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Streptococcal Pharyngitis Therapy: Comparison of Clindamycin Palmitate and Potassium Phenoxymethyl Penicillin

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Clindamycin palmitate and potassium phenoxymethyl penicillin were evaluated in 103 children with upper respiratory illnesses and pharyngeal group A streptococci, from November 1970 to July 1971. The children were assigned randomly by weight to one of the antibiotic regimens given orally for 10 days. Clindamycin palmitate and potassium phenoxymethyl penicillin dosages were 75 and 125 mg, respectively, in 5 ml tid for children weighing less than 25 kg, and 150 and 250 mg, respectively, in 10 ml bid for children weighing 25 kg or more. Recurrences of the original streptococcal group A, M, and T types within 3 weeks after the end of treatment were classified as failures. The failure rates were: clindamycin palmitate, 10% (5 of 52), and potassium phenoxymethyl penicillin, 18% (9 of 51). Possible drug-related rashes were observed in 8 of 52 clindamycin palmitate-treated patients. The geometric mean minimal inhibitory concentrations of clindamycin and penicillin against 103 isolates of group A streptococci were 0.033 and 0.007 μg/ml, respectively. The serum concentrations about 70 min after ingesting 150 mg of clindamycin palmitate averaged 3.8 μg/ml and after 250 mg of potassium phenoxymethyl penicillin averaged 0.9 μg/ml. Clindamycin palmitate was as effective as potassium phenoxymethyl penicillin in eradicating group A streptococci from the pharynx in tid and bid regimens. Nevertheless, because of its rash-producing tendency in some patients and higher cost, clindamycin palmitate should not be preferred to penicillin for treatment of streptococcal sore throat in the non-penicillin-allergic patient.

This investigation was initiated as a pilot study in evaluating the efficacy and side effects of two regimens of clindamycin palmitate and two of potassium phenoxymethyl penicillin (K penicillin V) against group A streptococci in upper respiratory illnesses.

Clindamycin palmitate, a new semisynthetic derivative of lincomycin in the form of flavored granules, is a water-soluble ester of clindamycin [7 (*S*)-chloro-7-deoxylincomycin] and palmitic acid. The palmitate ester is rapidly hydrolyzed to the microbiologically active clindamycin base after ingestion of the granules in a pediatric suspension. The suspension of clindamycin palmitate was introduced in place of clindamycin hydrochloride, which is available in capsule form because of the objectionable taste of the hydrochloride. In vitro antimicrobial activity of clindamycin against group A streptococci is approximately the same as that of lincomycin on a weight basis (10, 11, 14). In mice infected with group A streptococci, the oral mean culture dose is significantly lower for clindamycin than for lincomycin (9). In men, oral clindamycin is absorbed two or three times more efficiently than is oral lincomycin, but the average half-life of serum clindamycin activity (2.4 h) after a single usual 150-mg dose is less than the average half-life of serum lincomycin activity (5.2 h) after a single usual 500-mg dose (11, 20). Oral clindamycin produces less diarrhea than oral lincomycin after recommended doses (3, 5).

In one study of group A streptococcal pharyngitis, clindamycin hydrochloride, administered in a dose of about 10 mg per kg per day for 10 days, was more effective than penicillin (15). In earlier, studies, lincomycin hydrochloride, in a dose of 30 to 40 mg per kg per day for 10 days, was as effective as penicillin in two studies (8, 16) and was more effective than penicillin in two other studies (1, 6).

This paper was presented at the Eleventh Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N.J., 21 October 1971.

MATERIALS AND METHODS

One hundred and nine private pediatric patients with untreated acute pharyngitis associated with group A streptococci were studied from the end of November 1970 through July 1971. At the initial visit, throat swabs of all patients with upper respiratory illnesses were inoculated onto 5% sheep blood agar plates and into broth. The blood agar was streaked, stabbed, and incubated at 37 C for 18 to 24 h, and observed for an additional 12 to 24 h. The number of surface beta-hemolytic colonies was graded as 1+ to 4+ (18). Group A streptococci were identified presumptively by susceptibility to a bacitracin disk (Taxo A, BBL) and definitively by Lancefield grouping and by M-precipitin and T-agglutination typing at the Center for Disease Control (12). (Group A streptococci were tested with antisera for M-types 1 through 60; no antisera were available for M-types 9, 28, 34, 44, 48, 50, and 58.) Only patients harboring serologically determined group A streptococci, grades 2+ to 4+, were evaluated. Complete aerobic bacteriology was performed on cultures of practically all patients when group A streptococci were found.

