Cefprozil versus Penicillin V in Treatment of Streptococcal Tonsillopharyngitis

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In a randomized multicenter study, the efficacy and safety of cefprozil were compared with those of penicillin in the treatment of group A streptococcal tonsillopharyngitis in children. Of the 409 patients enrolled, 323 were evaluable for their clinical and bacteriological responses; of these 323 children, 172 received cefprozil and 151 received penicillin V. The clinical responses in patients treated with cefprozil were significantly better than those in patients who received penicillin (95.3 versus 88.1%; P = 0.023). Eradication of the original serotype of group A streptococci was achieved in 91.3% of patients treated with cefprozil and 87.4% of patients treated with penicillin, the difference not being statistically significant (P = 0.125). However, there were significantly more symptomatic patients among the bacteriological failures in the penicillin group (68.4%) than in the cefprozil group (26.7%). β-Lactamase-producing Staphylococcus aureus was more frequently isolated from the throat flora during penicillin therapy than during cefprozil treatment. No difference in the incidence of adverse events probably related or of unknown relationship to the study drugs was observed in the two treatment groups (5.2% of those treated with cefprozil and 6.0% of those treated with penicillin). Cefprozil can be considered a safe and reliable drug for the treatment of streptococcal pharyngitis in children.

Streptococcal tonsillopharyngitis is one of the most common bacterial infections in pediatric patients. Penicillin is still considered the drug of choice, although failure rates of up to 30% have been reported (7, 10, 12). Since no penicillin-resistant group A beta-hemolytic streptococci (GABHS) have been isolated, other reasons for the failure of therapy have been discussed, such as inactivation of penicillin by the β-lactamases produced by the concomitant throat flora or penicillin tolerance of the pathogen (2, 13, 14).

Cephalosporins are stable to hydrolysis by the β-lactamases of the bacteria that commonly colonize the mucous membranes of the upper respiratory tract. A meta-analysis of 19 different studies has shown that cephalosporins are more efficacious than penicillin in the treatment of streptococcal tonsillopharyngitis (19).

Cefprozil is a new semisynthetic oral cephalosporin which has an in vitro spectrum that includes Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, and Moraxella catarrhalis (3, 6). Its half-life of 1.3 h allows for once- or twice-daily dosing. In one comparative study, cefprozil was evaluated for the treatment of streptococcal pharyngitis in adults, and it was found to be as efficacious as cefaclor (4). It has recently been approved in the United States for the treatment of upper respiratory tract infections in adults. We performed a multicenter trial comparing the efficacy and safety of cefprozil with those of penicillin V in 409 children with streptococcal tonsillopharyngitis.

MATERIALS AND METHODS

Patients. A total of 409 patients attending 11 pediatric practices in the Munich area in Germany, 20 general practices in The Netherlands, and 1 pediatric practice in Belgium were enrolled in the study. Eligibility criteria were as follows: age between 3 and 18 years; signs and symptoms of acute tonsillopharyngitis such as sore throat, tonsillogryphangeal erythema and/or exudate, cervical adenitis, and fever; and receipt of informed consent from the patient or the patient’s parents. Patients with a history of hypersensitivity to penicillins or cephalosporins, pregnant women, patients with severe renal and hepatic dysfunction, or those who had taken antibiotics within the previous 48 h or who had received long-acting penicillins within 2 weeks before enrollment were excluded from the study.

Before treatment, the patient’s medical history was recorded, the patients were subjected to physical examination, and throat swabs were taken. Treatment was started when the throat culture was positive for GABHS or a rapid test for streptococcal antigen (Abbott) was positive. For patients who entered the study on the basis of a positive antigen test result, confirmation of the result had to be made by culture in order to continue the study protocol. Prestudy laboratory tests were performed for all children to establish baseline values, including hematology (platelet count, leukocyte count, hemoglobin, hematocrit), blood chemistry (liver enzymes, total bilirubin, blood urea nitrogen, creatinine), and urinalysis. The study protocol did not require repeat laboratory tests. Clinical and bacteriological follow-up evaluations took place once during therapy and twice after treatment had been completed, between days 1 and 12 and between days 13 and 40 posttherapy.

