Comparative Efficacy and Safety of Cefprozil (BMY-28100) and Cefaclor in the Treatment of Acute Group A Beta-Hemolytic Streptococcal Pharyngitis

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Cefprozil (BMY-28100) is a semisynthetic 7-phenylglycyl cephalosporin with broad-spectrum antibacterial activity and prolonged serum elimination half-life allowing for once-a-day oral administration. In vitro, cefprozil demonstrates excellent activity against Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, and Moraxella catarrhalis. Cefprozil (500 mg once daily) was compared to cefaclor (250 mg three times daily) in an open, randomized, comparative trial for the treatment of acute group A beta-hemolytic streptococcal pharyngitis. Ninety-four patients were enrolled in this study; 53 patients were evaluable for clinical and bacteriological response assessment. Seventy-eight patients were evaluable for safety assessment. Three patients (all in the cefprozil treatment group) required disenrollment because of side effects, mainly nausea. Clinical and bacteriological responses were comparable for both study drugs. Leukopenia and nausea, the most common side effects observed, were more common in the cefprozil-treated group. Cefprozil appears to be an appropriate alternative to cefaclor for the treatment of acute group A beta-hemolytic streptococcal pharyngitis. However, because of the small number of patients eligible for efficacy assessment, a large type II (beta) error was expected in our study, which may have resulted in a potential failure to detect a difference between both treatment groups. A larger study would be required to determine the proper role of cefprozil in the treatment of group A beta-hemolytic streptococcal infections.

Cefprozil, formerly known as BMY-28100, is a new semisynthetic 7-phenylglycyl cephalosporin developed for oral administration. Its broad-spectrum antibacterial activity and stability to hydrolysis by many β-lactamase enzymes, in combination with a more prolonged half-life when compared to other oral cephalosporins, has elicited interest in its potential clinical benefits for the treatment of various infections. In vitro data suggest that cefprozil is more active than either cefaclor or cephalexin against Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, and Moraxella catarrhalis (4, 5, 7, 10, 13). The average half-life in blood of cefprozil is 1.2 h, in contrast to the serum half-life of cefaclor of 0.6 to 0.9 h (2). Phase I studies have demonstrated that the incidence and types of side effects observed with cefprozil are similar to those reported with other oral cephalosporins (1).

Recent reports have documented high failure rates in some patients treated with penicillin for group A streptococcal pharyngitis (3, 8, 14). The inability to eradicate group A streptococci may be due to a residual or recurrent infection; the persistence of a carrier state may be due to the presence of β-lactamase-producing aerobic and anaerobic bacteria in the oropharynx (3, 9). Clinical trials with β-lactamase stable compounds and anti-anaerobe agents have been found to be more effective in eradicating the carrier state and preventing recurrent infection (3, 9, 14). Cefprozil, with its stability to hydrolysis by plasmid-mediated β-lactamase enzymes, may be a good drug to evaluate under this assumption (4, 7). Its once-a-day dosing may also result in increased compliance with the treatment regimen.

The purpose of this study was to compare the efficacy and safety of cefprozil administered once a day with that of cefaclor, in the management of group A beta-hemolytic streptococcal (GABHS) pharyngitis.

MATERIALS AND METHODS

Patients were enrolled in an open, randomized, comparative clinical study between 1987 and 1988 at the Departments of Internal Medicine and Pediatrics of the Bryner Clinic, an outpatient multispecialty clinic in the metropolitan area of Salt Lake City. Patients 12 years of age or older with documented or suspected acute streptococcal pharyngitis were candidates for enrollment in this study. Signs and symptoms considered to be consistent with acute GABHS pharyngitis were fever, sore throat, palatal petechiae, erythematous pharynx, tonsillar exudate, and swollen tender cervical lymph nodes. The risks and benefits of participating in this clinical study were explained and discussed with all potential candidates. An informed consent document was signed by all patients (and parents or guardians, when applicable) enrolled into the study. All female patients of childbearing age had a documented negative pregnancy test prior to initiation of study drug. Patients surgically sterilized by hysterectomy or tubal ligation were enrolled without satisfying this requirement.

Patients were excluded from enrollment if they met any of the following criteria: history of anaphylaxis to penicillin or cephalosporins; history of allergies to cephalosporins; use of a long-acting parenteral penicillin within 2 weeks prior to enrollment; pregnancy or lactation; history of major renal or significant hepatic disease; history of gastrointestinal malabsorption. Before treatment, a complete evaluation consisting

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of medical history, physical examination, and laboratory studies was performed, including a hematologic analysis (leukocyte count and differential, hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate), chemical analysis (liver enzymes, blood urea nitrogen, creatinine), urine analysis (with microscopic examination), prothrombin and partial thromboplastin times, anti-streptolysin O titer, and pharyngotonsillar area culture. The posterior pharyngeal wall and tonsils, if present, were swabbed vigorously. Swabs were cultured on blood agar plates soon after collection. A positive culture was defined as 10 or more CFU of GABHS on a blood agar plate. Patients were reevaluated (clinical and bacteriologic assessments) 3 to 5 days into therapy, between 2 and 6 days after therapy, and between 10 and 20 days after therapy.

