

Use of Available Dosage Forms of Cephalexin in Clinical Comparison with Phenoxymethyl Penicillin and Benzathine Penicillin in the Treatment of Streptococcal Pharyngitis in Children

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Received for publication 18 April 1974

The effectiveness of cephalexin, an oral cephalosporin using a dosage equivalent to available capsular dosage forms, was studied in relation to the effectiveness of phenoxymethyl penicillin and benzathine penicillin in the treatment of 128 patients with beta-hemolytic streptococcal pharyngitis, all but six of whom had group A streptococci isolated from throat cultures. Approximately one-half, 66 patients, received cephalexin for 10 days; 34 patients received phenoxymethyl penicillin for 10 days; and 28 patients had a single injection of benzathine penicillin. There were four treatment failures determined bacteriologically post-therapy, two in the cephalexin treatment group and one each in the oral penicillin and intramuscular penicillin groups. Similar cure rates of 96.7, 97.1, and 96.4% were computed for the respective treatment regimens. Whereas intramuscular benzathine penicillin remains the regimen of choice in most instances, cephalexin appeared to be as effective as oral penicillin in the elimination of group A streptococci from the pharynx when oral treatment was desired for streptococcal pharyngitis.

Cephalexin, an orally absorbed cephalosporin, is a broad-spectrum antimicrobial agent giving satisfactory blood levels after oral administration, and has been demonstrated to be very active in vitro against beta-hemolytic streptococci (11, 12, 15, 19). It supplants an earlier developed member of the cephalosporin family, cephaloglycin, which was demonstrated to be clinically effective but was associated with low serum levels and with an unacceptably high incidence of side effects (9, 10).

The drug of choice in the treatment of beta-hemolytic streptococcal pharyngitis has been intramuscular benzathine penicillin and, to a lesser degree, the various oral penicillins and erythromycin. However, penicillin in any form is contraindicated in the treatment of patients with penicillin allergy. Erythromycin is a well-established alternative to penicillin in this circumstance (16). A similarly effective and versatile agent might merit consideration by physi-

cians to augment his or her options in the treatment of streptococcal disease when an alternative to penicillin is necessary.

The purpose of this study was the comparison of the clinical efficacy of the orally administered cephalosporin, cephalexin, in doses consistent with available capsular dose forms, with an oral penicillin, phenoxymethyl penicillin, and with the standard intramuscular form of penicillin, benzathine penicillin.

MATERIALS AND METHODS

Patient population. Patients in this study presented with symptoms suggestive of beta-hemolytic infection at the pediatric outpatient departments of St. Paul Ramsey Hospital, St. Paul, and Hennepin County General Hospital, Minneapolis, Minn. A presumptive diagnosis of streptococcal pharyngitis was made on the basis of clinical findings and, in the case of those on whom treatment was deferred, culture evidence of group A *Streptococcus*.

Bacteriological methods. Throat swabs were streaked on 5% sheep blood agar plates and examined for beta-hemolytic colonies at 24 and 48 h. Strains were identified as group A or non-group A by the bacitracin disk method of Maxted (13) and confirmed by the Lancefield grouping method (8) in the laboratory of Lewis W. Wannamaker. M typing by the

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capillary precipitin technique (18) and T agglutination reactions by the Griffith slide agglutination technique (14) were performed on selected isolates.

Administration and dosage. Patients received either cephalixin or one of the penicillins, phenoxymethyl or benzathine penicillin. The oral agents cephalixin and phenoxymethyl penicillin were administered for 10 days. The dosage of cephalixin was related to the available clinical capsular dose form of the antibiotic. The dosage of the penicillins was adjusted by the weight category of the patient.

Cephalixin was administered four times daily to 66 patients, with 59 (89%) receiving doses of 250 mg; three receiving 500 mg; three receiving 187 mg; and one receiving 125 mg. A cephalixin oral suspension was used in the four patients under 5 years of age, who received 187 and 125 mg. Thirty-eight patients received phenoxymethyl penicillin: 250-mg doses were administered to 18 patients three times daily and to 12 four times daily; 125 mg was given to six patients three times daily, and to two four times daily. Thirty patients received an intramuscular injection of benzathine penicillin administered as 600,000 U if under 60 pounds (about 27 kg) or 1.2-ml U if over 60 pounds.

