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Randomized, Single-Blind Evaluation of Cefadroxil and Phenoxymethyl Penicillin in the Treatment of Streptococcal Pharyngitis

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A total of 150 children from two pediatric practices with clinical and bacteriologic evidence of acute group A beta-hemolytic streptococcal (GABHS) pharyngitis randomly received cefadroxil monohydrate (75 children) or phenoxymethyl penicillin (75 children). Cefadroxil was given once daily, while penicillin was given three times daily. The treatment groups were similar in age, sex, race, illness severity, and acute GABHS symptomatology. Throat cultures were routine 3 to 5 days after the start of therapy and 2 and 14 days after the end of therapy. The bacterial cure rates were 90% (62 of 69) for cefadroxil-treated patients and 76% (52 of 68) for penicillin-treated patients. This difference was significant ($P < 0.04$). The clinical response was satisfactory in 91% of cefadroxil-treated patients and 89% of penicillin-treated patients. We conclude that once-daily cefadroxil is at least as effective as three-times-daily penicillin in producing bacteriologic eradication and clinical symptomatic improvement in children with GABHS pharyngitis.

Cefadroxil is a broad-spectrum, semisynthetic cephalosporin for oral administration. It has in vitro activity against a wide range of gram-positive and gram-negative organisms. Cefadroxil is active against group A beta-hemolytic streptococci (GABHS), *Streptococcus pneumoniae*, staphylococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains), *Escherichia coli*, *Klebsiella* species and *Proteus mirabilis*. While cefadroxil resembles cephalexin in antibacterial activity, against GABHS cefadroxil is comparable to cefaclor and three to four times more active than cephalexin (20). The serum half-life of cefadroxil in children is about 1.5 h, as compared with 1.0 h for cephalexin and 0.6 h for cefaclor. Owing to a slower rate of absorption and elimination, the bioavailability of cefadroxil is about twice that of cefaclor and 75% greater than that of cephalexin (10). The bioavailabilities of cefadroxil and cefaclor are not affected by food, while peak concentrations of cephalexin in serum are reduced after a milk feeding in children (10). The MIC range of cefadroxil for GABHS is 0.063 to 0.125 μg/ml. The MIC for 90% of GABHS is 0.11 μg/ml (20). The peak concentrations of cefadroxil in serum following a 25-mg/kg dose are 21.2 ± 5 and 24.8 ± 53 μg/ml for infants and young children, respectively (10). The 5% incidence of adverse side effects with cefadroxil (11), consisting predominantly of intestinal disturbances and cutaneous reactions, is similar to that seen with other cephalosporins.

Compliance of the prescribed course of antibiotic therapy is a vital component of any successful treatment regimen. The 10 to 30% recurrence rate in GABHS-infected patients treated with penicillin (7, 16) may well be due to its generally recommended three-times-a-day dosing schedule or to the presence of penicillinase-producing bacteria which cocolonize pharyngeal tissues, excrete penicillinase, and thereby prevent eradication of GABHS (3, 19). In this study, we examined the bacteriologic and clinical outcomes of treatment with a single daily dose of cefadroxil in comparison with three daily doses of penicillin for GABHS pharyngitis.

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MATERIALS AND METHODS

Population studied. Patients were recruited to participate in the study from two pediatric practices composed primarily of middle-class families from private practices in Rochester, N.Y., and Atlanta, Ga.

Enrollment criteria. Investigators but not parents or patients were uninformed as to treatment group assignment, which was randomized 1:1 (cefadroxil/phenoxymethyl penicillin). The two practices enrolled a total of 150 children with clinical and bacteriologic evidence of acute GABHS pharyngitis. Enrollment criteria were as follows: (i) children between the ages of 3 and 18 years; (ii) clinical evidence of acute pharyngitis or tonsillitis, including sore throat, fever, tonsillar erythema or tonsillar exudate or both, and cervical adenitis; and (iii) no evidence of an acute upper respiratory tract viral infection, such as rhinorrhea or cough or both. A pretreatment swab culture was done for the posterior pharynx and tonsillar area. The recovery of 10 or more CFU of GABHS from the throat swab plated on sheep blood agar was required for the patient to be included as a potentially evaluable case. Patients with a history of sensitivity to cephalosporins or penicillin were excluded. Written informed consent was obtained from parents of all participants. Patients did not receive any other antimicrobial agents during the course of the study, nor had they received any antibiotics in the 48 h prior to enrollment.

