

REACTIONS FOLLOWING THE USE OF BACITRACIN, TYROTHRIN, GRAMICIDIN, AND POLYMXIN B TROCHES: A CONTROLLED STUDY

AUSTIN H. KUTSCHER, D.D.S., JACK BUDOWSKY, D.D.S., AND
NEAL W. CHILTON, D.D.S., M.P.H., NEW YORK, N. Y.

THE authors have previously reported in this JOURNAL^{1,2} on the incidence and types of reactions following the use of terramycin, aureomycin and procaine penicillin G troches. These studies stemmed from the widespread evidence of local and systemic side effects observed during antibacterial therapy.³⁻¹⁷ The incidence of reactions to bacitracin, gramicidin, tyrothricin, and polymixin B troche medication has not been reported. The present study was intended to evaluate the reactions which might result from the administration of these four antibiotics in troche form, and to compare the incidence and types of such reactions with those previously observed by us in the terramycin, aureomycin, and procaine penicillin G troche studies.

METHODS

Group I was composed of 20 normal subjects, aged 23 to 27, all men, comprising a volunteer group of dental students. Four troches per day, each containing 1,000 units (0.1 mg.) of bacitracin, were administered to each subject until 10 troches had been allowed to dissolve completely in the mouth.

Group II was composed of 80 patients, aged 16 to 58, 27 male and 53 female, who were treated for various types of minor oral disorders with bacitracin troches (1,000 units per troche), 5 troches per day for four days.

Group III, a control group for the bacitracin study, was composed of 50 patients, aged 18 to 61, 16 male and 34 female, similar to those in Group II. This group was treated exactly as Group II except that placebo troches were administered 5 per day for four days. Placebo troches were identical in content and appearance with the medicated troches except for the inert filler which replaced the active ingredient, bacitracin.

Group IV was composed of 17 normal subjects, aged 23 to 28, all male, comprising a volunteer group of dental students. Four troches per day each containing 1 mg. of tyrothricin were administered to each subject until 10 troches had been allowed to dissolve completely in the mouth.

From the Divisions of Research (Hannah and Harry Posner Research Laboratory) and Diagnosis of the School of Dental and Oral Surgery and the School of Public Health of the Faculty of Medicine, Columbia University.

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Gramicidin troches (Gramolets) were supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. George Babcock.

Polymixin B-bacitracin troches were supplied by Chas. Pfizer & Co., Inc., Brooklyn, N. Y., through the courtesy of Dr. W. Alan Wright and Mr. George Penny.

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TABLE I. TYPE, FREQUENCY, AND SEVERITY OF REACTIONS TO BACTRACIN, TYROTHRICIN, POLYMXIN B-BACTRACIN, AND GRAMICIDIN TROCHES

REACTIONS	BACTRACIN						TYROTHRICIN						POLYMXIN B-BACTRACIN						GRAMICIDIN												
	GROUP I			GROUP II			GROUP III (PLACEBO)			GROUP IV			GROUP V			GROUP VI (PLACEBO)			GROUP VII			GROUP VIII (PLACEBO)			GROUP IX			GROUP X			
	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	
Abdominal ache and pain																															
Aggravation of symptoms																															
Aphthae																															
Cheilosis																															
Constipation																															
Diarrhea																															
Dizziness																															
Drowsiness																															
Fever																															
Flatulence																															
Glossitis																															
Headache																															
Increased freq. of stool																															
Intestinal upset																															
Joint pains																															
Loose stool																															
Malaise																															
Nausea																															
Pharyngitis																															
Pruritus ani																															
Rectal burning																															
Stomatitis																															
Taste disturbance																															
Tiredness																															
Vomiting																															
Total no. reactions	7	0	0	11	0	0	8	0	0	6	0	0	12	0	0	9	0	0	4	0	0	6	0	1	8	0	0	6	0	0	
Total no. reactions in group	7	11					8	8	6			12	9	9		50	50	20	4	7	80	50	8	50	8	6	50	6			
Total no. patients in group	20			80			50		17			83																			
Total no. patients showing react.	4			7			5		4			8				6		3		6					5			4			

1+ = reported, but not inconvenienting.

