

REACTIONS FOLLOWING THE USE OF AUREOMYCIN AND PROCAINE PENICILLIN TROCHES: A CONTROLLED STUDY

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THE authors have previously reported on the incidence and types of reactions following the use of terramycin troches.¹ The terramycin study stemmed from widespread evidence of local and systemic side effects observed during antibacterial therapy.²⁻¹⁵ Reactions have previously been reported during or after topical Aureomycin or penicillin medication in a considerable percentage of subjects. The present study was intended to investigate and evaluate the reactions resulting from therapy with Aureomycin Hydrochloride and procaine penicillin G troches and to compare the incidence and types of these reactions with those previously observed in the terramycin troche study.

METHODS

Three hundred patients were observed during and after medication with crystalline Aureomycin Hydrochloride troches or crystalline procaine penicillin G troches or placebo troches. The patients were divided into 6 groups, as follows:

Group I was composed of 27 normal volunteer subjects (aged 24 to 28, all males) comprising nearly the entire second-year class of the dental school. Four troches per day, each containing 15 mg. of Aureomycin Hydrochloride, were administered to each subject until 10 troches had been allowed to dissolve completely in the mouth.

Group II was composed of 73 patients (aged 12 to 60, 44 females and 29 males) who were treated for various types of minor oral disorders with Aureomycin troches (15 mg.), five troches per day for four days.

Group III, a control group for the Aureomycin study, was composed of 50 patients (aged 15 to 58, 35 females and 15 males) similar to those in Group II. This group was treated exactly as Group II except that placebo troches were administered five per day for four days. The placebo troches were identical in content and appearance with the medicated troche except for the inert filler which replaced the active ingredient, Aureomycin.

Group IV was composed of 37 normal volunteer subjects (aged 25 to 29, all males) comprising nearly the entire first-year class of the dental school.

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Four troches per day each containing 5,000 units of procaine penicillin G were administered to each subject until 10 troches had been allowed to dissolve completely in the mouth.

Group V was composed of 72 patients (aged 11 to 66, 41 females and 31 males) who were treated for various types of minor oral disorders with identical procaine penicillin G troches (5,000 units per troche), five per day for four days.

Group VI, a control group for procaine penicillin G, was composed of 50 patients (aged 16 to 55, 30 females and 20 males) similar to those in Group V. This group was treated exactly as Group IV except that placebo troches were administered five per day for four days. The placebo troches were identical in content and appearance with the medicated troche except for the inert filler which replaced the active ingredient, procaine penicillin G.

A careful history concerning their previous experience with antibacterial agents, their reactions to previous antibiotic therapy, drug sensitivity, and other allergies was obtained from each patient. During and after the completion of therapy, patients were examined orally and each patient was specifically questioned as to whether or not any reaction had been noted. If a reaction was observed or reported the patient was queried concerning the character and severity of the reaction or reactions which had been manifested.

The advisability of routine examination of stained smears for presence or absence of *Monilia* organisms prior to, and after, antibiotic troche medication was considered. However, since *Monilia* are a common inhabitant of the oral mucous membranes in the normal state, their presence on a slide or in a culture before or after medication would not be confirmatory of fungus infection unless numerous detailed culture studies were performed. Also, according to Kligman,¹⁶ most reported instances of localized moniliasis, occurring in association with antibiotic therapy, "are not actually cases of this disease." Since daily comprehensive cultures of each subject before and after medication were outside the scope possible for our study, this aspect was not covered.

RESULTS

The incidence and types of reactions observed during and after Aureomycin, procaine penicillin G, and placebo control troche therapy are detailed and summarized in Table I.

Reactions to Aureomycin troches were observed in 51 (51 per cent) of the 100 patients treated. These 51 patients reported a total of 142 reactions distributed among 21 symptoms. Reactions which necessitated discontinuation of therapy occurred in 14 (14 per cent) patients. Slight reaction was recorded in 27 (27 per cent). Moderate reactions were noted in 10 (10 per cent). Delayed gastrointestinal reactions were noted in 12 cases one to four days after cessation of therapy.

