnic origin (Caucasian versus all other ethnic origins) and investigational centers, there was still a significant difference in the clinical responses but there was no difference in the bacteriological responses.

**Adverse events.** In general, adverse events were mild to moderate in severity. One patient discontinued cefuroxime axetil because of diarrhea, which resolved spontaneously without further treatment. One patient discontinued cefadroxil because of a rash, which resolved spontaneously. Adverse events considered by the clinician to be possibly, probably, or almost certainly related to the study drugs occurred in 7.9 and 6.1% of all cefuroxime axetil and cefadroxil recipients, respectively (\( P = 0.641 \)) (Table 6). The adverse event profiles were similar in both treatment groups and consisted primarily of gastrointestinal disturbances (e.g., diarrhea or loose stools) and diapher rash. Only one patient, a cefuroxime axetil recipient, experienced an abnormal laboratory value, which consisted of an increase in serum glutamic oxalacetic transaminase from 30 U/liter at the initial visit to 48 U/liter at the posttreatment visit and to 52 U/liter 2 weeks later. The patient remained asymptomatic throughout this period of time. The patient's mother refused further testing, and the physician observer thought that the abnormality could be drug related. Otherwise, there were no clinically significant changes in hematologic or chemistry parameters.

Drug stop dates showed that study drug was taken for 10 days or more by 153 (81.0%) and 84 (85.7%) of cefuroxime axetil and cefadroxil recipients, respectively. One of the study medications was taken for 8 to 9 days by 11 (5.8%) cefuroxime axetil recipients and 3 (3.1%) cefadroxil recipients. Nine (4.7%) cefuroxime axetil-treated patients and two (2.0%) cefadroxil-treated patients took drug for less than 8 days. Of the nine cefuroxime axetil-treated patients who took drug for less than 8 days, six withdrew from the study because of refusal to take the study medication. In addition, one cefuroxime axetil-treated patient was withdrawn from
the study because of refusal to take the study medication, but the drug stop date was not recorded. In total, seven (3.7%) cefuroxime axetil-treated patients were withdrawn for this reason. The disposition of these patients for analysis was discussed above. No cefadroxil-treated patients withdrew from the study because of refusal to take the study drug. Drug stop dates were not available for 33 patients (16 cefuroxime axetil recipients, 9 cefadroxil recipients), of which 14 (7.4%) cefuroxime axetil recipients and 7 (7.1%) cefadroxil recipients were lost to follow-up. Of the remaining patients, none were withdrawn because of refusal to take study medication.

DISCUSSION

This is the first comparative study of a new formulation of cefuroxime axetil suitable for oral administration to children with skin or skin structure infections. Clinical (97.1%) and bacteriological (97.8%) response rates in the current study approximated those reported in adults receiving the tablet formulation. The overall clinical improvement rate was 95% in 97 patients who participated in a noncomparative study (5). In a study with a design similar to that of the study described here, cefuroxime axetil in the tablet formulation produced clinical and bacteriological response rates (97 and 96%, respectively) higher than those of cephalixin (89 and 85%, respectively; \( P < 0.05 \)) and similar to those of cefadroxil (94 and 93%, respectively; \( P > 0.05 \)) (4). In other comparative studies, the authors concluded that cefuroxime axetil is as effective as amoxicillin-clavulanate (14) and cefaclor (11). In those trials, clinical and bacteriological response rates from 92 to 97% were achieved.

In the study described here, bacteriological response rates were comparable to those achieved with the cefadroxil suspension (approximately 97% in each group), but clinical responses were higher in cefuroxime axetil recipients (97.8 versus 90.3%; \( P = 0.009 \)). The difference between treatment groups did not appear to be due to a spuriously low response rate in the cefadroxil group, because the response rate was consistent with those previously reported in comparative trials of patients with skin or skin structure infections (1, 6).

The new cefuroxime axetil suspension was well tolerated in the study described here. The incidence and profile of adverse events of the cefuroxime axetil suspension closely resembled that of the cefadroxil suspension. Only 7.9% of children experienced adverse events during cefuroxime axetil therapy; these adverse events were primarily manifested as gastrointestinal disturbances (e.g., diarrhea or loose stools) or diaper rash. No episodes of nausea or vomiting were reported in the cefuroxime group.

In this single-blind, randomized study, a suspension formulation of cefuroxime axetil produced bacteriological response rates comparable to those of the cefadroxil suspension (97.1 versus 94.3%) in children with skin or skin structure infections. The clinical response rate was higher in the cefuroxime axetil group (97.8 versus 90.3%; \( P < 0.05 \)). Both regimens were well tolerated. These results indicate that the cefuroxime axetil suspension is safe and efficacious in the treatment of skin and skin structure infections in children.

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