Therapy. Patients were randomized in a 1:1 ratio according to a computer-generated list to receive either cefprozil, 7.5 mg/kg of body weight twice a day (maximum, 250 mg twice a day), or penicillin V, 16.25 mg/kg of body weight three times a day (maximum, 260 mg three times a day). Both drugs were administered for 10 days. Patients were asked to return unused drugs to evaluate compliance.

Bacteriology. The throat swabs obtained pretherapy, during therapy, and posttherapy were immediately cultured on sheep blood agar and streptococcal selective-elective agar (Medco). Streptococcal selective-elective agar is a slight

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modification of the medium originally described by Lieberman and Bravery (15), which is based on the reduction of nutrients and enhancement of streptolysin S production. Thus, beta-hemolytic streptococci are easily recognized by their characteristic growth (very small colonies surrounded by a large hemolytic zone). The isolation rate of GABHS from throat swabs on this medium has been shown to be 5.5 to 11.6% higher than that on sheep blood agar (1, 16). All plates were incubated aerobically overnight at 37°C in the physician’s practice. Since only streptococci grow on streptococcal selective-elective agar, antibiotic treatment was initiated if beta-hemolytic colonies were detected. Both plates were sent to the central microbiology laboratory. Serogroups of the streptococcal isolates were determined by a latex agglutination test (Streptex; Oxoid). If GABHS were isolated from follow-up throat cultures, pre- and posttherapy isolates were serotyped by means of T-antigen agglutination and M-antigen precipitation, which were performed at the Zentralinstitut für Mikrobiologie und Experimentelle Therapie in Jena, Germany. The presence of β-lactamase-producing S. aureus in the concomitant throat flora was investigated in 214 evaluable patients from the Munich area. β-Lactamase production of the strains was tested by the nitrocefin method (20).

Evaluation. Patients whose pretreatment cultures were positive for GABHS were eligible for evaluation of efficacy if the drug had been taken for at least 8 consecutive days and no other antimicrobial agents had been taken during the study period, i.e., during treatment and follow-up, and if at least one posttreatment evaluation had been performed.

Patients were classified as clinically cured if there was complete resolution of signs and symptoms, clinically improved if there was significant but incomplete resolution of signs and symptoms, or treatment failures if the signs and symptoms worsened, persisted, or reappeared.

The bacteriological response was categorized as eradication if no GABHS were isolated from any of the posttreatment cultures. Only those patients in whom GABHS belonging to the same serotype as the pretreatment isolate either persisted or recurred after antibiotic treatment was completed were designated as bacteriological failures. The bacteriological failures were categorized as persistent if a strain of the original serotype was isolated at the first posttreatment evaluation and as recurrent if a strain was recovered at the second posttreatment evaluation after initial eradication. Recurrence was defined as isolation from any of the posttreatment cultures of GABHS belonging to a serotype different from that of the pretreatment isolate.

Statistical analysis. The two-tailed Fisher exact test was used to compare clinical and bacteriological efficacy and safety in the two treatment groups. The level of significance was set at \( P < 0.05 \).

RESULTS

Of the 409 patients enrolled in the study, 323 (79.0%) were evaluable for treatment efficacy; of the 323 evaluable patients, 172 received cefprozil and 151 received penicillin V. The main reason for exclusion from analysis was failure to isolate GABHS from pretreatment cultures (30 in the cefprozil group and 37 in the penicillin V group). No follow-up was available for six patients, five patients received an improper dosage, in four patients pretreatment cultures were not performed within the appropriate time frame, three patients did not complete therapy, and one patient was not eligible because of his age. The two treatment groups were similar with respect to age distribution and the severity of infection (Table 1). The clinical and bacteriological outcomes are summarized in Table 2. Of the 172 evaluable patients treated with cefprozil, 164 (95.3%) had a satisfactory clinical outcome (cure or improvement); this was significantly greater than the response rate of 88.1% in the 151 patients treated with penicillin V (\( P = 0.023 \)). Nineteen (11.0%) of the patients treated with cefprozil and 24 (15.9%) of the patients treated with penicillin V had positive posttherapy cultures for GABHS. Only those patients whose pre- and posttreatment isolates belonged to the same serotype were designated as bacteriological failures. The bacteriological failure rate was 8.7% (15 of 172 patients) in the cefprozil group and 12.6% (19 of 151 patients) in the penicillin V group; the difference was not statistically significant (\( P = 0.280 \)). Five of the 15 homologous strains from patients treated with cefprozil were isolated at the first follow-up, and 10 recurred at the second follow-up, whereas 12 of the 19 penicillin V failures were detected at the first follow-up and 7 were detected at the last follow-up.