Reactions to procaine penicillin G troches were observed in 38 (38 per cent) of the patients treated. These 38 patients reported a total of 101 reactions distributed among 21 symptoms. Reactions which necessitated discontinuation of therapy occurred in 11 (11 per cent) patients. Moderate reactions were

TABLE I. TYPE, FREQUENCY, AND SEVERITY OF REACTIONS TO AUREOMYCIN AND PENICILLIN TROCHES

REACTIONS	AUREOMYCIN						PENICILLIN					
	GROUP I			GROUP II			GROUP III (PLACEBO)			GROUP IV		
	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+
Abdominal ache and pain	2									1		
Aggravation of symptoms				1		2				1	1	
Aplthae												
Cheilosis												
Constipation	1											
Diarrhea	4	2		2	3	4	1			1		3
Dizziness	1											
Drowsiness	6											
Fever									4			
Flatulence	1			6	2				1			
Glossitis	3			1		3				2	2	2
Headache	3	1		1					1	4	1	
Increased freq. of stool	3									2		
Intestinal upset	4								4			
Joint pains										1		
Loose stool	4								2	1		
Malaise	2			3			1		2	1		
Nausea	5	2	1	1	6	4	1		2	1	1	2
Pharyngitis	1			1	1	2	5	2	3	1	5	3
Pruritis ani				2	3				2	1	1	
Rectal burning	1			3								
Stomatitis	1		1	2	2					1	2	
Taste disturbance	9	1	1	13	3		3		9	2	11	3
Tiredness	6			1					3	1		
Vomiting	1								1			
Total no. reactions	58	6	3	43	15	18	11	3	0	41	2	7
		67			76			14		50	51	
Total no. reactions in group												10
Total no. patients in group	27				73		50			28	72	50
Total no. patients showing reaction	14	3	3	13	7	11	4	3	0	10	12	4
										6	9	7
											5	2
												0

1+—reported, but not inconvenienting.

2+—moderate, uncomfortable but not forcing discontinuation therapy.

3+—severe, forced discontinuation of therapy.

noted in 11 (11 per cent). Slight reaction was recorded in 16 (16 per cent). Delayed gastrointestinal reactions were noted in 3 cases, one to four days after cessation of therapy.

Of the 50 patients receiving control troches in the Aureomycin group, 7 (14 per cent) reported reactions, none oral or pharyngeal. Of these, none complained of a severe reaction, 3 reported moderate reactions, while 3 had only slight complaints.

Of the 50 patients in the procaine penicillin G control group, 7 reported reactions (14 per cent), none severe, 2 (4 per cent) moderate, and 5 (10 per cent) slight. No oral or pharyngeal reactions were noted.

As previously reported,¹ reactions to terramycin troches were observed in 76 (53 per cent) of the 143 patients treated. These 76 patients reported a total of 203 reactions distributed among 24 symptoms. Reactions which necessitated discontinuation of therapy occurred in 21 (14.7 per cent) patients. Moderate reactions were noted in 23 (16.1 per cent). Slight reactions were recorded in 32 (22.4 per cent) of the cases. Delayed gastrointestinal reactions were noted by 26 patients one to four days after cessation of therapy. A summary of the reactions from terramycin troches and placebo troches appears in Table II.

Of the 75 patients receiving placebo troches in the terramycin group, 8 (10.7 per cent) reported reactions, none oral or pharyngeal. Of these 1 (1.4 per cent) complained of a severe reaction, none reported moderate reactions, while 7 (9.3 per cent) had only slight complaints.

Tabulation of the histories of the three groups compared in this study revealed the following: 28 (28 per cent) cases of the Aureomycin-treated groups recollected having previously received Aureomycin (18 systemically and 12 topically), 5 (3.5 per cent) of the terramycin-treated groups had previously received terramycin (all systemically), and 73 (73 per cent) of the procaine penicillin G-treated groups had previously received penicillin therapy (20 topically and 63 systemically). Previous reactions which had been reported by the patients included: to systemic Aureomycin, 2 reactions; to topical Aureomycin, 4 reactions; to terramycin systemically and topically, no reactions; to systemic penicillin, 2 reactions; to topical penicillin, 2 reactions. Since these patients had not been studied at the time specifically for toxic reactions, and since the administration of these drugs had, in many cases, been many months in the past, the reported previous incidence of reactions is understandably smaller than those reported in this study. In addition, the accuracy of recollection of previous therapy and reactions is questionable.