Antibiotic therapy was instituted immediately after pharyngeal swabbing when patients manifested pronounced symptoms. In most patients, however, therapy commenced after bacteriological confirmation. An instruction and information form explaining the need for treating streptococcal pharyngitis was given to the parents of each patient, and the importance of a 10-day course of therapy was stressed. Blood was drawn for antistreptolysin O (ASO) determination at the time of initiation of therapy. For follow-up: a second throat culture was obtained 3 to 5 days after the beginning of therapy, a third culture was obtained 4 to 6 days after completion of therapy, and another culture was obtained 21 to 28 days after therapy ended. On return visits, physical examination and urinalysis were performed and blood was drawn for ASO determination. Therapy was considered successful if the 4- to 6-day post-therapy culture was negative for the original organism, i.e., beta-hemolytic streptococci had been eliminated from the pharynx.

ASO titer. ASO determinations were performed according to the protocol of Edwards (3). After blood was drawn and centrifuged, serum was removed and stored in a frozen state at -15°C . All serum specimens of a given patient were run at the same time. In determining which titers were abnormally elevated, the upper limits of normal were those established by Klein et al. (7). Upper limits of normal for ASO titers in the different age groups were defined as the level of antibody titer exceeded by no more than 15% of the subjects in that age group. These upper limits were 85 Todd units in children less than 1 year of age, 60 units (1 to 4 years), 170 units (5 to 8 years), 120 units (9 to 12 years), 170 units (13 to 15 years), and 85 units in adults. A 0.2-log or greater increment in titer was considered a significant rise.

Antibiotic susceptibility testing. Data on minimal inhibitory concentration (MIC) was obtained on 47 isolates from the cephalixin treatment group.

Susceptibility was determined by agar dilution technique (11, 12).

RESULTS

Patient population. Beta-hemolytic streptococci were recovered from the throats of 152 patients, the initial study population, of whom 128 were continued in the study until the end. Twenty-three of the 24 were dropped because they did not complete an appropriate course of therapy or because of failure to obtain appropriate follow-up cultures. Eight cephalixin-treated patients and five phenoxymethyl penicillin-treated patients failed to provide end of treatment (14-day) cultures and had admitted dubious compliance histories. Four cephalixin-treated patients failed to provide 3-week follow-up cultures, as did four phenoxymethyl penicillin-treatment patients and two benzathine penicillin-treated patients. In addition, one patient was withdrawn from the study because of an adverse reaction to cephalixin during treatment.

In the study group of 128, 63 were males and 65 were females. There were 112 school-age patients 5 to 16 years old and 12 pre-schoolers 2 to 4 years old. Another four patients, over age 16, were included because they were seen concurrently with a younger family member in the study group. Sex and age information are shown in Table 1.

Bacteriological findings. All but six of the 128 patients of the study population were found to have group A *Streptococcus*; of the six non-group A, three were group C and three were group G. The number of non-group A isolates is low because of the initial screening of cultures of patients included in the study population. The non-group A isolates were all eliminated from the pharynx, and their inclusion here was not felt to alter efficacy comparison results.

TABLE 1. Sex and age of patients

Patient group	Cephalixin (no. of patients)	Phenoxy-methyl penicillin (no. of patients)	Benzathine penicillin (no. of patients)
Preschool (<5 years)	5	2	5
School age (5-16 years)	58	31	23
Adult (>16 years)	3	1	0
Female	33	20	12
Male	33	14	16

Four bacteriological failures were recorded, two in the cephalixin treatment group and one each in the phenoxymethyl and benzathine penicillin groups. All of the failures were school age children 10 years or older. The daily dose of antibiotic received by each of the four patients whose treatment failed was at or below the median for his respective treatment group, when computed as milligrams or units per kilogram.