Antistreptococcal therapy. Table 1 shows the antistreptococcal regimens: two for clindamycin palmitate and two for K penicillin V according to the patient's weight. The oral penicillin doses corresponded to those recommended by the American Heart Association.

The median dose for clindamycin palmitate- and K penicillin V-treated patients was 10 mg per kg per day (range 4.5 to 17 mg per kg per day) and 18 mg per kg per day (range 8 to 29 mg per kg per day), respectively. Each patient was assigned from a table of randomized numbers to one of the regimens, except that siblings requiring treatment were assigned to the alternate drug from that of the previous patient in the family. Very sick patients were given antistreptococcal therapy without waiting for culture findings. Doses were measured and administered orally by syringe. The oral suspension of clindamycin palmitate was accepted by all patients for whom it was prescribed, even though many graded the taste as fair. All parents and older children were reminded at the start of therapy and at times of culture, or by telephone during therapy, of the importance of administering the prescribed dose. Record cards for listing daily temperatures, symptoms, and administered antibiotic were given to parents of all patients. Completed forms were returned by all except nine of the patients evaluated.

Follow-up. Throat cultures for group A streptococci were routine on the 4th and 10th days of therapy, 4 days after the end of therapy, and weekly for 2 to 3 weeks thereafter. The average number of follow-up cultures per patient was five. Complete bacteriology was included on cultures taken 4 days after the beginning and 4 days after the end of therapy. Physical examinations and urinalyses were done at follow-up visits.

Evaluation. The effectiveness of therapy was determined by the disappearance of group A streptococci from the pharynx, by clinical response, and by occurrence of nonsuppurative complications. The bacterial outcome was classified as failure, cure, or indeterminate. "Failure" means recurrence of the original streptococcal group A, M-precipitin and T-agglutination types within 21 days after the end of therapy. "Cure" denotes either patients in whom all cultures for group A streptococci were negative after the 7th day of therapy, with at least one culture between 8 and 21 days after the end of therapy, or recurrence of a different streptococcal type, provided that the recurrence was preceded by a negative culture 8 to 21 days after the end of therapy. When such a recurrence was not preceded by a culture 8 to 21 days after the end of therapy, the patient was excluded from the study because of inadequate follow-up. "Indeterminate" refers to recurrence of the original type 22 to 28 days after the end of therapy in the absence of a negative culture 8 to 21 days after the end of therapy. There were no indeterminate cases. Clinical response was measured by the number of days after starting the antibiotic that the elevated temperatures dropped to normal and sore throats disappeared.

Number of patients evaluated. Of the original 109 patients, 103 qualified for evaluation. All patients included in the final evaluation received at least 90% of the total dose in 9 to 11 days of therapy, judged by frequent questioning, medicine check at the end of treatment, review of antibiotic record forms, urine tests of practically all patients for antibiotic activity, and blood of one-third of patients for the presence of antibiotic during therapy. An exception was made in the case of six patients included in the evaluation; in three, clindamycin palmitate was discontinued on the 8th day because a rash developed, one received the total clindamycin dose in 8.5 days, and two siblings received 80 to 85% of the total dose in 10 days. The number of patients and the distribution of their

TABLE 1. *Antistreptococcal regimens*

Antibiotic	Patient's wt (kg)	Oral dose	Frequency	Daily dose for 10 days (mg)
Clindamycin palmitate	<25	75 mg in 5 ml	tid	225
	≥25	150 mg in 10 ml	bid	300
K penicillin V	<25	125 mg in 5 ml	tid	375
	≥25	250 mg in 10 ml	bid	500

selected characteristics (see Table 3) did not differ significantly in the two regimens and conformed with those in similar studies (1, 19).

Streptococcal carriers were not categorized for evaluation because of difficulty in distinguishing a viral from a group A streptococcal pharyngitis.