In this investigation, as in the terramycin series, reactions were limited primarily to the gastrointestinal tract. Severe glossitis or stomatitis occurred in 6 cases and pharyngitis occurred in 2 cases in the Aureomycin group (8 per cent); severe glossitis or stomatitis was noted in 6 cases in the procaine penicillin G group (6 per cent). In the terramycin series of 143 patients, severe glossitis or stomatitis occurred in 8 cases and pharyngitis occurred in 5 cases (9 per cent). The percentages of cases in these groups showing oral reactions do not differ significantly from each other ($\chi^2 = 0.77$; $d = 2$).

TABLE II. COMPARISON OF REACTIONS TO AUREOMYCIN, PENICILLIN, AND TERRAMYCIN TROCHES

REACTIONS	AUREOMYCIN				PENICILLIN				TERRAMYCIN				% OF TOTAL REAC- TIONS WITH MED- ICATED TROCHES	
	GROUPS I AND II		GROUP III (PLACEBO)	GROUPS IV AND V		GROUP VI (PLACEBO)	GROUPS I, II, III, AND IV		GROUP V (PLACEBO)					
	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+		
Abdominal ache and pain	2						1							3.1
Aggravation of symp- toms						2								0.9
Aphthae	1		2											0.9
Cheilosis														0.4
Constipation	1													1.1
Diarrhea	6	5	4	1	3							1		14.3
Dizziness	1													0.4
Drowsiness	6					4						1		3.1
Fever						1								0.9
Flatulence	7	2		1	2									8.7
Glossitis	4		3		1									4.5
Headache	4	1										1		2.5
Increased freq. of stool	3					4								2.9
Intestinal upset	4					3								1.1
Joint pains						2								4.9
Loose stool	7			1		5	1					2		2.7
Malaise	3			1		3	2							17.2
Nausea	11	6	6	5	4	9	5	2	25	8	3	7	1	2.5
Pharyngitis	2		2			2			2					3.4
Pruritus ani	2	3			1	1	1		3	5				1.1
Rectal burning	4								1	1	4			3.8
Stomatitis	3		3		4	1	4	3	1	1		3		13.4
Taste disturbance	22	4	1	3		21	4		2	4				2.9
Tiredness	7					3	1		2					0.9
Vomiting	1					1			1					
Total no. reactions	101	21	21	11	72	14	15	8	133	47	23	16	10	100.0
Total no. reactions in groups	143				101			10	203			27		
Total no. patients in groups	100				100			50	143			75		
Total no. patients show- ing reaction	51				38			7	76			8		

Some of the reactions to Aureomycin and procaine penicillin G, especially the oral ones, were found to be persistent and required from one to twenty-one days to regress. Diarrhea was usually accompanied by intense pruritus ani. As was noted with terramycin troches,¹ the incidence of gastrointestinal complaints in the placebo control groups indicates that some reactions observed during antibiotic troche administration may be the result of the elaborate tastemasking bases in which antibiotics are sometimes incorporated. Impurities in antibiotic preparations have also frequently been reported as causing untoward reactions to therapy. Irritative excipients and impurities may, therefore, be instrumental in either producing or causing exacerbation of reactions.

In comparing clinically the type of reactions to Aureomycin, procaine penicillin G, and terramycin troches, it will be noted that a great similarity exists. The most frequently occurring reactions were nausea, diarrhea, taste disturbance, flatulence, loose stool, and pruritus ani. Aphthous ulcers were seen only after Aureomycin, and cheilosis occurred only after terramycin, although we have noted this latter reaction after Aureomycin and procaine penicillin G therapy in cases outside of this study. It will be noted from Table II that the frequency of reactions varied somewhat with the different antibiotic troches employed. Thus, abdominal pain occurred in a greater percentage of cases with terramycin troches than with Aureomycin or procaine penicillin G. Diarrhea was noted with decreasing frequency with terramycin, Aureomycin, and procaine penicillin G troches. Flatulence occurred more frequently with terramycin than with the other two antibiotic troches. On the other hand, taste disturbance occurred in a greater percentage of cases with Aureomycin and procaine penicillin G troches than with terramycin.

