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Efficacy of Cefuroxime Axetil Suspension Compared with That of Penicillin V Suspension in Children with Group A Streptococcal Pharyngitis

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The bacteriological and clinical efficacies of cefuroxime axetil suspension (20 mg/kg of body weight per day in two divided doses) were compared with those of penicillin V suspension (50 mg/kg/day in three divided doses) in a multicenter, randomized, evaluator-blinded study. Children aged 2 to 13 years with clinical signs and symptoms of acute pharyngitis and a positive throat culture for group A beta-hemolytic streptococci (GABHS) were eligible. Patients were assessed and samples from the throat for culture were obtained at the time of diagnosis, 3 to 7 days after the initiation of treatment, and 4 to 8 days and 19 to 25 days after the completion of 10 days of therapy. Of the 385 evaluable patients, GABHS were eradicated from 244 of 259 (94.2%) cefuroxime-treated patients and 106 of 126 (84.1%) penicillin-treated patients ($P = 0.001$). Complete resolution of the signs and symptoms present at the time of diagnosis was achieved in 238 of 259 (91.9%) cefuroxime-treated patients and 102 of 126 (81.0%) penicillin-treated patients ($P = 0.001$). Potential drug-related adverse events were reported in 7.0 and 3.2% of the cefuroxime- and penicillin-treated patients, respectively ($P = 0.078$). In the present study, cefuroxime axetil suspension given twice daily resulted in significantly greater bacteriological and clinical efficacies than those of penicillin V suspension given three times daily to pediatric patients with acute pharyngitis and a positive throat culture for GABHS.

Penicillin is the treatment of choice for group A streptococcal infections (5) except in patients with a history of hypersensitivity to penicillin. It remains the standard by which other antibiotics are compared, despite reports of bacteriological treatment failures (7, 12, 13). Noncompliance with the prescribed regimen (12), the presence of β-lactamase-producing organisms in the oropharynx (4), and possible tolerance of group A beta-hemolytic streptococci (GABHS) to penicillin (16) are proposed but unproven explanations for penicillin's failure to eradicate GABHS from the upper respiratory tracts of some patients.

GABHS are highly susceptible to cefuroxime in vitro (10). Cefuroxime axetil is the esterified form of cefuroxime that can be given orally. Following oral administration, cefuroxime axetil is rapidly deesterified to the parent antibacterial agent cefuroxime. Previous studies in small numbers of patients have suggested that cefuroxime axetil, given as tablets, is an alternative to penicillin for the treatment of group A streptococcal pharyngitis (8, 21). Recently, a suspension formulation has been developed to facilitate the administration of cefuroxime axetil to infants and children. In the present study, we compared the bacteriological and clinical efficacies of the cefuroxime axetil suspension with those of the penicillin V suspension in pediatric patients with acute pharyngitis and a positive throat culture for GABHS.

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MATERIALS AND METHODS

Population studied. The randomized, evaluator-blinded study was conducted at 10 pediatric centers located throughout the United States between October 1989 and April 1990. Children between the ages of 2 and 12 years were eligible if they had one or more signs (e.g., tonsillopharyngeal exudate, cervical lymphadenitis, scarlatiniform rash, strawberry tongue) and one or more symptoms (e.g., fever, sore throat, difficulty swallowing, abdominal pain, headache) compatible with a presumptive diagnosis of acute group A streptococcal pharyngitis. Patients were ineligible if they had a history of hypersensitivity to beta-lactam antibiotics or if they had received any systemic antibiotics within 7 days of enrollment in the study. No patient had received benzathine penicillin G. The protocol was approved by an institutional review board at each center, and the parents or legal guardian of all patients provided written informed consent.

At the time of enrollment in the study, a throat culture obtained by swabbing the posterior pharyngeal and tonsillar areas was plated onto 5% sheep blood agar. A physical examination was performed, and blood was collected for complete blood count with differential, platelet count, prothrombin time, and 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.

Treatment. Patients were randomly assigned to receive either cefuroxime axetil suspension, 20 mg/kg of body weight per day (maximum, 500 mg/day) in two divided doses (every 12 h with meals) for 10 days, or penicillin V suspension, 50 mg/kg/day (maximum 750 mg/day) in three divided

doses (every 8 h on an empty stomach) for 10 days, according to a randomization schedule generated by computer before the study and administered on the basis of the chronological order that the patients presented for treatment. Randomization of treatment was on a 2:1 (cefuroxime axetil:penicillin V) schedule to increase the number of patients receiving cefuroxime axetil suspension. A graduated dosing syringe was given to parents for accurate medication administration.