At the start of treatment, 9 of the 30 children tested had antistreptolysin O (ASO) titers of 250 Todd units or higher, indicating a recent preceding streptococcal infection and possible carrier state or a mixed old and new infection. ASO titers were determined on convalescent-phase sera from 27 of those patients to study the relation of the ASO response to the result of treatment and to the day after onset of illness on which treatment was started. All sera were tested for heterophile antibodies.

Retreatments. Recurrences of presumptive group A streptococci within 21 days after an initial course of either antibiotic were retreated with the other antibiotic.

Toxicity. Tests for drug toxicity were performed at the beginning and end of therapy only in patients receiving clindamycin palmitate: serial urinalyses in all (an average of four for each), serial hemoglobin, white blood and differential cell counts in 24, and serial blood urea nitrogen and serum glutamic pyruvic transaminase determinations in 11.

Absorption. Seventeen sera obtained an average of 70 min after ingesting 150 mg of clindamycin palmitate and 13 sera obtained an average of 73 min after ingesting 250 mg of K penicillin V were frozen until assayed by the *Sarcina lutea* cup-plate method at the Upjohn Research Laboratory. The mean weights of the patients whose sera were analyzed for clindamycin and penicillin were 36 kg (range 25 to 73 kg) and 34 kg (range 26 to 57 kg), respectively. The sera were drawn a median of 3 and 4 days after beginning therapy with clindamycin and K penicillin V, respectively.

Antibiotic activity in urine. The urine of 95 of the 103 patients was tested for antibiotic activity during therapy at least once, and two or more times in many patients, by instilling a drop of urine onto an absorbable blank paper disk placed on a blood agar subculture of group A streptococci. The presence of antibiotic activity, indicated by a clear zone of inhibition around the disk, was found in all patients tested and in all but two of 143 urines tested during therapy. This compared with the absence of a similar reaction to the urines of 25 control children not receiving antibiotics.

Susceptibility tests. One hundred three isolates of group A streptococci were examined for susceptibility to clindamycin and penicillin G by disk diffusion and serial broth-dilution methods (7).

Household contacts were cultured routinely shortly after the diagnosis was established in the index patient and at the time of recurrences in search of infection in contacts who might be a source of reinfection to the index patient at the completion of therapy.

RESULTS AND DISCUSSION

Clinical response. The pattern of general improvement, manifested by subsidence of acute pharyngitis and return of elevated temperatures to normal within 48 h, was approximately the same for the two regimens.

Cultures before and during therapy. Group A streptococci were identified before treatment in all 103 patients evaluated (52 on clindamycin palmitate and 51 on K penicillin V). The cultures were 3+ to 4+ positive in 91%. A heavy growth of streptococci is more indicative of an active streptococcal infection than a prolonged carrier state. Of 102 patients cultured at least once during therapy, group A streptococci were recovered once on day 1 (but not on day 5) from one of 51 patients on clindamycin, once on day 1 (but not on day 5) from one patient, and once on day 8 from a second of 51 patients on K penicillin V.

Penicillin-β-lactamase-producing *S. aureus* was isolated from 42 of 94 patients evaluated before therapy. Of those 42, a significantly smaller proportion showed these staphylococci during than before therapy with clindamycin palmitate (4:26), whereas these microorganisms were recovered from more during than before therapy with K penicillin V (18:16). The activity of clindamycin palmitate against the pharyngeal pretreatment penicillin-β-lactamase-producing staphylococci in this study is similar to that of cephalexin in a previous study (19).

Diplococcus pneumoniae were isolated in pretreatment cultures of three of 94 patients. During therapy of those three patients, the microorganisms were not found in cultures of the two patients on K penicillin V and the one on clindamycin.

Bacterial outcome after primary treatment. Table 2 shows the bacterial failure rates in the clindamycin palmitate and K penicillin V regimens by patient's weight. The difference

TABLE 2. *Bacterial failure rates after primary treatments*

Patient's wt (kg)	Clindamycin palmitate			K penicillin V			Probability value
	Total	Failures		Total	Failures		
		No.	%		No.	%	
<25[a]	31	3	10	29	6	21	>0.10
≥25[b]	21	2	10	22	3	14	>0.50
All	52	5	10	51	9	18	>0.10

[a] Dose of clindamycin palmitate was 75 mg in 5 ml tid, and dose of K penicillin V was 125 mg in 5 ml tid for 10 days.