The average number of reactions per patient and per reactor for the three antibiotic troches studied occur in a certain order (Table III). No significant

TABLE III. COMPARISON OF THE AVERAGE NUMBER OF REACTIONS SEEN WITH AUREOMYCIN, PENICILLIN, AND TERRAMYCIN TROCHES

	AUREOMYCIN		PENICILLIN		TERRAMYCIN	
	AVE.	S.E.*	AVE.	S.E.*	AVE.	S.E.*
Reactions per patient	1.43	0.032	1.01	0.023	1.42	0.016
Reactions per reactor	2.80	0.051	2.66	0.046	2.67	0.013

*S.E. is the standard error of the average, and is calculated as $S.E. = \sigma/\sqrt{N}$, where σ is the standard deviation and N is the number of patients.

difference (1 per cent level) can be found between these averages. Since the distributions of reactions among 1+, 2+, and 3+ are about the same for the three medicated troches studied (Table IV), it follows that any system of weighting the 2+ and 3+ reactions for the purpose of calculating a weighted average would produce essentially the same order (Table IV).

TABLE IV. COMPARISON OF DISTRIBUTION OF SEVERITY OF REACTIONS SEEN WITH AUREOMYCIN, PENICILLIN, AND TERRAMYCIN TROCHES

	AUREOMYCIN			PENICILLIN			TERRAMYCIN		
	1+	2+	3+	1+	2+	3+	1+	2+	3+
Per cent distribution of reactions	70.6	14.7	14.7	71.3	13.9	14.8	65.5	23.2	11.3
Weighted ave. per patient	2.17			1.50			2.08		
Weighted ave. per reactor	4.25			3.94			3.92		

As reported in the literature, Aureomycin, penicillin, and terramycin administered systemically in dosages many times higher than those involved in troche medication have not been noted to cause reactions as frequent or as severe as those which have been reported in our studies and in other studies on oral topical antibiotic therapy. Increased gastrointestinal symptoms were probably due in part to the continued ingestion of substances so nauseating to the taste of some individuals as Aureomycin and penicillin. The more continuous passage through the digestive tract of troche medicaments, following slow dissolution in the oral cavity, compared with systemic therapy, may result in more continuous irritation, thereby causing increased oropharyngeal and gastrointestinal disturbances. Although all reactions were of necessity recorded in this and in the previous study, many should be considered of slight importance. If the malady under treatment is sufficiently severe and therefore warrants antibiotic therapy, minor reactions should be weighted extremely slightly or ignored.

CONCLUSIONS AND SUMMARY

In a controlled study involving 150 patients in the Aureomycin group and 150 patients in the procaine penicillin G group, the reactions to Aureomycin Hydrochloride and procaine penicillin G therapy were evaluated. Of 100 patients receiving Aureomycin medicated troches 51 (51 per cent) evidenced untoward reactions, compared with 7 (14 per cent) of the 50 patients who received placebo troches, a statistically significant difference. Of 100 patients receiving procaine penicillin G troches, 38 (38 per cent) evidenced untoward reactions, compared with 7 (14 per cent) of the 50 patients who received placebo troches, also a statistically significant difference.

The reactions to Aureomycin troche therapy were sufficiently severe to warrant cessation of therapy in 14 per cent of the cases. The reactions were classified as moderate in 10 per cent and as slight in 27 per cent of the patients treated with Aureomycin. Therapy was of necessity discontinued in 11 per cent of procaine penicillin G troche treated cases; and the reactions were classified as moderate in 11 per cent, and as slight in 16 per cent of the patients treated with procaine penicillin G troches.

Comparison of the findings discloses that the types of reactions observed with Aureomycin and procaine penicillin G troches are similar in nature to those previously found with terramycin troches. However, the frequency of occurrence of some of these reactions differs according to the medication used.

It is suggested that antibiotic troche medication be utilized whenever its application is specifically indicated but is not indicated for promiscuous use, or when the administration of medication less likely to produce reactions is possible.

In this investigation, as in the terramycin series, reactions were limited primarily to the gastrointestinal tract except for severe glossitis or stomatitis occurring in 6 cases and pharyngitis occurring in 2 cases in the Aureomycin group as well as severe glossitis or stomatitis noted in 6 cases in the procaine penicillin G groups.

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