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Cefprozil versus Penicillin V in Treatment of Streptococcal Tonsillopharyngitis

D. MILATOVIC,[1]* D. ADAM,[2] H. HAMILTON,[3] AND E. MATERMAN[3]

Institute of Medical Microbiology, Technical University of Munich,[1] and D. von Haunersches Children's Hospital, University of Munich,[2] Munich, Germany, and Bristol-Myers Squibb Pharmaceutical Research Institute, Brussels, Belgium[3]

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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, tonsillopharyngeal 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

* Corresponding author.

modification of the medium originally described by Liebermeister and Braveny (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. Reinfection 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 follow-up 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 1. Characteristics of the patients in the two treatment groups

Characteristic	Cefprozil (n = 172)	Penicillin V (n = 151)	P value
No. of males/no. of females	86/86	77/74	0.878
Avg age (yr)	7.4 ± 3.4	6.8 ± 3.0	0.244
Mean wt (kg)	27.7 ± 12.9	25.1 ± 9.8	0.108
Signs and symptoms (%)			
Mild	24	30	0.260
Moderate	66	59	0.249
Severe	10	11	0.856

TABLE 2. Clinical and bacteriological responses

Response	No. (%) of patients treated with:		P value
	Cefprozil (n = 172)	Penicillin V (n = 151)	
Clinical			
Cure	136 (79.1)	103 (68.2)	0.031
Improvement	28 (16.3)	30 (19.9)	
Failure	8 (4.7)	18 (11.9)	0.023
Bacteriological			
Eradication	153 (89.0)	127 (84.2)	0.251
Persistence	5 (2.9)	12 (7.9)	
Recurrence	10 (5.8)	7 (4.6)	
Reinfection	4 (2.3)	5 (3.3)	

TABLE 3. Percentage of the 214 evaluable German patients harboring β-lactamase-producing *S. aureus* in the concomitant throat flora

Evaluation	No. of patients with β-lactamase-producing *S. aureus*/total no. of patients (%)		*P* value
	Cefprozil	Penicillin V	
Pretreatment	10/114 (8.8)	10/100 (10.0)	0.817
During treatment	5/112 (4.5)	13/100 (13.0)	0.046
First follow-up	8/113 (7.1)	12/95 (12.6)	0.238
Second follow-up	10/112 (8.9)	11/93 (11.8)	0.500

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 β-lactamase-producing *S. aureus* from pre- and posttherapy cultures (Table 3). In Table 4, only those adverse effects considered to be probably related or of unknown relationship 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 group; $P = 0.242$).

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 cefaclor against staphylococci, beta-hemolytic streptococci, and *Streptococcus pneumoniae* 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 streptococcal 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 literature for other cephalosporins such as cefalexin, cefadroxil, cefaclor, 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 statistical significance was not achieved in many of them (19).

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

Adverse effect	No. (%) of patients	
	Cefprozil ($n = 210$)	Penicillin V ($n = 199$)
Diarrhea, loose stools	4 (1.9)	10 (5.0)
Vomiting, nausea	3 (1.4)	1 (0.5)
Stomach ache	3 (1.4)	0
Skin rash	1 (0.5)	1 (0.5)

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 β-lactamase-producing microorganisms such as *S. aureus*, *M. catarrhalis*, and anaerobes. In a previous study (17), we were able to demonstrate a correlation between the failure of penicillin therapy and the presence of β-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 *S. aureus* from the throat flora during therapy in comparison with penicillin (4.5 versus 13.0%).

The clinical outcomes for our patients treated with cefprozil 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 symptomatic.

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 macrolide, 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.