The daily dose in the cephalixin treatment group, using doses equivalent to the available capsular dose amounts (250 and 500 mg), ranged from 13.7 mg/kg per day to 80.2 mg/kg per day, with the median being 35.8 mg/kg per day. For the failures, daily dose was 35.5 mg/kg per day and 24.6 mg/kg, per day respectively. In the phenoxymethyl penicillin group the dose amounts ranged from 12.7 to 59 mg/kg, with a median of 25.1 mg/kg, and the single treatment failure was associated with a dose of 19.4 mg/kg per day. The dosage range for benzathine penicillin was 13,968 to 61,395 U/kg, with a median of 31,415 U/kg. The one patient for whom benzathine penicillin treatment failed received a dose calculable as 14,699 U/kg, the next to the lowest ratio recorded in the benzathine treatment group.

Recurrences occurred in four patients, three in the phenoxymethyl penicillin treatment group and one in the benzathine penicillin treatment group. A "recurrence" refers to a positive culture 21 to 28 days after completion of therapy when a culture taken 4 to 6 days after the completion of therapy had been negative.

Toxicity. Adverse reactions were seen in four of the 66 patients receiving cephalixin treatment (6.7%). Only one of these patients (1.5%) had a reaction, angioneurotic edema, severe enough to cause discontinuance of treatment altogether. In another patient with onset of diarrhea 1 day after treatment started, withdrawal of the antibiotic for 1 day brought relief and thereafter the therapeutic regimen was re-

sumed. The remaining two patients reported mild diarrhea.

Angioneurotic edema developed in a 15-year-old male, weighing 96 pounds (about 44 kg), after he received a single 250-mg dose of cephalixin. Laboratory studies showed an essentially similar eosinophil count of 5% pretherapy and 6% after administration of cephalixin. A Coombs test was negative. Mild diarrhea continued for 3 days in a 6-year-old male patient, weighing 35 pounds (about 16 kg), who was receiving 250 mg of cephalixin four times daily. The eosinophil count in this patient went from 0% pretherapy to 9% during therapy and was 10% at the time of post-therapy follow-up. Also in this patient, serum glutamic oxalacetic transaminase was elevated at 14 days. Pretherapy urinalysis showed 2+ acetone, but findings on serial urinalysis thereafter were unremarkable.

Urinalysis. Fifty-eight cephalixin-treated patients (88%) had urinalysis pretherapy and/or during therapy plus at least one post-treatment urinalysis result. In none was there a constellation of findings suggesting glomerulonephritis.

ASO. Three serial ASO responses were recorded for 86 patients with group A streptococcal pharyngitis in the three treatment regimens. Fifty-five of the 86 (64%) had a significant rise over pretherapy levels (Table 2). Fifty-two percent of those treated with cephalixin demonstrated a rise in titer as compared to 78 to 80% of those treated with phenoxymethyl and benzathine penicillin, respectively.

Approximately one-half (28 strains or 48%) of the strains typed during the period of the study on which complete ASO profiles were obtained were M type 5, T agglutination pattern 5/27/44. The ASO titer was either initially elevated with no subsequent rise (6) or demonstrated at least a 0.2-log titer rise (20) in every patient from whom this strain was isolated. The distribution of this M type 5, T agglutination pattern

TABLE 2. ASO antibody responses (Todd units) in 86 patients with group A streptococcal pharyngitis

Treatment group	No. tested	With 2-tube or 0.2-log titer rise				With no significant titer rise			
		Initial titer elevated		Initial titer not elevated		Initial titer elevated		Initial titer not elevated	
		No.	%	No.	%	No.	%	No.	%
Cephalixin	48	18	37	7	15	17	35	6	13
Phenoxymethyl penicillin	18	12	67	2	11	4	22	0	0
Benzathine penicillin	20	11	55	5	25	4	20	0	0

5/27/44 strain was equivalent in each treatment group. The remaining approximately one-half (30) of strains isolated from patients on whom complete ASO profiles were obtained comprised 18 M- and T-type patterns alone. There were 19 of 31 (61%) of these in which an 0.2-log or greater ASO titer rise was demonstrated, with 11 of 15 (73%) showing rises in the benzathine and phenoxymethyl penicillin treatment groups and only 8 of 16 (50%) in the cephalixin treatment group.