Bacteriological and clinical evaluations. Patients were scheduled to return to the center 3 to 7 days after the initiation of therapy and 4 to 8 days and 19 to 25 days after the completion of therapy for bacteriological and clinical assessments. In addition, parents and guardians were instructed to return the patients to the center if their clinical condition worsened. Drug therapy was stopped in patients from whom GABHS was not isolated from the pretreatment throat culture. At each scheduled or unscheduled visit, a sample from the throat was obtained for culture to determine the presence or absence of GABHS. The GABHS were presumptively identified by susceptibility to a 0.04-U bacitracin disk (6). The susceptibility of each isolate to cefuroxime (30-μg disk) and penicillin (10-U disk) was tested by the Kirby-Bauer method (2) by using the following breakpoint criteria: resistant to cefuroxime, <14 mm; resistant to penicillin, <19 mm (19). All isolates were serologically grouped and typed by T-agglutination pattern, M typing, and serum opacity factor as described previously (9, 15).

Bacteriological efficacy was defined as either success or failure. A success was recorded if the pretreatment serotype was eradicated from all subsequent cultures or if the pretreatment serotype was eradicated from all subsequent cultures but a different serotype was isolated. A failure was recorded if the pretreatment serotype was isolated from a culture of a sample obtained at either posttreatment visit.

Clinical efficacy was defined by the following criteria: success, resolution of signs and symptoms during treatment and throughout the follow-up period; failure, persistence of signs and symptoms after at least 5 days of treatment; recurrence, initial improvement of signs and symptoms during treatment, but with recurrence of signs or symptoms considered by the clinician to be consistent with the diagnosis of streptococcal pharyngitis during the follow-up period.

Safety evaluations. Clinical laboratory tests performed at the initial visit were repeated at 4 to 8 days posttreatment. The patients and the parents of the patients were asked at each study visit whether they had experienced any problems (adverse events) during the course of the study.

Compliance. Compliance was assessed by modifying a previously described method (17) for detecting the presence of antibiotic activity in urine. A 5% sheep blood agar plate was inoculated with GABHS and streaked for confluent growth. A 6-mm filter paper disk saturated with urine obtained from each patient at the 3- to 7-day intratreatment visit was placed on the agar plate, which was then incubated overnight (for a sufficient time to allow bacterial growth). Any zone of inhibition of growth around the disk was considered evidence that the antibiotic was present in the urine. Compliance was also assessed by measuring the volume of returned study drug.

Statistical analyses. Age and weight were compared between the two treatment groups by the test of van Elteren (26). Sex and race were compared by the Mantel-Haenszel test (18). Bacteriological and clinical efficacy results were also compared by the Mantel-Haenszel test. Incidence rates of adverse events were compared by Fisher's exact test. All statistical testing was done by using two-tailed statistical tests. Statistical significance was defined as $P \leq 0.05$.

TABLE 1. Patients excluded from primary efficacy analyses[a]

Characteristic	No. (%) of patients receiving:	
	Cefuroxime axetil suspension (n = 343)	Penicillin V suspension (n = 190)
Did not complete both follow-up visits	32 (9.3)	19 (10.0)
Use of non-study antimicrobial agent	13 (3.8)	8 (4.2)
Pathogen not isolated	12 (3.5)	12 (6.3)
Culture not submitted for serotyping	12 (3.5)	9 (4.7)
Received drug for <10 days	8 (2.3)	2 (1.0)
Withdrew for personal reasons	7 (2.0)	10 (5.2)
Poor compliance	6 (1.7)	6 (3.2)
Bacteriological failure but clinically unevaluable	2 (0.6)	9 (4.7)
Clinical recurrence but bacteriologically unevaluable	1 (0.3)	2 (1.1)

[a] Some patients were excluded for more than one reason.

The null hypothesis in the present study was that the cefuroxime axetil suspension and the penicillin V suspension were equally efficacious with respect to bacteriological outcome. From past studies (22), it was estimated that 80 to 85% of patients treated with penicillin would have a successful bacteriological outcome. A clinically relevant difference between penicillin and cefuroxime axetil in a successful outcome was set at 10%. Setting the two-sided significance level at 0.05 and given the number of patients treated with cefuroxime axetil and penicillin, the probability of failing to detect a real difference in treatments (beta or type II error) was 0.06, resulting in a power of 94%.

RESULTS

A total of 533 children were enrolled in the study. Of these, 84 of 343 (24.5%) cefuroxime-treated patients and 64 of 190 (33.7%) penicillin-treated patients were excluded from the primary bacteriological and clinical efficacy analyses for protocol violations or incomplete data collection (Table 1). These patients were included as bacteriological and clinical failures in an intent-to-treat efficacy analysis. Of the 385 patients who adhered to all protocol features and were included in the primary efficacy analysis, 259 patients received cefuroxime axetil and 126 patients received penicillin V. There were no statistically significant differences between these two treatment groups with respect to demographic characteristics (Table 2).