2+ = moderate, uncomfortable but not forcing discontinuation of therapy.

3+ = severe, forced discontinuation of therapy.

TABLE II. COMPARISON OF REACTIONS TO BACITRACIN, TYROTHRICIN, POLYMXIN B.

REACTIONS	BACITRACIN						TYROTHRICIN						POLYMXIN B					
	GROUPS I & II			GROUP III (PLACEBO)			GROUPS IV & V			GROUP VI (PLACEBO)			GROUPS VII & VIII			GROUP IX (PLACEBO)		
	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+
Abdominal ache and pain	1									1			1					
Aggravation symptoms																		
Aphthae							1											
Cheilosis																		
Constipation																		
Diarrhea	1			1			1			1						1		
Dizziness																		
Drowsiness	2									1								
Fever																		
Flatulence	1						1						1					
Glossitis																		
Headache							1											
Increased freq. of stool	1						1											
Intestinal upset	1			1			1			1						1		
Joint pains																		
Loose stool	1						2						1					
Malaise																		
Nausea	1			2			4			2			3		1	2		
Pharyngitis																		
Pruritus ani																		
Rectal burning																		
Stomatitis																		
Taste disturbance	8			3			6			3			4			3		
Tiredness	1			1												1		
Vomiting																		
Total no. reactions	18	0	0	8	0	0	18	0	0	9	0	0	10	0	1	8	0	0
Total no. reactions in groups	18			8						18	9		11			8		
Total no. patients in groups	100			50						100	50		100			50		
Total no. patients showing reaction	11			5						12	6		9			5		
Percentage of patients showing reactions	11%			10%						12%	12%		9%			10%		

Group V was composed of 83 patients, aged 21 to 55, 33 male and 50 female, who were treated for various types of minor oral disorders with tyrothricin troches (1 mg. tyrothricin per troche), 5 troches per day for four days.

Group VI, a control group for the tyrothricin study, was composed of 50 patients, aged 19 to 49, 18 male and 32 female, similar to those in Group V. This group was treated exactly as Group V except that placebo troches were administered 5 per day for four days. Placebo troches were identical in content and appearance with the medicated troches except for the inert filler which replaced the active ingredient tyrothricin.

Group VII was composed of 20 normal subjects, aged 20 to 26, 13 male and 7 female, comprising a volunteer group of students. Five troches per day each containing polymixin B and bacitracin (1,000 units of polymixin B and 50 units of bacitracin per troche) were administered to each subject for four days.

[illegible]

Group IX, a control group for the polymixin B-bacitracin study, was composed of 50 patients, aged 16 to 51, 32 male and 28 female, similar to those in Group VIII. This group was treated exactly as Group VIII except that placebo troches were administered 5 per day for four days. The placebo troches used in this study were identical in content and appearance to the medicated troches except for the absence of the active ingredient, polymixin B and bacitracin.

Group X was composed of 50 patients, aged 18 to 56, 18 male and 32 female, who were treated for various types of minor oral disorders with gramicidin troches (0.25 mg. per troche), 5 troches per day for three days. There was no placebo control group for gramicidin since placebos for the bacitracin troches were substantially the same as the gramicidin troches.

A careful history concerning previous experience with antibacterial agents, reactions to previous antibiotic therapy, drug sensitivity, and other allergies was obtained from each patient. During and after the completion of therapy, each patient was examined orally and specifically questioned as to whether any reaction of any type had been noted. If a reaction was observed or reported, the patient was queried in detail concerning the character and severity of the reaction(s) which had been manifested.

RESULTS

The types, frequency, and severity of reactions observed during and after bacitracin, tyrothricin, gramicidin, polymixin B-bacitracin, and placebo control troche therapy are detailed and summarized in Table I. Reactions were graded as follows:

- 1+ = reported, but not inconveniencing
- 2+ = moderate, uncomfortable but not forcing discontinuation of therapy
- 3+ = severe, forced discontinuation of therapy

In this study it will be noted that with one exception (severe nausea with polymixin B-bacitracin) all reactions were of grade 1+ severity. A summary of the reactions noted and those reported in the two previous articles in our series appears in Table II. It will be noted that the range of percentage of patients showing reactions with the four antibiotic preparations and the three placebos studied here is very small (8 to 12). The percentages of patients showing reactions in the present study are quite similar to those observed for the placebo troches used in our previous studies^{1, 2} (10.7 to 14) and are very much less than the percentages determined for terramycin (53 per cent), aureomycin (51 per cent), and procaine penicillin G troches (38 per cent). When the over-all percentage of patients showing reactions following the use of bacitracin, tyrothricin, polymixin B, and gramicidin troches is compared with that following the use of aureomycin, procaine penicillin, and terramycin troches pooled together, a statistically significant difference is obtained.