Pretreatment screening. Each patient underwent a physical examination before treatment was initiated. Blood was obtained for a complete blood count and a differential count. Urine was obtained for evaluation of albumin, glucose, casts, leukocytes, and erythrocytes.

Treatment. Patients received orally either cefadroxil, 30 mg/kg once daily, not to exceed 1 g, or phenoxymethyl penicillin, 15 mg/kg, not to exceed 250 mg every 8 h.

Medication was dispensed by a study nurse and administered for 10 days.

Assessment during and after treatment. Subjects were evaluated 2 to 9 days, 11 to 17 days, and 18 to 33 days after the initiation of therapy. The midtreatment evaluation was performed on days 3 to 5 of treatment for 89% of cefadroxil-treated patients and 97% of penicillin-treated patients and involved an examination to assess clinical efficacy, a throat culture to determine bacteriologic efficacy, and a measurement of remaining medication to evaluate compliance. The evaluations performed 11 to 17 and 18 to 33 days after the initiation of antimicrobial therapy included an overall assessment of clinical efficacy, the return of any unused medication (days 11 to 17), and follow-up throat cultures.

Clinical evaluation. At the time of initial examination, the presence or absence of a series of typical GABHS-associated symptoms was determined. Symptoms and signs evaluated included the following: fever; pharyngeal redness, exudate, or petechiae or all of these; sore throat; swollen or tender anterior cervical lymph glands or both; headache; facial flush; breath odor; nausea; and vomiting.

Bacteriologic evaluation. GABHS grouping and typing by T-antigen agglutination and M-antigen precipitation were performed by Hugh Dillon, Birmingham, Ala. All isolates were tested by the Kirby-Bauer method (1) for susceptibility to the antimicrobial agent used. Bacteriologic responses were classified in accordance with the following definitions. (i) Eradication meant that the initial pathogen was eliminated and did not recur in the repeat throat cultures on days 11 to 17 or 18 to 33. (ii) Persistence meant the identification of 10 or more colonies of the same GABHS strain from the culture obtained during treatment or at the first posttreatment visit. (iii) Recurrence meant the eradication of GABHS during treatment (days 3 to 5) and in the immediate posttreatment interval (days 11 to 17) but the subsequent isolation of the original strain during days 18 to 33. (iv) Reinfection was the same as recurrence except that serotyping showed the original and reinfecting strains to be different. (v) Not evaluable meant the failure to obtain necessary throat cultures to categorize as described above.

Statistics. Initial analyses with the Cochran-Mantel-Haenszel test for categorical data and the Friedman test on Ranks for nonnormal continuous data examined the possibility of an investigator effect. Since none was found, the analysis was performed without controlling for the investigator.

Categorical data were analyzed with the chi-square or Fisher exact test when appropriate. Continuous data were analyzed with the Wilcoxon rank sum test because of the nonnormality of the underlying distributions. Initial tests for normality were performed with the Shapiro-Wilks statistic. These tests were conducted with a two-tailed alternative hypothesis at the $P = 0.05$ level of significance.

RESULTS

Of the 150 children enrolled in the study, 145 were evaluable for clinical responses, and 140 were evaluable for bacteriologic responses. Compliance was excellent, as determined by medication diaries and counts. Four cefadroxil-treated and three penicillin-treated patients did not complete the 10-day treatment course as prescribed. All GABHS isolates were susceptible to the prescribed antibiotic.

Most patients in the study were 4 to 12 years old; the mean ages were 8.1 and 7.5 years for the cefadroxil and penicillin groups, respectively. All infections occurred in the winter and spring. The majority of children had elevated leukocyte counts, and all infections were considered acute. There were no statistical differences between the groups with regard to any of these epidemiologic characteristics.

TABLE 1. Signs and symptoms of GABHS pharyngitis present at enrollment prior to cefadroxil and phenoxymethyl penicillin treatment of GABHS pharyngitis

Signs and symptoms at initial visit[a]	No. (%) in indicated group:	
	Cefadroxil	Penicillin
Breath odor	23 (31)	29 (39)
Facial flush	26 (35)	26 (35)
Fever	69 (92)	71 (95)
Headache	54 (72)	57 (76)
Nausea	21 (28)	25 (33)
Pharyngeal redness	72 (96)	74 (99)
Sore throat	75 (100)	73 (97)
Swollen cervical lymph nodes	66 (88)	72 (96)
Tender cervical lymph nodes	52 (69)	61 (81)
Tonsillar exudate	51 (68)	52 (69)
Tonsillar petechiae	50 (67)	45 (60)
Vomiting	12 (16)	10 (13)

[a] As determined by the Fisher exact test, there were no differences in treatment groups for any sign or symptom.