MIC. In the cephalixin treatment group, isolates from 47 patients (44 group A, three group C) were susceptible to MICs of the antibiotic within the range 0.1 to 6.3 $\mu\text{g/ml}$. All but four isolates were susceptible to an MIC of 0.8 $\mu\text{g/ml}$ or less, with two isolates of group A streptococci susceptible at each of the 1.6- and 6.3- μg levels. Susceptibility testing results are available on only one of the isolates from the two cephalixin treatment group failures. This organism was susceptible at the 0.4- μg level.

DISCUSSION

The therapeutic outcome in this study with cephalixin as given according to available capsular dosage amounts is consistent with results reported by other investigators. The dosage range on a per kilogram basis was considerable, but seemed not to play a role in the success of cephalixin as an antistreptococcal agent. Dosages as low as 13.7 mg/kg per day resulted in bacteriological cures without recurrence, indicating the considerable therapeutic potency of cephalixin against the group A *Streptococcus*. The high rate of elimination of streptococci with the oral agents used in this study is felt to be in part attributable to the close contact and supervision of the patients. The use of an information and explanation form, the easily visible dosage administration check list, the mid-therapy visit, and the realization of the impending follow-up visit all undoubtedly contributed to the high success rate. In a recent study, Shapera et al. (16), using a comparable approach to encourage compliance, found similar high success rates by using oral phenoxymethyl penicillin and erythromycin estolate. In that study urine samples were obtained for measurement of antibiotic presence to verify patient compliance.

In four therapeutic trials (1, 4, 10, 18) comparing cephalixin with other antistreptococcal agents (Table 3), the cure rate in cephalixin-treated patients, ranged from 90 to 96.7%. In an additional study of the therapeutic efficacy of cephalixin, Disney et al. (2) cite a lower cure rate of 80.9%, but they include as failures recurrences

(12.4%) and carriers (5.6%) defined as those with a 5-week positive culture after negative cultures in the earlier convalescent period. Clearly, final determination of results at an earlier point in the post-therapy period would yield a higher figure, although Aximi et al. (1), who did periodic cultures until 5 weeks elapsed, found only two bacteriological relapses (.08% incidence). Similarly, we found no recurrences with cephalixin-treated patients.

It should be stressed that the success rate with oral therapy in these studies can be misleading to the physician. Oral therapy in a study setting is reinforced by the enthusiasm and follow-up of the investigators. Compliance in most situations will not be as complete, especially if all of the measures used herein are not followed. Therefore, when possible, benzathine penicillin should be used and should be administered in the appropriate dosage. As was pointed out earlier, the single failure with benzathine penicillin occurred in a patient who received only 14,699 U/kg, the next to the lowest ratio recorded in that treatment group. A more appropriate dose may well have resulted in a cure.

The results of ASO titer rises obtained in this study are high compared to other results in our laboratory (16) and from other studies carried out here in Minnesota in the same patient population a few years earlier (5). However, approximately one-half of the strains recovered during this winter-months study were of a single epidemic strain with an M type 5 pattern not seen during the earlier study period (5) and which in this study was shown to be ubiquitously associated with either an already elevated ASO titer (25%) or with at least a 0.2-log titer rise (75% of these strains). This could also be interpreted to indicate that during this period of epidemic streptococcal pharyngitis a higher percentage of patients were truly infected with streptococcus and there were fewer carrier states included in the study population. These M type 5 strains were all from the same community and represented, in this study, an M type not found in this population previously (5), and not common in this area in the experience of the streptococcal research group at the University of Minnesota (E. L. Kaplan, personal communication). In addition, the patient population, i.e., county hospitals outpatients, may represent patients who were in high percentage activity infected at the time of being seen for treatment. Since most patients were not treated until bacteriological confirmation was obtained, the additional 2 to 3 days necessary to confirm the presence of group A orga-

