

REACTIONS FOLLOWING THE USE OF TERRAMYCIN TROCHES: A CONTROLLED STUDY

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THERE is apparent from the literature an increasing awareness of the local and general side effects observed during topical and systemic antibacterial therapy.¹⁻¹² Kutscher has reviewed the literature in detail concerning the oral reactions to antibiotic and sulfonamide therapy.¹³

Reports on systemic terramycin therapy indicate that its administration is accompanied by reactions of varying types and severity associated chiefly with the oropharyngeal region and the gastrointestinal tract.^{3, 14, 15, 16} However, considering the severity of the diseases under treatment and their response to systemic terramycin, the reported reactions have not usually been of sufficient importance to be considered a detriment to therapy. The topical application of terramycin in troches introduces the factor of prolonged contact of the drug with the oral mucosa. The side actions thus encountered should be weighed against the severity of the oral infection which requires specific treatment with topical terramycin.

This study was undertaken to: (1) study and evaluate the reactions resulting from oral terramycin troche therapy; (2) attempt treatment of the reactions resulting from terramycin troche medication, the therapy to be based upon the possible causes of the reactions¹³; (3) inquire into the possibility of chemotherapeutic prophylaxis against such reactions; and (4) determine the occurrence of systemic sensitization from topical terramycin medication.

METHODS

Two hundred eighteen subjects (98 men and 120 women), aged 10 to 60 years, were studied.

Group 1 was composed of 37 normal volunteer subjects comprising the entire second year class of a dental school. Four troches per day, each containing 15 mg. terramycin hydrochloride, were administered to each subject until ten troches had been allowed to dissolve completely in the mouth. Two weeks following the course of terramycin troche medication each subject in this group was scratch tested for terramycin sensitivity.

Group 2 was composed of 66 patients who were treated for varying oral disorders* with identical 15 mg. terramycin troches, five troches per day for four days. Each patient was observed for untoward reactions.

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*Reports concerning the therapeutic effect of terramycin troches upon oral disease, the effect of terramycin troches on the oral lactobacillus count, and upon the oral flora when viewed by dark field are to be published separately.

Group 3 was composed of 25 patients, similar to those in *Group 2*. In this group, however, each patient ingested 2 Vifort* capsules (multi-vitamin, high potency) and 10 μ g. vitamin B₁₂† before sucking each terramycin troche.

Group 4 was composed of 15 patients similar to those in *Group 2*. Pyribenzamine hydrochloride,‡ 50 mg. three times a day, was administered to each patient during the period of terramycin troche medication.

Group 5, the control group, was composed of 75 patients similar to those in *Groups 2* and *3*. This group was treated exactly as *Group 2* except that placebo troches were administered, 5 placebo troches per day for four days. In the placebo troches, which were identical in appearance with the medicated troches, inert filler replaced the active ingredient terramycin. Twenty-five of these patients ingested two Vifort capsules and 10 μ g. vitamin B₁₂ before dissolving each placebo troche in the mouth.

A careful history concerning their previous experiences with antibacterial agents, their reactions to previous antibiotic therapy, drug sensitivities, and other allergies was obtained from each patient in all five groups. The oral mucosa of each patient was examined carefully so as to be able to note any change from the initial oral picture. After the completion of therapy, each patient was specifically questioned concerning the type and severity of reactions manifested.

Following the appearance of a reaction to terramycin troche medication, treatment of the resulting lesions was attempted.¹³ A 0.01 per cent solution of Bradosol§ was administered (when oral reactions were observed) as a mouth wash 8 times a day to combat possible oral monilial overgrowth. Pyribenzamine was administered 50 mg. three times per day as treatment for possibly allergic phenomena. Vifort capsules and vitamin B₁₂ were each administered four per day to restore depleted tissue stores of vitamins.

RESULTS

The incidence and types of reactions observed during or after terramycin troche and control therapy are detailed in Table I. A summary of the severity of reactions of each group appears in Table II. The effect of using multi-vitamin therapy with vitamin B₁₂, Bradosol, and Pyribenzamine in the prophylaxis of reactions to terramycin troches also appears in Table II.

*Vifort was supplied through the courtesy of Dr. Samuel Gordon of Endo Products Inc., Long Island, N. Y.