The clinical signs and symptoms of GABHS pharyngitis present at the initial visit are presented in Table 1. At enrollment, the mean temperature of the cefadroxil-treated children (38.3 ± 0.7°C) was not significantly different from that of the penicillin-treated children (38.4 ± 0.7°C). The highest temperatures recorded prior to the initiation of antibiotic therapy were 40.0°C in the cefadroxil group and 40.6°C in the penicillin group. At the midtreatment visit, all children were afebrile; pharyngeal redness and the degree of enlargement and tenderness of anterior cervical lymph nodes were persistent in a greater percentage of penicillin-treated children than of cefadroxil-treated children (18 versus 6%, 29 versus 10%, and 12 versus 6%, respectively). However, these differences and similar, quantitatively smaller differences in the other signs and symptoms assessed were not statistically significant (Fisher exact test, $P > 0.05$). The clinical outcome was excellent in both groups when evaluated at the two end-of-treatment visits; there were no differences between the two treatment groups. The rate of complete disappearance of all signs and symptoms of pharyngitis for cefadroxil was 90% (68 of 73); that for penicillin was 89.3% (67 of 72). Of those who had a clinically unsatisfactory response, none had a positive culture during treatment, although all were subsequently found to be bacteriologic failures.

The bacteriologic responses in the two treatment groups are presented in Table 2. The bacteriologic cure rate for cefadroxil was 89.9% (62 of 69); that for penicillin was 76.4% (52 of 68). Of the 7 cefadroxil-treated and 16 penicillin-treated patients experiencing a persistent or recurrent infection, no GABHS strain predominated. Three children in the cefadroxil-treated group experienced a reinfection with a GABHS strain different from the initial infecting strain. Unevaluable cases resulted from loss of cultures at the follow-up visits such that a bacteriologic outcome could not be ascertained. All these children had shown a clinically satisfactory response to therapy. A statistical analysis of eradication rates compared with failure rates (combination of persistent and recurrent rates) for the two treatment groups showed the bacteriologic response to be superior for cefadroxil (chi-square test = 4.39, $P = 0.04$).

A total of 2 patients in the cefadroxil group and 11 in the penicillin group were considered to be clinically cured but bacteriologic failures. These children may have been GABHS carriers at the start of antibiotic treatment who developed intercurrent viral pharyngitis with signs and symptoms mimicking GABHS pharyngitis or may have developed the carrier state following antibiotic treatment in this study (2, 17). We do not have data to differentiate these alternative possibilities. If the disproportionate representation of asymptomatic, culture-positive patients in the penicillin group following treatment was due to the inclusion of a disproportionate number of carriers (and these patients, so identified, were excluded from the analysis), there would be no statistical difference in bacteriologic outcomes between the treatment groups. On the other hand, if the three cases in the cefadroxil group who cleared the original GABHS strain but later acquired another were considered to be successful bacteriologic eradications, then the bacteriologic cure rate for cefadroxil-treated patients would be higher, and the significance of the treatment group difference would be even greater.

No abnormality in hematology findings or renal function was noted in any patient, as determined by complete blood counts or urinalysis or both, in either treatment group. No patients experienced adverse effects from penicillin. One child in each group developed otitis media while receiving treatment and was withdrawn from the study, and the GABHS pharyngitis response was classified as undetermined. One child in the cefadroxil group experienced mild diarrhea which did not require cessation of the drug. No suppurative or nonsuppurative complications or any rashes were detected in any patient.

DISCUSSION

In this and a companion (9) study, once-daily cefadroxil was at least as effective as three-times-daily penicillin in producing bacteriologic eradication and clinical symptomatic improvement in children with GABHS pharyngitis. Neither drug produced significant side effects with the dosage schedule used. The once-daily dose of cefadroxil used in the treatment of uncomplicated urinary tract infections in children (13, 21) had not heretofore been applied in the treatment of acute GABHS pharyngitis in children. Its demonstrated effectiveness, combined with the dosage schedule reported here, should promote improved compliance and represents an important convenience for working mothers.