[b] Dose of clindamycin palmitate was 150 mg in 10 ml bid, and dose of K penicillin V was 250 mg in 10 ml bid for 10 days.

between the percentage of failures in the clindamycin- and K penicillin V-treated patients is not statistically significant for the two weight groups or dosage regimens individually or combined.

The comparative effectiveness of clindamycin palmitate in bid and tid doses merits further study.

The overall failure rates (10% [5 of 52] for clindamycin palmitate-treated and 18% [9 of 51] for K penicillin V-treated patients), which were not significantly different in this study,

TABLE 3. *Bacterial failure rates after primary treatments*

Factors evaluated	Clindamycin			K penicillin V			Both drugs		
	Total	Failures		Total	Failures		Total	Failures	
		No.	%		No.	%		No.	%
Patients with pharyngitis	52	5	10	51	9	18	103	14	14
Associated conditions at initial exam									
Scarlet fever rash	2	0	0	2	1	50	4	1	25
Rhinitis (streptococcal)	6	1	17	2	1	50	8	2	25
Cervical adenitis	20	2	10	25	2	8	45	4	9
Pyoderma (streptococcal)	3	1	33	2	0	0	5	1	20
Nonstreptococcal upper respiratory symptoms	13	2	15	14	3	21	27	5	19
November–December 1970	6	0	0	5	1	20	11	1	9
January–March 1971	24	3	12	29	5	17	53	8	15
April–July 1971	22	2	9	17	3	18	39	5	13
Male	27	1	4	29	5	17	56	6	12
2–4 years old	5	1	20	11	5	45	16	6	37
5–7 years old	30	3	10	25	2	8	55	5	9
8–10 years old	11	1	9	12	2	17	23	3	13
11–17 years old	6	0	0	3	0	0	9	0	0
Tonsils present	50	5	10	51	9	17	101	14	14
Treated < 72 h after onset	34	3	9	36	6	17	70	9	13
Temperature peak, recorded, ≥ 103 F, 39.4 C	23	2	9	17	3	18	40	5	12
Temperature elevated at time of therapy	32	2	6	36	7	19	68	9	13
Temperature normal in 24 h	20	2	10	21	3	14	41	5	12
Temperature normal in 48 h	7	0	0	6	0	0	13	0	0
Pretreatment group A streptococci									
2+	8	1	12	1	0	0	9	1	11
3+ to 4+	44	4	10	50	9	18	94	13	14
M-typable	19	2	10	16	4	25	35	6	17
M-nontypable	33	3	9	35	5	14	68	8	11
Pretreatment *S. aureus*									
Penicillin resistant	26	3	12	16	3	19	42	6	14
Penicillin susceptible	4	0	0	4	1	25	8	1	12
Absent	17	2	12	27	4	15	44	6	13
Not done	5	0	0	4	1	25	9	1	11
Homologous streptococci in household contacts after end of therapy									
Present	7	4	57	5	3	60	12	7	58
Absent	45	1	2	46	6	13	91	7	8
Antistreptolysin O titers									
Initial, < 250 Todd units	11	0	0	10	0	0	21	0	0
Initial, ≥ 250 Todd units	4	0	0	5	2	40	9	2	22
Serial, no rise	7	0	0	8	1	12	15	1	7
Serial, 1-tube rise	3	0	0	2	0	0	5	0	0
Serial, ≥ 2-tube rise	4	0	0	3	0	0	7	0	0
Urines positive for antibiotic activity during therapy	48	4	8	47	8	17	95	12	13
Urines not tested for antibiotic activity during therapy	4	1	25	4	1	25	8	2	25

correspond individually with previously published failure rates (7% [4 of 59] for clindamycin hydrochloride-treated and 21% [16 of 72] for K penicillin V-treated patients), which were significantly different in a similar study (15).