Each Vifort capsule contains: vitamin A—5000 USP Units; vitamin D—500 USP units; Ascorbic acid (C)—60 mg.; Thiamine Monocitrate (B₁)—3 mg.; Nicotinamide—20 mg.; Calcium Pantothenate—5 mg.; Pyridoxine hydrochloride—0.3 mg.; and Tocopherol—2 mg.; Riboflavin (water soluble)—2 mg.

†Vitamin B₁₂ was supplied through the courtesy of Mr. B. R. Fullerton of the Sherman Laboratories, Detroit, Mich.

‡Pyribenzamine hydrochloride (brand of Tripelenamine Hydrochloride, USP) and Bradosol for this study were supplied through the courtesy of Dr. C. H. Sullivan of the Ciba Pharmaceutical Co., Summit, N. J.

§Bradosol as used in this study is a .01 per cent solution of a quaternary ammonium salt of definite composition (phenoxy-ethyl-dimethyl-dodecyl-ammonium bromide) which has bactericidal, bacteriostatic, and detergent properties. The following data on the activity of Bradosol against monilia albicans have been supplied by Ciba Pharmaceutical Products, Inc.: Test organisms were inoculated into suitable culture media and held at 37° C. for 24 hours. The highest dilution of Bradosol capable of completely inhibiting growth of monilia albicans was 1:96,000. In the course of the similar administration of Bradosol as a mouthwash to 50 normal individuals no evidence of any type of reaction was observed.

TABLE I. INCIDENCE OF DIFFERENT TYPES OF REACTIONS OBSERVED DURING AND AFTER TERRAMYCIN TROCHIE MEDICATION

GROUP	1			2			3			4			1-4			5		
	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+
<i>Reactions</i>																		
Nausea	8		1	9	3	1	4	3	1	4	2		23	8	4	7		1
Vomiting	1		1							1			1					
Intestinal upset	1			1	2			1					3	3				
Taste disturbance	3	2		1	1			1					4	4		3		
Diarrhea	7	3	2	12	4	3	5	3	1	3	1	1	27	11	7	1		
Flatulence	8	4		10			2	1		2			20	5		1		
Abdominal ache and pain	4		1	1			2	1		2			8	1	2			
Increased freq. stool	2			1						1			4					
Loose stool	1			3	2		3						7	2		2		
Constipation	2						1						3					
Drowsiness	2									2			4			1		
Malaise	2			3			1						6					
Fever	1				2								1					
Headache	1			1	1		2						1			1		
Tiredness	1			1									2					
Aggravation of symptoms				1	1								1					
Dizziness					1								1					
Stomatitis						3			1	1	1		1		4			
Glossitis					1	3		1	1				2	2	4			
Pharyngitis	2		1			1			1				2		3			
Cheilosis	1												2					
Pruritus ani	3	1		1				4					3	5				
Rectal burning	1												1					
Joint pains				3									3					
Total number of reaction	51	10	6	48	18	11	20	15	5	14	4	1	130	47	25	16	0	1
Total reactions in each group	67			77			40			19			202			17		
Number of patients in each group	37			66			25			15			143			75		

1+ Slight—reported, but not inconveniencing.

2+ Moderate—uncomfortable, but not forcing discontinuation of therapy.

3+ Severe—forced discontinuation of therapy.

Reactions to terramycin troches were observed in 76 (53.2 per cent) of the 143 patients treated. These 76 patients reported a total of 200 reactions distributed among 24 symptoms. Reactions necessitating 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 appeared in 26 cases 1 to 4 days after cessation of therapy.

TABLE II. EFFECT OF PROPHYLAXIS UPON REACTIONS FROM TERRAMYCIN TROCHES

GROUP	PROPHY. AGENT	TYPE OF REACTION				TOTAL CASES
		NONE	SLIGHT	MODERATE	SEVERE	
1 and 2	none	47 (45.6%)	24 (23.3%)	15 (14.6%)	17 (16.5%)	103 (100%)
3	Vit. B complex with B ₁₂	11 (44.0%)	6 (24.0%)	5 (20.0%)	3 (12.0%)	25 (100%)
4	Pyribenzamine	9 (60.0%)	2 (13.3%)	3 (20.0%)	1 (6.7%)	15 (100%)
Total		67 (46.8%)	32 (22.4%)	23 (16.1%)	21 (14.7%)	143 (100%)

Of the 75 patients receiving control troches, 8 (10.7 per cent) reported reactions, none oral or pharyngeal. Of these, one complained of a severe reaction while the remainder had only slight complaints.