The use of cephalosporins as alternative oral agents in the treatment of GABHS pharyngitis dates back to 1967. Since that time, more than a dozen comparative trials have been performed. All have shown cephalosporins to be as effective as (4–6, 8, 12, 14, 15, 22, 24–26; M. E. Pichichero, F. A. Disney, G. H. Aronovitz, C. Ginsburg, and M. Stillerman, Clin. Pediatr., in press) or more effective than (27) penicillin. In these studies, two-, three- and four-times-daily but not once-daily adminstrations of cephalosporins and penicillin have been proven to be equally efficacious and, under study conditions, to yield similar rates of bacteriologic and clinical treatment failures. A consideration of cost and broader antimicrobial activity than thought necessary for GABHS has led to the continued recommendation of penicillin as the treatment of choice.

TABLE 2. Summary of bacteriologic responses with cefadroxil and phenoxymethyl pencillin for GABHS pharyngitis treatment

Response	No. (%) in indicated group:	
	Cefadroxil	Penicillin
Eradication	62 (89.9)[a]	52 (76.4)[a]
Persistence	2 (2.9)	6 (8.8)
Recurrence	5 (7.2)	10 (14.7)
Not evaluable	2	2
Reinfection	3	0

[a] Significantly different when compared with failures (combination of persisted and recurrence). Chi-square test = 4.39, $P = 0.04$.

In 1980 and again in 1982, Ginsburg et al. (12, 14) reported on a controlled comparative study of penicillin-treated children (8-mg/kg doses administered three times daily) and cefadroxil-treated children (15-mg/kg doses administered twice daily) with GABHS pharyngitis. In the first study, they found that 4 days after the discontinuation of antibiotics, 21% of the penicillin-treated but only 5% of the cefadroxil-treated patients had positive GABHS cultures. In the second study, the cumulative failure rate and relapse rate for penicillin-treated children were 20 and 12%, respectively, while for cefadroxil-treated children, the rates were 14 and 6%, respectively. In a similarly designed study, with identical dosing, Henness found the overall clinical and bacteriologic combined cure rates to be 81% for children receiving penicillin and 96% for those receiving cefadroxil (15). The findings of the current study are quite consistent with these prior reports, showing similar or superior results with cefadroxil treatment of GABHS pharyngitis, but our study and that of Gerber et al. (9) are the first to compare single-daily doses of cefadroxil with twice-daily doses.

While penicillin is effective in reducing the acute symptoms of GABHS pharyngitis, bacteriologic failure rates as high as 30% can occur with penicillin treatment. Several studies have led to speculation that bacteriologic failures after treatment with penicillin might be explained by the presence of beta-lactamase-producing strains of staphylococci (19) or anaerobes, particularly *Bacteroides* spp. (3), or both which inactivate penicillin at the local site of infection. This concept has been refuted by the work of Quie et al. (23) and Ginsburg et al. (14), who could find no correlation between the presence of beta-lactamase-producing *Staphylococcus* spp. and bacteriologic failures in children with GABHS pharyngitis who were treated with penicillin. However, the numbers may have been too small to detect such a difference. A trend was seen in the study of Ginsburg et al. (14) for an increased relapse rate in children harboring beta-lactamase-positive *Staphylococcus* spp. (16.7%) as compared with those who did not (7.3%). Cefadroxil is active against staphylococci but not against beta-lactamase-producing *Bacteroides* spp. Nevertheless, since cefadroxil is stable against beta-lactamases, it would be effective in eradicating GABHS even if beta-lactamases produced by other organisms, such as *Bacteroides* spp., were present in the pharynx. The relative role, if any, of these different beta-lactamase-producing bacteria in precluding the effective treatment of GABHS pharyngitis with penicillin seems worthy of additional research.

When confronted with a penicillin-allergic or erythromycin-intolerant patient or a patient whose infecting GABHS strain is erythromycin or penicillin tolerant (18) or resistant (R. Dagan, M. Ferne, M. Alkan, and E. Katzenelson, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 972, 1986) treatment with an alternative agent would be recommended. While the 5 to 10% cross-reaction rate between penicillins and cephalosporins

should be considered, this study adds once-daily cefadroxil as a therapeutic choice for these subgroups of patients.

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