Table 3 summarizes the bacterial failure rates for the clindamycin palmitate- and K penicillin V-treated patients by selected variables. They do not differ significantly at the 5% level for the factors evaluated. Even though there was no significant difference between failure rates for clindamycin- and K penicillin V-treated patients according to the presence or absence of homologous streptococci in household contacts after the end of therapy, the failure rates were significantly higher in patients exposed to homologous streptococci than in those not exposed. Thus the high failure rate in K penicillin V-treated 2- to 4-year-olds (5 of 11) could be attributed in two of the five children to exposure to homologous streptococci in household contacts.

A two-tube or greater rise of acute- and convalescant-phase antistreptolysin O titers occurred in four of 14 clindamycin-treated patients and in three of 13 K penicillin V-treated patients. Among the seven patients with a twofold or greater ASO rise, the following was noted: the initial titers were low (in five, <60 Todd units; in one, 60 Todd units; and in one, 85 Todd units); antistreptococcal therapy was started early after the onset of illness (in one patient on the first day and in six on the second day); and all follow-up cultures showed no group A streptococci. In this study, clindamycin and K penicillin V equally suppressed ASO responses. Also, in this and in several previous studies (2, 4, 21), antistreptococcal therapy incompletely prevented a significant ASO response despite complete eradication of group A streptococci and early institution of therapy. There is no relation between the development of ASO and type-specific streptococcal antibody.

Table 4 gives the distribution and bacterial failure rates in patients with M-typable and M-nontypable group A streptococci by M-precipitin types. The failure rates tended to be lower for the M-nontypable streptococci. In the eight patients with failures associated with M-nontypable streptococci, the original and recurrent isolates were the same T-agglutination types, i.e., 28, 2/28, 8/25, and 8/25/Imp 19. The preponderance of M-nontypable over M-typable strains indicated a non-epidemic year. Of the 35 M-typable streptococci, M-types 12, 4, and 1 were most frequent. Of the 68 M-nontypable streptococci, T-agglutination types 12, 28, 8/25/Imp 19, and 5/27/44 were most frequent. The 68 M-nontypable streptococci included 15 with characteristic pyoderma T-typing patterns: T-8/25/Imp 19; T-5/27/44; and T-3/13/B3264 (13). Pyoderma, however, was detected in only one of the 15 patients harboring those pharyngeal T-typing patterns.

Bacterial outcome after retreatment. Clindamycin palmitate retreatment in seven of nine patients with bacterial failures after K penicillin V resulted in two failures. Potassium penicillin V retreatment in four of five patients with failures after clindamycin palmitate resulted in no failures. The number of patients with bacterial failures retreated with the alternate antibiotic was too small to evaluate.

Failure intervals. Figure 1 shows the intervals in days between the end of primary therapy and bacterial failures in the 14 patients with and without clinical manifestations. In 11 of the 14 patients, pharyngitis or rhinitis was observed at the time of bacterial recurrence. The majority of bacterial failures after both antibiotics were detected during the first week after the end of therapy.

TABLE 4. *Bacterial failures in patients with M-typable and M-nontypable group A streptococci*

M-type[a]	Clindamycin palmitate		K penicillin V		Both drugs	
	Total	Failures	Total	Failures	Total	Failures
1	3	0	1	0	4	0
4	5	0	3	1	8	1
6	1	0	2	1	3	1
12	7	2	7	2	14	4
5, 19, 29, 33	3	0	3	0	6	0
1 to 33	19	2	16	4	35	6
NT[b]	33	3	35	5	68	8
Total	52	5	51	9	103	14

[a] Lancefield M-precipitin types.

[b] NT, Nontypable by Lancefield M-precipitin antisera.

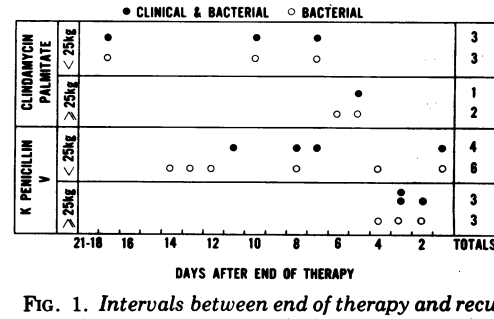

FIG. 1. *Intervals between end of therapy and recurrences of group A streptococci of the same type in 14 patients. Clinical manifestations were present in 11 of the 14 patients.*