Scratch tests to terramycin performed two weeks following terramycin troche medication were negative in all of the 37 subjects tested. Reactions had previously been observed during or after the terramycin troche medication in a large percentage of these subjects.

No significant differences in the type of reactions were noted among the various groups receiving terramycin troches (in Table II, chi-squared = 3.08 with 6 degrees of freedom).¹⁷ It would therefore appear that neither vitamin B complex therapy nor Pyribenzamine acted as efficient prophylactic agents against these reactions.

Of the agents (Bradosol, multi-vitamin therapy, and Pyribenzamine) used in treating the oral reactions which occurred, only Bradosol, which seemed to alleviate the reactions in 4 of the 12 cases in which it was administered, was at all effective therapeutically. It is possible that any bland mouth wash might have been as efficacious. Bradosol was administered in this study only following the appearance of oral reactions. It could not be administered as a prophylactic agent owing to its own bactericidal and bacteriostatic properties which might have confused the conclusions drawn from the results of terramycin therapy. Neither multi-vitamin therapy (in 21 cases) nor Pyribenzamine therapy (in 22 cases) seemed beneficial in treating reactions occurring orally or elsewhere in the gastrointestinal tract. Most reactions, especially the oral ones, were found to be persistent and required from 1 to 21 days to regress. Diarrhea was often accompanied by intense pruritus ani.

DISCUSSION

The incidence of gastrointestinal complaints in the placebo control group indicates that some of the reactions observed during terramycin troche administration may be the result of the elaborate taste-making base in which the antibiotic is incorporated.

In the past, impurities in antibiotic preparations have frequently been reported as causing untoward reactions to therapy.¹⁸ When a tendency toward a reaction to terramycin exists, irritative excipients and impurities may be instrumental in producing a reaction.

As reported in the literature, and in our experience, terramycin administered systemically in dosages 22 times as high as that involved in troche medication has not been observed to cause reactions as frequent or as severe as those reported in this study. There was the clinical impression that the increased gastrointestinal symptoms were probably due to the continued ingestion of a substance so nauseating to the taste of some individuals as terramycin. Also, the more continuous passage through the digestive tract of the troche medication, following slow dissolution in the oral cavity, may result in more continuous irritation thereby causing increased oropharyngeal and gastrointestinal disturbances.

The relatively extreme acidity (pH 2) of terramycin preparations might also be a factor in causing frequent gastrointestinal upset. Owing to their low pH, terramycin troches might be considered a potential cause of tooth decalcification following prolonged use.

Although all reactions were of necessity recorded, many were of slight importance. Provided the malady under treatment warrants antibiotic therapy, minor reactions might be weighted extremely lightly or ignored when considering the treatment of severe oral disease.

CONCLUSIONS AND SUMMARY

In a controlled study involving 218 patients, the reactions to terramycin troche therapy were evaluated. Of the 143 patients receiving terramycin troches 76 (53.2 per cent) evidenced untoward reactions, compared with 8 (10.7 per cent) of the 75 patients who received placebo troches, a statistically significant difference.

The reactions to terramycin troches were sufficiently severe to warrant cessation of therapy in 14.7 per cent of the cases. The reactions were classified as moderate in 16.1 per cent and as slight in 22.4 per cent of the patients treated. Terramycin troche medication may be utilized whenever the application of its individual antibacterial and antiviral spectrum is specifically indicated, but should not be used promiscuously or when the administration of other medication less likely to produce reactions is possible. In this series, reactions were limited principally to the gastrointestinal tract except for severe glossitis or stomatitis which occurred in 8 cases and pharyngitis which occurred in 5 cases. Multi-vitamin therapy and Pyribenzamine were not effective when used as prophylactic or therapeutic agents against the oropharyngeal and gastrointestinal reactions. In 37 subjects, 23 of whom had reported reactions during or after terramycin troche medication, no instance of sensitivity to terramycin by scratch test was observed two weeks following the administration of the troches.

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