TABLE III. SUMMARY OF HISTORIES OF PREVIOUS MEDICATION OF PATIENTS INGESTING BACITRACIN, TYROTHRIN, POLYMYXIN B-BACITRACIN, GRAMICIDIN, TERRAMYCIN, AUREOMYCIN, AND PROCAINE PENICILLIN G TROCHES

DRUG	NO. OF CASES STUDIED	SPECIFIC ANTIBIOTIC AD- MINISTERED TO THE GROUP HAD PREVIOUSLY BEEN AD- MINISTERED TO PATIENT (RECOLLECTED BY PATIENT)			PREVIOUS REACTION NOTED OR RECOLLECTED BY PA- TIENT TO THE DRUG		
		SYSTEMIC	TOPICAL	TOTAL #	SYSTEMIC	TOPICAL	TOTAL #
Terramycin	143	5	0	5	0	0	0
Aureomycin	100	18	12	28	2	4	6
Procaine penicillin	100	63	20	73	2	2	4
Bacitracin	100	0	2	2	0	0	0
Tyrothricin	100	0	8	8	0	0	0
Polymixin B	100	0	0	0	0	0	0
Gramicidin	50	0	1	1	0	0	0

Tabulations of the histories of the four groups compared in this study and also of the three groups previously reported (terramycin, aureomycin, procaine

TABLE IV. COMPARISON OF THE AVERAGE NUMBER OF REACTIONS SEEN WITH BACTRACIN, TYROTHRICIN, POLYMYXIN B-BACTRACIN, GRAMICIDIN, AUREOMYIN, PROCAINE PENICILLIN G AND TERRAMYCIN TROCHES

	BACTRACIN		TYROTHRICIN		POLYMYXIN B-BACTRACIN		GRAMICIDIN		AUREOMYCIN		PROCAINE PENICILLIN G		TERRAMYCIN	
	AVE.	S.E.*	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.
Reactions per patient	0.180	0.084	0.180	0.077	0.11	0.048	0.12	0.052	1.43	0.032	1.01	0.023	1.42	0.016
Reactions per reactor	1.64	0.606	1.50	0.493	1.22	0.539	1.50	0.581	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.

penicillin G) appear in Table III. Since the patients had not been studied at the time of previous treatment specifically for toxic reactions, and since the administration of the drug had in most cases been many months in the past, the reported incidence of previous reactions is subject to question, and in any event probably would be understandably smaller than those reported herein. Also, the accuracy of patients' recollection of previous therapy and reactions is questionable.

A comparison of the average number of reactions per patient and per reactor for all the four antibiotics studied at this time and for the three antibiotics studied previously appears in Table IV. Again it will be noted that terramycin, aureomycin, and penicillin G troches tend to be similar, while bacitracin, tyrothricin, polymixin B, and gramicidin tend to group together with respect to these averages. Roughly, the average number of reactions per patient are about ten times greater per patient for aureomycin, penicillin, and terramycin than for bacitracin, tyrothricin, polymixin B, and gramicidin; and about twice as great in terms of the average number of reactions per reactor.