TABLE 3. *Efficacy of cephalixin in comparative studies*

Study (reference)	Cephalexin cure (%) (no. of patients)	Phenoxy-methyl cure (%) (no. of patients)	Benzathine cure (%) (no. of patients)	Other oral agents cure (%) (no. of patients)	Regimen and criteria of cure (day 1 = 1st day of medication)
Present study Azimi et al. (1)	96.7 (66) 92 (25)	97.1 (34)	96.4 (28)		Medication for 10 days, 250 mg four times daily (125 if patient was <1 year old). Culture negative until 5 weeks
Disney et al. (2)	80.9 (89)			76.3 (58) ^a	Medication for 10 days, 30-40 mg of cephalixin per kg daily, 25,000-50,000 U of penicillin G. Culture negative until 5 weeks
Gau et al. (4)	96 (25)	92 (25)			Medication for 10 days, 750 mg daily (6-12 years), 1,000 mg (>12 years), 375 mg (<5 years). Culture negative on day 24
Gau et al. (4)	88 (25)				Same as above. Cephalixin-treated group on 5 days of medication
Leiderman et al. (9)	94 (94)			100 (84) ^b	Medication for 10 days, 20-25 mg/kg daily. Negative cultures until day 20 (or day 30 in 4 patients)
Stillerman et al. (17)	90 (84)	78 (89) ^d		73 (37) ^c	Medication for 10 days, 0.05 g daily. Negative culture after day 7 and at least one negative between days 18-31

^a Penicillin.^b Cephaloglycin.^c Ampicillin.^d Integrates data from earlier study by same author.

nisms may have allowed an additional opportunity for antibody production.

The incidence of clinical side effects associated with cephalixin treatment in four of the studies cited in Table 3 was lower than the incidence (6.7%) for the present study. Aximi et al. (1) did not report any clinical side effects. Leiderman et al. (9) reported one instance of erythematous papular rash at 8 days, disappearing 2 days after withdrawal of therapy. Disney et al. (2) reported extensive maculopapular rash in two patients on day 9, persistent diarrhea in one patient, transient diarrhea in one patient, and urticaria of limited duration in one patient. Stillerman et al. (17) found mild diarrhea in three patients and petechial rash in one patient on days 11 to 13 after start of therapy. Gau et al. (4), who had a higher incidence of side effects reported than the other studies (14%), uniquely listed as side effects headache in five patients and vaginal discharge in two others.

In considering cephalixin as an alternative to benzathine penicillin in patients for whom a

history of penicillin allergy is present, it is important to consider that approximately 5% of patients demonstrating true penicillin allergy will also have an adverse reaction to the cephalosporins. Similarly, as erythromycin is the historical alternative to penicillin for streptococcal pharyngitis in penicillin-sensitive patients, it is of note that the rate of erythromycin adverse reactions (7%) (16) is similar in our experience to that seen in this investigation with cephalixin, although in the erythromycin population (86 patients) there were three patients who developed rashes and three patients who developed gastrointestinal symptoms of sufficient severity to warrant using an alternative antibiotic.

Any discussion of cephalixin as an alternative to erythromycin in penicillin-allergic individuals must include the consideration of cost to the patient. At this time a course of therapy is more expensive with cephalixin.

The efficacy of cephalixin in the treatment of beta-hemolytic streptococcus in this study proved to be on a par with efficacy of oral and

intramuscular penicillin as measured by the elimination of group A streptococci from the pharynx. Although the percentage of bacteriological cures with benzathine penicillin was no greater than with either of the oral regimens, this route of administration remains the treatment of choice, especially when compliance with an oral regimen seems in doubt. Careful explanation of the importance of administering the full course of treatment, the use of an easily visible dosage administration checklist, and follow-up reminders during the treatment period appear to result in improved bacteriological cures, making the results of oral therapy approach those of parenteral therapy. The low incidence of side effects and the generally mild nature of side effects, as determined in this study and others surveyed, make cephalexin appear to be an acceptable alternative to penicillin in treatment of streptococcal pharyngitis when an oral agent is desired.

ACKNOWLEDGMENTS

This investigation was supported in part by a grant from Eli Lilly and Co., in part under the Sponsorship of the Commission on Streptococcal and Staphylococcal Diseases, Armed Forces Epidemiological Board, and in part by the U.S. Army Medical Research and Development Command under contract no. DADA 17-70-C00181 (L. W. Wannamaker, principal investigator).

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