Adverse reactions. Possible drug-related rashes developed in eight of 52 patients on clindamycin palmitate. They were first detected in one child on the 3rd day, one on the 7th day, one on the 8th day, three on the 9th day, one on the 10th day, and one on the 11th day after beginning therapy. Of the eight children, six had delayed generalized maculopapular rashes (duration 1 to 7 days), similar to those observed previously by one of the authors in three of 37 children during the second week after beginning a 10-day course of ampicillin (19) and in 11 of 93 children during the second week after beginning a 10-day course of cephaloglycin (17). One of the children who developed a delayed generalized maculopapular rash on clindamycin had a similar delayed generalized maculopapular rash after a 10-day course of ampicillin for a streptococcal sore throat in 1969. Five of the eight children received the smaller clindamycin dose and four had a history of allergies. The 15% incidence of rashes in this study compares with a reported incidence of delayed maculopapular rashes in 10 of 50 clindamycin hydrochloride-treated patients (5) and an incidence of less than 3% rashes, typically maculopapular, appearing after 5 to 10 days of therapy and clearing despite continuation of therapy in 1,500 clindamycin palmitate-treated children from case reports filed with The Upjohn Co. (3). The cause of maculopapular rashes occurring during the second week after starting a 10-day drug regimen is unknown (19). Tests for heterophile antibodies were negative in acute and convalescent sera obtained from four of the eight children with rashes. The incidence of rashes after clindamycin in this study appears to be higher than that reported after lincomycin (1). No rashes were observed in the K penicillin V-treated patients.

Mild diarrhea developed in two of 52 children on clindamycin and in none on K penicillin V. The lesser frequency of diarrhea after clindamycin in this study than that reported after lincomycin (3, 10) might be attributable to the smaller dose and more rapid absorption of clindamycin.

A rise in the total eosinophile count developed in serial differential blood counts in two of 24 tested children who were on clindamycin and in two of eight tested children who were on K penicillin V.

Of 11 children tested for blood urea nitrogen and serum glutamic pyruvic transaminase at the beginning and end of clindamycin therapy, the only abnormal finding was a slight transient rise of the serum glutamic pyruvic transaminase from 12 to 33 units, falling thereafter to 11, in one of three tested children who developed rashes referred to above.

Susceptibility tests. The geometric mean minimal inhibitory concentrations of clindamycin and penicillin against 103 group A streptococcal isolates were 0.033 and 0.007 μg/ml, respectively (Table 5).

Absorption. Figure 2 illustrates the serum concentrations obtained an average of 73 and 70 min, respectively, after ingesting 250 mg of K penicillin V and 150 mg of clindamycin palmitate during therapy. The average serum concentration of clindamycin (3.8 μg/ml) was significantly higher than that of penicillin (0.9 μg/ml). Those concentrations of clindamycin and penicillin are about 100 times higher than the average minimal inhibitory concentrations of those antibiotics against the group A streptococci shown in Table 5. Such high ratios suggest that clindamycin and K penicillin V would be effective therapeutically. This was borne out clinically.

No rheumatic fever or acute glomerulonephritis was detected in our patients.

TABLE 5. *Susceptibility of 103 group A streptococci to clindamycin and penicillin*

MIC[a] (μg/ml)	Number of strains susceptible	
	Clindamycin	Penicillin
0.004	0	41
0.008	4	40
0.016	24	18
0.032	43	4
0.062	27	0
0.125	5	0

[a] The geometric mean minimal inhibitory concentration (MIC) was 0.033 μg/ml for clindamycin and 0.007 μg/ml for penicillin.

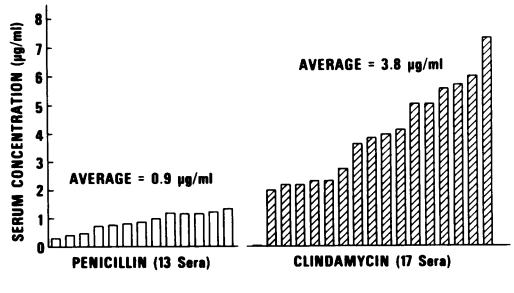

FIG. 2. *Antibiotic concentrations in 30 sera after ingesting 250 mg of K penicillin V (13 sera) and 150 mg of clindamycin palmitate (17 sera) during therapy.*

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