In four patients treated with cefprozil, GABHS of a different serotype were isolated after the completion of therapy; two of these patients had symptoms of an infection. In the penicillin V group, five patients, two of whom were symptomatic, had positive posttherapy cultures with a new serotype of GABHS.

There were significantly more symptomatic patients among the bacteriological failures in the penicillin group (13 of 19; 68.4%) than among those in the cefprozil group (4 of 15; 26.7%) (\( P = 0.037 \)).

The presence of β-lactamase-producing S. aureus in the concomitant throat flora was investigated in the 214 evaluable patients from Germany. During therapy, these bacteria were isolated more frequently from throat swabs of patients.

<table>
<thead>
<tr>
<th>Response</th>
<th>Cefprozil (n = 172)</th>
<th>Penicillin V (n = 151)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>136 (79.1)</td>
<td>103 (68.2)</td>
<td>0.031</td>
</tr>
<tr>
<td>Improvement</td>
<td>28 (16.3)</td>
<td>30 (19.9)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>8 (4.7)</td>
<td>18 (11.9)</td>
<td>0.023</td>
</tr>
<tr>
<td>Bacteriological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>153 (89.0)</td>
<td>127 (84.2)</td>
<td>0.251</td>
</tr>
<tr>
<td>Persistence</td>
<td>5 (2.9)</td>
<td>12 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>10 (5.8)</td>
<td>7 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Reinfection</td>
<td>4 (2.3)</td>
<td>5 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>
in the penicillin V group (13.0%) than from those of patients treated with cefprozil (4.5%) \( (P = 0.046) \). No difference was seen between the groups in the rate of isolation of \( \beta \)-lacta-
amase-producing \( S. \) aureus from pre- and posttherapy cul-
tures (Table 3). In Table 4, only those adverse effects considered to be probably related or of unknown relation-
ship to the study drugs are summarized. Seven patients in the
cefprozil group experienced 11 adverse events, and 12 patients in the penicillin V group experienced one adverse
event each. The adverse events mainly originated from the
gastrointestinal tract. No difference in the incidence of
adverse effects was observed in the two treatment groups
(5.2% in the cefprozil group and 6.0% in the penicillin
\[ P = 0.242 \] ).

Because repeated laboratory tests were not mandatory,
follow-up evaluations of blood chemistry and hematology
were performed for only 15 patients in each treatment group.
No abnormal values were observed in any of these patients.

**DISCUSSION**

Cefprozil, a new semisynthetic oral cephalosporin, has in
vitro activity superior to that of cefacor against staphylo-
cocci, beta-hemolytic streptococci, and *Streptococcus pneu-
moniae* and is comparably active against *H. influenzae* and
*M. catarrhalis* (3, 6). Numerous comparative studies have
shown that oral cephalosporins are more effective than or at
least as effective as penicillin V for the treatment of strep-
tococcal tonsillopharyngitis (5, 7, 9, 10, 11, 12, 18). This was
also confirmed by the results of our study. Cefprozil was
clinically more effective than and bacteriologically as effective
as penicillin V.