Patients were randomized to receive either 500 mg of cefprozil (BMY-28100, Bristol-Myers Squibb Company) orally once daily or 250 mg of cefaclor (Ceclor, Eli Lilly & Co.) three times a day (2:1 randomization). Randomization was performed by research assistants, utilizing a computer-generated randomization list provided by the sponsor. Both drug regimens were administered for a total of 10 days. To document compliance with the study, the patient was asked to return all unused capsules at the completion of the study. Patients needed to receive the study drug for at least 9 consecutive days in order to be eligible for evaluation of efficacy. No other antimicrobial therapy was given concomitantly with the study drug. Assessment of efficacy was performed only on patients with a duration of symptoms of less than or equal to 4 days.

Clinical responses were classified as follows: satisfactory, resolution or improvement of all pretreatment signs and symptoms without the appearance of any new signs or symptoms at the time of the posttreatment evaluation; unsatisfactory, pretreatment signs or symptoms unchanged or worsened or all pretreatment signs symptoms resolved but new symptoms appearing at the time of posttreatment evaluation.

Bacteriologic responses were categorized as follows: eradicated, all cultures negative after the completion of treatment and at the time of the posttreatment cultures; persisted, a positive culture with GABHS taken 2 to 6 days after completion of therapy; recurrence, a positive culture at 7 to 20 days following a negative at 2 to 6 days, after completion of treatment.

GABHS were identified by bacitracin disk screening followed by slide agglutination with specific antiserum (PathoDx, Los Angeles, Calif.). All bacterial isolates were tested for antimicrobial susceptibility, by using disks impregnated with 30 μg of cefprozil or cephalothin, by the Kirby-Bauer method of disk diffusion on Mueller-Hinton agar (11). Organisms were considered resistant if the zones of inhibition were less than 14 mm; they were considered susceptible if the zones of inhibition were >18 mm.

Patients were disenrolled from the study if they met any of the following criteria: no GABHS isolated in pretreatment culture; in vitro susceptibility testing indicating resistance of the pathogen to either cefprozil or cefaclor; poor clinical response after 72 h of therapy; serious or alarming adverse reaction related to the study drug.

The study drugs were compared for their overall clinical and bacteriologic response rates and incidence and severity of adverse reactions. Statistical analysis was performed by using Fisher's exact test. A P value equal to or less than 0.05 was considered to be significant.

## RESULTS

Ninety-four patients were enrolled in this clinical trial. Sixteen patients were subsequently disenrolled because they did not meet criteria for eligibility to be evaluated (12 because of no pathogen isolated, 3 because of lack of compliance with study protocol, 1 because of abnormal pretreatment laboratory test values). A total of 78 patients (50 treated with cefprozil, 28 treated with cefaclor) were eligible for safety evaluation. Only those patients who were prematurely disenrolled because of adverse events or those who received drug for at least 9 days were included in the statistical evaluation of safety, although no adverse events were observed among the other patients. Four patients required discontinuation of study drugs because of adverse effects (3 for cefprozil, 1 for cefaclor). Five patients (three with non-GABHS pharyngeal pathogens [group G or C beta-hemolytic streptococci], two with GABHS isolates not tested for antimicrobial susceptibility) not eligible for efficacy analysis, who completed 10 days of treatment, were included in the safety analysis. Seventeen patients with symptoms of disease of more than a 4-day duration were excluded from the efficacy analysis; they were included in the analysis for safety. Fifty-three patients were eligible for evaluation for efficacy.

Both treatment groups were comparable in sex distribution, underlying illnesses, and type and severity of signs and symptoms of pharyngitis-tonsillitis. The mean ages for patient groups were as follows: cefprozil, 33.6 years (range, 14 to 66 years; median, 31 years); cefaclor, 31.2 years (range, 13 to 50 years; median, 31 years), \( P = 0.41 \). The mean durations of signs and symptoms of disease (in patients eligible for efficacy analysis) for cefprozil and cefaclor were 2.95 and 2.52 days, respectively (median, 3 days for each group).

The clinical and bacteriologic responses are summarized in Table 1. The percentages of patients responding favorably, either with clinical improvement or resolution of signs and symptoms of disease, were equal for both treatment groups. None of the patients who had unsatisfactory clinical responses to a study drug had a concomitant positive pharyngeal or tonsillar culture. GABHS were eradicated at a similar percentage in both treatment groups. All patients with bacteriologic persistence or recurrence were asymptomatic. All patients evaluable for efficacy analysis took the study drug for 10 days; this was confirmed by a pill count.