REFERENCES

1. **Braveny, I.** 1971. Fortschritte beim Nachweis betahämolytischer Streptokokken. Dtsch. Med. Wochenschr. **96**:396–397.
2. **Brook, L.** 1984. The role of β-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. Rev. Infect. Dis. **6**:601–607.
3. **Chin, N. X., and H. C. Neu.** 1987. Comparative antibacterial activity of a new oral cephalosporin, BMY-28100. Antimicrob. Agents Chemother. **31**:480–483.
4. **Christenson, J. C., E. Swenson, W. M. Gooch III, and J. N. Herrod.** 1991. Comparative efficacy and safety of cefprozil (BMY-28100) and cefaclor in the treatment of acute group A beta-hemolytic streptococcal pharyngitis. Antimicrob. Agents Chemother. **35**:1127–1130.
5. **Disney, F. A., B. B. Breese, A. B. Francis, J. L. Green, and W. B. Talpey.** 1979. The use of cefaclor in the treatment of beta-haemolytic streptococcal throat infections in children. Postgrad. Med. J. **55**(Suppl. 4):50–52.
6. **Eliopoulos, G. M., E. Reizner, C. Wennerstein, and R. C. Moellering, Jr.** 1987. In vitro activity of BMY-28100, a new oral cephalosporin. Antimicrob. Agents Chemother. **31**:653–656.
7. **Gastanaduy, A. S., E. L. Kaplan, B. B. Huwe, and L. W. Wannamaker.** 1980. Failure of penicillin to eradicate group A streptococci during an outbreak of pharyngitis. Lancet **ii**:498–501.

8. **Gau, D. W., R. F. H. Horn, R. M. Solomon, and P. Johnson.** 1972. Streptococcal tonsillitis in general practice: a comparison of cephalexin and penicillin therapy. Practitioner **208:**276–281.
9. **Gerber, M. A., M. F. Randolph, J. Chanatry, L. L. Wright, L. R. Anderson, and E. L. Kaplan.** 1986. Once daily therapy for streptococcal pharyngitis with cefadroxil. J. Pediatr. **109:**531–537.
10. **Ginsburgh, C. M., G. H. McCracken, S. D. Crow, J. B. Steinberg, and F. Cope.** 1980. A controlled comparative study of penicillin V and cefadroxil therapy of group A streptococcal tonsillopharyngitis. J. Int. Med. Res. **8**(Suppl. 1):82–86.
11. **Gooch, W. M., III., E. Swenson, M. D. Highbee, D. M. Cocchetto, and E. C. Evans.** 1987. Cefuroxime axetil and penicillin V compared in the treatment of group A beta-hemolytic streptococcal pharyngitis. Clin. Ther. **9:**670–677.
12. **Hennes, D. M.** 1982. A clinical experience with cefadroxil in upper respiratory tract infection. J. Antimicrob. Chemother. **10**(Suppl. B):125–135.
13. **Kim, K. S., and E. L. Kaplan.** 1985. Association of penicillin tolerance with failure to eradicate group A streptococci from patients with pharyngitis. J. Pediatr. **107:**681–684.
14. **Kundsin, R. B., and J. M. Miller.** 1964. Significance of the Staphylococcus aureus carrier state in the treatment of disease due to group A streptococci. N. Engl. J. Med. **271:**1395–1397.
15. **Liebermeister, K., and I. Braveny.** 1971. Ein Nährsubstrat zur Isolierung von hämolytischen Streptokokken. Z. Med. Mikrobiol. Immunol. **156:**149–153.
16. **Milatovic, D.** 1981. Comparison of five selective media for beta-haemolytic streptococci. J. Clin. Pathol. **24:**556–558.
17. **Milatovic, D., and J. Knauer.** 1989. Cefadroxil versus penicillin in the treatment of streptococcal tonsillopharyngitis. Eur. J. Clin. Microbiol. Infect. Dis. **8:**282–288.
18. **Pichichero, M. E., F. A. Disney, G. H. Aronovitz, W. B. Talpey, J. L. Green, and A. B. Francis.** 1987. Randomized, single-blind evaluation of cefadroxil and phenoxymethylpenicillin in the treatment of streptococcal pharyngitis. Antimicrob. Agents Chemother. **31:**903–906.
19. **Pichichero, M. E., and P. A. Margolis.** 1991. A comparison of cephalosporins and penicillins in the treatment of group A beta-hemolytic streptococcal pharyngitis: a meta-analysis supporting the concept of microbial copathogenicity. Pediatr. Infect. Dis. J. **10:**275–281.
20. **Schassan, H. H.** 1978. A new method for evaluating of β-lactamase production of resistant Enterobacteriaceae strains. Zentralbl. Bakteriol. Hyg. Immunol. Reihe A **242:**347–354.