The bacteriological failure rate with cefprozil was 8.7%,
which corresponds well to the figures reported in the litera-
ture for other cephalosporins such as cefalexin, cefadroxil,
cefclor, and cefuroxime axetil (5, 8, 9, 11, 18), ranging
between 2 and 10%. Although the failure rate for penicillin
was somewhat higher than that for cefprozil, the difference
was not statistically significant. A recently published meta-
analysis has shown that in 16 of 19 comparative studies, the
cephalosporins were superior to penicillin, although statisti-
cal significance was not achieved in many of them (19).

A number of hypotheses for the lower elimination rate of
GABHS by penicillin compared with that by cephalosporins
have been discussed in the literature. The most reasonable
explanation seems to be the inactivation of penicillin at the
site of infection by \( \beta \)-lactamase-producing microorganisms
such as *S. aureus, M. catarrhalis*, and anaerobes. In a previous
study (17), we were able to demonstrate a corre-
lation between the failure of penicillin therapy and the pres-
ence of \( \beta \)-lactamase-producing *S. aureus* in the commensal
throat flora. The cephalosporins are stable to hydrolysis
by these enzymes, which, in our opinion, has a major impact on
the better efficacies of these agents in the clinical setting of
the present study. In the present study we did not analyze
the relationship between *S. aureus* carriers and penicillin
treatment failure. We could demonstrate, however, as
shown in Table 3, that cefprozil significantly reduced the
isolation rate of the throat flora during therapy in comparison with penicillin (4.5 versus 13.0%).

The clinical outcomes for our patients treated with cef-
prozil were significantly better than those for patients who
received penicillin. A satisfactory response was obtained in
95.3 and 88.1% of the patients, respectively. Interestingly,
among those patients who were designated as bacteriological
failures, 68.4% in the penicillin group were symptomatic,
whereas only 26.7% in the cefprozil group were sympto-
amtic.

Despite the repeatedly documented bacteriological or clinical
superiority of the oral cephalosporins, penicillin V still
remains the drug of choice because of its considerably lower
price. On the other hand, one must consider the fact that
the cephalosporins offer a variety of advantages, such as a better
taste, which subsequently leads to better acceptance,
and the possibility of once- or twice-daily dosing, which results
in better compliance. In addition, it is obvious that more
patients who are initially treated with penicillin must be
retreated with another drug such as a cephalosporin,
a macroside, or clindamycin.

The results of our study indicate that cefprozil could be
considered a safe and reliable drug for the treatment of
streptococcal tonsillopharyngitis in children.

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**TABLE 3. Percentage of the 214 evaluable German patients harbor-
ing \( \beta \)-lactamase-producing \( S. \) aureus in the concomitant
throat flora**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>No. of patients with ( \beta )-lactamase-producing ( S. ) aureus/total no. of patients (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>10/114 (8.8)</td>
<td>0.817</td>
</tr>
<tr>
<td>During treatment</td>
<td>5/112 (4.5)</td>
<td>0.046</td>
</tr>
<tr>
<td>First follow-up</td>
<td>8/113 (7.1)</td>
<td>0.238</td>
</tr>
<tr>
<td>Second follow-up</td>
<td>10/112 (8.9)</td>
<td>0.500</td>
</tr>
</tbody>
</table>

**TABLE 4. Adverse effects considered to be probably related or of unknown relationship to the study drugs**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefprozil (n = 210)</td>
</tr>
<tr>
<td>Diarrhea, loose stools</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Vomiting, nausea</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

\( \text{TABLE 4. Adverse effects considered to be probably related or of unknown relationship to the study drugs} \)

\( \text{No. (%) of patients} \)

\( \text{Cefprozil (n = 210) Penicillin V (n = 199)} \)

\( \text{Diarrhea, loose stools} \)

\( \text{4 (1.9)} \) \( \text{10 (5.0)} \)

\( \text{Vomiting, nausea} \)

\( \text{3 (1.4)} \) \( \text{1 (0.5)} \)

\( \text{Stomach ache} \)

\( \text{3 (1.4)} \) \( \text{0} \)

\( \text{Skin rash} \)

\( \text{1 (0.5)} \) \( \text{1 (0.5)} \)