Bacteriological and clinical outcomes. The pretreatment serotype of GABHS was eradicated from 244 of 259 (94.2%) cefuroxime-treated patients, whereas it was eradicated from 106 of 126 (84.1%) penicillin-treated patients (P = 0.001; Table 3). The pretreatment serotype of GABHS was eradicated from 15 (5.8%) patients who received cefuroxime axetil and 9 (7.1%) patients who received penicillin V, but a different serotype was isolated at a subsequent visit (P = 0.495; Table 3). Of the 15 cefuroxime-treated patients considered bacteriological failures, the pretreatment serotype was isolated from 13 patients at least once from a sample obtained for culture at 4 to 35 days (median 17.0 days) posttreatment, for one patient, the pretreatment serotype

TABLE 2. Demographic characteristics of evaluable patients

Characteristic	Cefuroxime axetil suspension (n = 259)	Penicillin V suspension (n = 126)
Age (yr)		
Mean	6.7	6.9
Range	2–12	2–13
Sex (no. [%])		
Male	122 (47.1)	54 (42.9)
Female	137 (52.8)	72 (57.1)
Race (no. [%])		
White	227 (87.6)	106 (84.1)
Black	22 (8.5)	16 (12.7)
Hispanic	6 (2.3)	2 (1.6)
Other	4 (1.5)	2 (1.6)
Weight (kg)		
Mean	25.3	27.0
Range	11.8–69.9	11.4–72.5

was isolated from a sample obtained for culture at 45 days posttreatment, and for one patient, the pretreatment serotype was isolated from a sample obtained for culture at 76 days posttreatment. For all 20 penicillin-treated patients considered bacteriological failures, the pretreatment serotype was isolated at least once from a sample obtained for culture at 1 to 30 days (median, 4.0 days) posttreatment.

The signs and symptoms of acute pharyngitis present at the time of enrollment in the study were comparable between treatment groups. The clinical success rate for cefuroxime axetil was 91.9% (238 of 259), and that for penicillin V was 81.0% (102 of 126) (P = 0.001; Table 3). In comparison with the patients who received penicillin V, more patients who received cefuroxime axetil had complete resolution of the signs and symptoms present at the time of diagnosis and remained asymptomatic throughout the follow-up period.

TABLE 3. Bacteriological and clinical outcomes of evaluable patients

Outcome	No. (%) of patients receiving: Cefuroxime axetil suspension (n = 259)	Penicillin V suspension (n = 126)
Bacteriological success		
Eradication of pretreatment serotype	229 (88.4)	97 (77.0)
Eradication of pretreatment serotype with subsequent isolation of different serotype	15 (5.8)[a]	9 (7.1)
Total	244 (94.2)[b]	106 (84.1)
Bacteriological failure, pretreatment serotype isolated from throat sample culture obtained posttreatment	15 (5.8)	20 (15.9)
Clinical success	238 (91.9)[b]	102 (81.0)
Clinical failure	0	1 (0.8)
Clinical recurrence	21 (8.1)	23 (18.3)

[a] P = 0.495 for cefuroxime axetil versus penicillin V (Mantel-Haenszel test).
[b] P = 0.001 for cefuroxime axetil versus penicillin V (Mantel-Haenszel test).

TABLE 4. Urine bioassay results

Bioassay result	No. (%) of patients receiving: Cefuroxime axetil suspension (n = 343)	Penicillin V suspension (n = 190)
Antibiotic present in urine bioassay	300 (95.5)	157 (92.4)
Antibiotic absent in urine bioassay[a]	5 (1.6)	4 (2.4)
Urine sample not obtained	9 (2.7)	9 (5.3)
Total	314	170
Urine bioassay not performed[b]	29	20

[a] Patients were subsequently excluded from bacteriological and clinical efficacy analyses.
[b] These patients were withdrawn from the study for one of the following reasons: administration of concurrent antibiotics during the study; inability to isolate GABHS from the pretreatment culture of a sample from the throat; susceptibility testing was not performed on the pretreatment isolate.

Compliance with each of the prescribed regimens was similar between treatment groups. Antibiotic activity was detected in the urine of 300 of 314 (95.5%) cefuroxime-treated patients and 157 of 170 (92.4%) penicillin-treated patients (Table 4).

An intent-to-treat analysis was performed to provide supportive evidence for the primary efficacy analysis. Of the 533 patients initially enrolled in the study, the pretreatment serotype was eradicated from 251 of 343 (73.2%) cefuroxime-treated patients and 113 of 190 (59.5%) penicillin-treated patients (P = 0.0001). Similarly, complete resolution of the signs and symptoms present at the time of diagnosis was achieved in 244 of 343 (71.1%) cefuroxime-treated patients and 105 of 190 (55.3%) penicillin-treated patients (P = 0.0001).

