PAPERS AND ORIGINALS

Levamisole in aphthous stomatitis: evaluation of three regimens

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British Medical Journal, 1977, 1, 671-674

Summary

One hundred and twenty-four patients who had had recurrent aphthous stomatitis (RAS) for two to 53 years took part in three studies to assess the effectiveness of levamisole and determine an adequate regimen. In study 1 and the first half of study 2, both of which were double-blind, levamisole 150 mg/day (or placebo) was given on three consecutive days in every fortnight. In the second two months of study 2 and in the open trial (study 3) three-day courses were given only when an episode of RAS occurred.

The drug was well tolerated. The signs and symptoms of RAS improved gradually and significantly in those treated with levamisole but not in those on placebo, and intergroup differences were also significantly in favour of the active drug. Improvement occurred earlier in study 3 than in the other two studies. Hence levamisole may prevent new episodes of RAS.

Introduction

Some preliminary data suggested that levamisole might be useful in aphthous stomatitis,^{1,2} but there have been no double-blind trials, and doubt remains about the optimal dose schedule.

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The restorative effects of levamisole on deficient host defence mechanisms have often been described.³⁻⁵ Recurrent aphthous ulcers are common in clinical practice, and a survey in armed Forces recruits and medical and paramedical students recently showed that more than a third of the men and about half the women had experienced two or more episodes of such ulcers.⁶ The pathogenesis of the disease is not completely understood, but recurrences are common in conditions such as tiredness or stress that tend to undermine host defence. Because levamisole produces few side effects and because of the high incidence of recurrent aphthous stomatitis (RAS) and the lack of a causal treatment, we thought that levamisole ought to be properly evaluated in this condition.

Our aim was to make a double-blind evaluation of levamisole in RAS and to find an appropriate dose regimen.

Patients and methods

One hundred and twenty-four patients with RAS, who had been suffering for years from their disease and who had experienced at least one episode per month, were selected for this series of trials (table I).

Three studies, each lasting four months, were performed. The first two trials were performed under strictly double-blind conditions, the patients being randomly assigned to treatment with tablets containing either 50 mg of levamisole or a placebo. These tablets looked identical and were supplied in individually coded bottles. In the third, uncontrolled study 50-mg tablets of levamisole were also used.

Study 1—Seventy one patients with a median age of 41 (range 14-68) years and weight of 69 (39-92) kg were included. Fifty-nine suffered from minor aphthae, while the rest had major ulcers (> 1 cm in diameter). All had suffered from RAS for two to 53 years (median 16 years). Each patient received three tablets a day (150 mg levamisole or placebo) on three consecutive days every fortnight for four months.

Study 2—Twenty patients with a median age of 41 (range 18-64) years and weight of 69 (55-90) kg were included. All had suffered from minor mouth ulcers for two to 34 years (median 21 years). These patients followed the same regimen as those in study 1 for two months. Subsequently the three day courses were given only with each new episode of RAS and no more often than once a fortnight. Treatment was started within a few hours of the outbreak.

Study 3—Thirty-three patients were studied. Their median age was 40 (28-61) years and weight 68 (59-80) kg. Three had major

aphthae. The rest had minor ulcers. All had had RAS for eight to 40 years (median 17 years). Every patient received one three day course of levamisole, but afterwards the regimen was the same as that in study 2—that is, treatment only when a new episode occurred.

Assessments—At the start of the study a careful history was taken and the patient underwent a routine physical examination. Each patient was given a form on which he or she had to record the days of treatment, the days of RAS episodes, and the number, site, and relative diameter of the oral ulcers (compared with the pretreatment lesions: larger, similar, or smaller) and the degree of painfulness (very painful, moderately painful, or no pain).

At the end of each month the patients returned for examination. The possible use of concomitant medication was considered and any side effects were noted. At the end of each study the investigator assessed whether treatment had had a good, moderate, or no effect.

Results

The results are given in table III and figs 1 and 2. In studies 1 and 2 the levamisole-treated patients were comparable with their controls ($P > 0.05$, Fisher test and median test, two-tailed probability) in their general characteristics and the features of the latest RAS episode (tables I and II). Levamisole was well tolerated by most patients. No one had to discontinue treatment because of side effects.