The incidence of adverse reactions is summarized in Table 2. These were more commonly observed in the cefprozil-treated patients. Leukopenia (defined as a leukocyte count <5,000/mm³) and nausea were more common in the cefprozil-treated group. Vaginal yeast infection, erythema no-

### Table 1. Clinical and bacteriological responses of 53 patients with GABHS pharyngitis (symptoms for ≤4 days)

<table>
<thead>
<tr>
<th>Response</th>
<th>Cefprozil (n = 33)</th>
<th>Cefaclor (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfactory</td>
<td>28 (85)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>5 (15)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Bacteriological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradicated</td>
<td>30 (91)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Persistence</td>
<td>2 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

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TABLE 2. Common adverse reactions observed in 78 patients

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. (%) of patients with treatment to drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefprozil (n = 50)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Increased PTT*</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>0</td>
</tr>
</tbody>
</table>

* Partial thromboplastin time.

dosum, thrombocytosis (>450,000/mm³), prolonged partial thromboplastin time (60 s) were reported once each in the cefprozil-treated group. All these adverse events were thought to be related to the study drug, and all resolved after discontinuation of the study drug. One patient treated with cefaclor suffered from serum sickness 2 days after completing therapy. Three patients were discontinued from the study because of their adverse reactions. Nausea was the cause for this discontinuation from study; all of these episodes occurred in cefprozil-treated patients. Nausea resolved after administration of cefprozil was discontinued. Although these adverse events were more common in the cefprozil-treated group, they did not reach statistical significance (nausea, \( P = 0.21 \); leukopenia, \( P = 0.14 \)). Elevated liver enzymes (defined as alanine aminotransferase and aspartate aminotransferase > 40 IU/liter), were observed in three patients in each treatment group. No study patients reported diarrhea as an adverse reaction.

**DISCUSSION**

Persistence of GABHS has been observed in up to 26% of patients after the first course of penicillin treatment and in 62% after treatment (8, 14). \( \beta \)-lactamase-producing microflora such as *S. aureus, H. influenzae, H. parainfluenzae, M. catarrhalis*, and anaerobic bacteria in the oropharynx have been suggested as possible causes of such treatment failures (3, 9). Results of previous attempts to decrease GABHS persistence by treating patients with oral narrow-spectrum cephalosporins have been inconsistent. However, trials with cefaclor have demonstrated statistically significant decreased failure rates when compared with penicillin (12, 14). Since in vitro data indicate that susceptibility of common pediatric pathogens to cefprozil is superior to that of cefaclor (4, 5, 9), cefprozil may be of benefit in the management of these infections. In addition, an antimicrobial agent requiring less-frequent administration may increase compliance (6).

The incidence of GABHS eradication was similar for both treatment groups. No GABHS was isolated in patients whose cases were considered clinical failures. It was thought that these patients may have had a concurrent or subsequent viral illness. If this is taken into consideration, the clinical failure rate for both groups would be much lower. Because of the good study drug compliance within both groups, we cannot correlate clinical failures with poor compliance. Uncomplicated GABHS pharyngitis is a self-limited illness; most of the symptoms will subside within a week. To avoid including patients in route to spontaneous recovery, we included only patients with ≤4 days of symptoms in our efficacy analysis.

Gastrointestinal side effects were the most common cause for discontinuation of study antibiotics, occurring only in patients receiving cefprozil. Our incidence of this, as well as other adverse events, is consistent with that previously reported (1). None of the patients in either study group reported diarrhea as an adverse event, although it has been reported by other investigators (1).

Cefprozil, given once a day, resulted in bacteriological responses similar to those of cefaclor administered three times a day. As mentioned above, the percentage of favorable clinical responses was equal for each treatment group. If we take into consideration the inability to detect GABHS in those patients with clinical failures within the cefprozil treatment group, it is possible that cefprozil is a better alternative to cefaclor. Because of the small number of patients eligible for efficacy assessment, a large type II (beta) error was expected. This may result in a failure to detect a difference between both treatment groups. This factor needs to be considered when analyzing our data. The power of this study, calculated by using the number of evaluable patients to detect a 20% difference between treatment groups, was approximately 0.17 (beta error, 0.83).

The incidence of adverse reactions was somewhat greater in patients treated with cefprozil, with leukopenia and nausea being the most common. None of the leukocyte counts were less than 3,700/mm³, and these were reversible after discontinuation of the study drug. Recently published phase I studies reported similar findings (1). A larger clinical double-blind study would be necessary to determine the proper role of cefprozil in the treatment of community-acquired GABHS infections and the exact incidence of gastrointestinal and other side effects.

**ACKNOWLEDGMENT**

This study was supported by a grant from Bristol-Myers Squibb Company.

**REFERENCES**