Safety. All 533 patients enrolled in the study received one of the study drugs and were included in the safety analyses. Adverse events considered by the clinician to be possibly, probably, or almost certainly related to one of the study drugs were reported in 24 of 343 (7.0%) cefuroxime-treated patients and 6 of 190 (3.2%) penicillin-treated patients (P = 0.078). Adverse gastrointestinal events (e.g., diarrhea, abdominal pain, and nausea) were reported in 5.2% of the cefuroxime-treated patients and in 2.1% of the penicillin-treated patients (P = 0.11). Thrombocytopenia was noted in one penicillin-treated patient. No other clinically significant change in any safety variable occurred during the study.

DISCUSSION

Twice-daily cefuroxime axetil suspension was significantly more effective than three-times-daily penicillin V suspension for treating pediatric patients with signs and symptoms of acute pharyngitis and a positive throat sample culture for GABHS. These results, together with the findings of previous reports (8, 21), suggest that cefuroxime axetil is an effective alternative to penicillin for the treatment of acute group A streptococcal pharyngitis.

Results of our study provide good evidence that cefuroxime axetil lessens the likelihood that GABHS will persist following an adequate course of therapy. GABHS were completely eradicated from 94% of the cefuroxime-treated

patients, whereas they were completely eradicated from 84% of the penicillin-treated patients. Patients with positive throat cultures for GABHS following an adequate course of antibiotic therapy remain a concern to clinicians because these patients may be at risk for the development of suppurative or nonsuppurative complications. Additionally, these patients remain a concern to clinicians because they may be carriers of streptococci (11).

Although penicillin remains the treatment of choice for group A streptococcal pharyngitis, bacteriological failure rates following the administration of either benzathine penicillin intramuscularly or penicillin V orally have increased from 5 to 10% to 20 to 30% over the past 30 years (3, 7, 12–14, 24). One hypothesis for these findings is that β-lactamase-producing organisms in the oropharynx contribute to bacteriological failures with penicillin (4). A recently published study (25) indicated that β-lactamase production by normal pharyngeal flora does not fully explain the failure of penicillin therapy for acute streptococcal pharyngitis. However, that conclusion was based on the identification of β-lactamase-producing strains by a method which is not standardized for many of the isolates identified in the penicillin-treated patients in that study (Cefinase; Becton Dickinson Microbiology Systems, Cockeysville, Md.).

Cefuroxime is a bactericidal antibiotic that demonstrates in vitro activity against a broad spectrum of gram-positive and gram-negative organisms, including β-lactamase-producing strains of common respiratory tract pathogens (1, 10, 20). In the present study, we did not attempt to identify β-lactamase-producing organisms; therefore, we cannot state whether our observations can be attributed to the influence of these organisms or to the β-lactamase stability of cefuroxime.

The pharmacokinetics of cefuroxime in infants and children following 10-, 15-, and 20-mg/kg doses of cefuroxime axetil suspension have been studied (23). A mean maximum cefuroxime concentration of 3.3 μg/ml was achieved in serum 3.6 h following a single 10-mg/kg dose of cefuroxime axetil suspension. This concentration exceeds the MIC of cefuroxime for 90% of GABHS tested (0.1 μg/ml) (10). In addition, the mean half-life of cefuroxime in infants and children following a 10-mg/kg dose was 1.9 h. In the present study, we obtained good results with 20 mg of cefuroxime axetil suspension per kg/day administered in two divided doses.

The issue of the increased cost of cephalosporin use in the treatment of tonsillopharyngitis is an important one. However, the 3- to 10-fold higher cost of a 10-day course of a cephalosporin in comparison with the cost of penicillin VK should be viewed in the context of the higher failure rate likely to occur following penicillin therapy. After a penicillin treatment failure, the cost of an additional physician's office visit, additional throat culture, additional time lost from school and/or work, and a disturbance in the confidence relationship between patient and physician because of unsuccessful therapeutic outcome all need to be weighed in the cost decision analysis. Furthermore, should an unsuccessful bacteriological eradication occur in a patient with bona fide infection (not a carrier) following penicillin therapy, then the consequences could include nonsuppurative streptococcal sequelae.

Cefuroxime axetil and penicillin V suspensions were well tolerated. Gastrointestinal disturbances were reported by more patients receiving cefuroxime axetil than by patients receiving penicillin V (5.2 versus 2.1%). However, the overall incidence of gastrointestinal events was low, and differences between treatment groups were not statistically significant ($P = 0.11$).

In the present study, cefuroxime axetil suspension given twice daily resulted in significantly greater bacteriological and clinical cure rates than did penicillin V suspension given three times daily to pediatric patients with acute pharyngitis and a positive throat sample culture for GABHS.

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