In the present investigation, in contrast to the terramycin, aureomycin, and procaine penicillin G studies, the reactions, although limited primarily to the gastrointestinal tract, did *not* include the oral cavity, pharyngeal passage-way, rectum, or anus. Glossitis, stomatitis, or pharyngitis did not occur in any case in the bacitracin, tyrothricin, gramicidin, or polymixin B-bacitracin groups. Reactions noted in the remaining portions of the gastrointestinal tract were considerably milder in nature for the troches studied at this time than those reported previously in the terramycin, aureomycin, and procaine penicillin G studies, and were significantly less frequent. No occurrence of delayed gastrointestinal reactions was reported. Diarrhea was rare and was not accompanied in any instance by pruritus ani. Nausea, diarrhea, taste disturbance, flatulence, loose stool, and pruritus ani were significantly decreased in comparison with the previously reported groups. Only one case of mild aphthous ulcers (after tyrothricin troches) and no case of cheilosis was noted following the administration of troches in the presently reported study.

The incidence of mild gastrointestinal complaints in the placebo groups in this study again indicates that some of the reactions observed during these antibiotic troche tests may be the result of the taste masking bases in which antibiotics are incorporated. Impurities in antibiotic preparations have also frequently been reported as causing untoward reactions to therapy. Irritative excipients, binders, and impurities may therefore be instrumental in either producing or causing exacerbation of the reactions.

DISCUSSION

The antibiotics described in this study either have not been administered systemically (tyrothricin and gramicidin), or else have been administered systemically with the greatest care (bacitracin and polymixin B) owing to the severe characteristics of the reactions sometimes appearing following full systemic therapeutic dosage. Consequently, in preparing the oral troche dosage forms, sufficiently small amounts of these antibiotics may have been incorporated in the troche so as to obviate the possibility of systemic reactions resulting from

topical oral troche therapy. In so doing, however, it is possible that insufficient amounts of the antibiotic were incorporated in the troche in order to produce: (1) a therapeutically beneficial effect and (2) oral, gastrointestinal, and other reactions. It cannot be concluded from this study what reactions might be observed from bacitracin, tyrothricin, gramicidin, or polymixin B-bacitracin troche therapy if higher concentrations of the active antibiotics were administered, in which case side reactions and also therapeutic efficiency might both, perhaps, be increased.

Those gastrointestinal symptoms which were observed in the groups reported on in this article were felt to be due mainly to the continued ingestion of substances as nauseating to the taste of some individuals as bacitracin, tyrothricin, gramicidin, and polymixin B and also to the relatively continuous passage through the digestive tract of troche medicaments following slow dissolution in the oral cavity. As was noted in the previous articles all reactions were of necessity recorded; many, and especially those in the present study, should be considered as of extremely slight importance. If therapy of disease warrants antibiotic troche therapy with these specific agents in dosages as above, the reactions reported in this article to bacitracin, tyrothricin, gramicidin, or polymixin B could be weighed extremely lightly or ignored.

CONCLUSIONS AND SUMMARY

In a controlled study in which bacitracin troches were administered to 100 patients, tyrothricin troches were administered to 100 patients, gramicidin troches were administered to 50 patients, and polymixin B-bacitracin troches were administered to 100 patients, the resulting side reactions were evaluated. Of 100 patients receiving bacitracin medicated troches, 11 (11 per cent) evidenced untoward reactions compared with 5 (10 per cent) of the 50 patients who received placebo troches; of 100 patients receiving tyrothricin medicated troches, 12 (12 per cent) evidenced untoward reactions compared with 6 (12 per cent) of the 50 patients who received placebo troches; of 100 patients receiving polymixin B-bacitracin medicated troches, 9 (9 per cent) evidenced untoward reactions compared with 5 (10 per cent) of the 50 patients who received placebo troches; of 50 patients receiving gramicidin medicated troches, 4 (8 per cent) evidenced untoward reactions.

The reactions which occurred were of the mildest degree (with one exception) and did not require cessation of medication. They did not particularly affect the oral, pharyngeal, rectal, or anal areas. When compared with the results of previous studies with terramycin, aureomycin, and procaine penicillin G troches, the percentage of patients showing reactions, the average number of reactions per patient, and the average number of reactions per reactor were appreciably lower with bacitracin, tyrothricin, polymixin B, and gramicidin troches.

However, despite the minimal number and slight severity of reactions accompanying bacitracin, tyrothricin, gramicidin, and polymixin B-bacitracin troche medication, it is suggested that antibiotic medication with these agents be utilized only when their administration is specifically indicated and not for promiscuous use.

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630 WEST 168TH ST.