Study 1—The symptoms and signs of RAS gradually and significantly improved in the levamisole-treated patients while no similar changes were observed in the controls (tables III and IV). Levamisole was significantly better than placebo in all indices studied (table IV). Treatment had no effect in 37 patients (7 on levamisole, 30 on placebo), a moderate effect in 10 patients (6 on levamisole, 4 on placebo), and good effect in 15 patients (all on levamisole). No rating was available for nine patients (4 on levamisole and 5 on placebo). In this respect,

TABLE II—Characteristics of latest episode

	Study 1 (n = 71)		Study 2 (n = 20)		Study 3 (n = 33)
	Levamisole (n = 32)	Placebo (n = 39)	Levamisole (n = 10)	Placebo (n = 10)	
Location of lesions:					
Inner lip	5	8	3	5	3
Inner cheek	6	9	2	2	6
Gingiva	10	6	5	3	9
Tongue	1	2	0	0	1
Floor of mouth	5	6	0	0	6
Palate	4	8	0	0	4
No data	1	0	0	0	4
Contour of lesions:					
Regular	21	19	8	4	4
Irregular	9	18	1	6	29
No data	2	2	1	0	0
Depth of lesions:					
Superficial	28	29	10	9	30
Deep	3	9	0	1	3
No data	1	1	0	0	0
Local inflammation:					
Absent	28	23	6	8	22
Slight	1	14	3	2	11
Severe	1	1	1	0	0
No data	2	1	0	0	0
Local oedema:					
Absent	25	27	9	9	27
Slight	4	9	1	1	2
Severe	1	2	0	0	0
No data	2	1	0	0	4
Regional adenopathy	0	2	1	1	0
Eye lesions	1	3	0	0	0

TABLE I—Patient data

	Study 1 (n = 71)		Study 2 (n = 20)		Study 3 (n = 33)
	Levamisole (n = 32)	Placebo (n = 39)	Levamisole (n = 10)	Placebo (n = 10)	
Sex:					
Men	25	29	6	7	20
Women	7	10	4	3	13
Diagnosis:					
Minor aphthae	29	30	10	10	30
Major aphthae	3	9	0	0	3
Incidence of RAS episodes:					
Continuous	2	8	0	0	3
Every month or more often	29	31	10	9	30
Not registered	1	0	0	1	0
Diameter of aphthous lesions:					
Pin-head size	7	14	6	6	12
1-5 mm	19	14	3	3	15
6-10 mm	2	2	1	1	0
>10 mm	3	9	0	0	2
No data	1	0	0	0	4
Degree of pain:					
Very painful	6	13	7	2	11
Moderately painful	25	24	3	8	18
Not painful	0	2	0	0	0
No data	1	0	0	0	4
Family incidence:					
Absent	17	14	0	0	26
Present	8	13	3	2	7
No data	7	12	7	8	0
Smoking habits:					
Does not smoke	14	25	7	8	21
Occasionally smokes	4	6	2	0	2
Smokes every day	13	8	0	2	6
No data	1	0	1	0	4
Concomitant diseases:					
None	29	30	9	10	25
Autoimmune diseases	1	2	0	0	5
Allergic disorders	2	7	1	0	3
Median values (and range)					
Age (years)	42 (22-68)	41 (14-67)	39.5 (18-64)	42 (30-60)	40 (28-61)
Weight (kg)	69 (50-85)	69 (39-92)	69 (55-90)	69 (55-89)	68 (59-80)
Duration of illness (years)	16 (2-53)	16 (2-32)	18 (7-34)	24 (11-31)	17 (8-40)
Duration of RAS with its present incidence (years)	5 (1-53)	5 (1-15)	5.5 (2-20)	5 (1-15)	4.5 (2-20)
No of lesions per episode	4 (3-8)	4 (1-8)	4 (2-7)	4 (3-4)	5 (2-10)
Duration of the episodes (days)	4 (2-continuous)	4 (2-continuous)	4 (2-14)	3 (2-10)	4 (2-30)

FIG 1—Mean ($\pm$ SE) duration of episodes of RAS in each group in each study.

too, levamisole was therefore better than placebo ($P < 0.05$, Fisher test, two-tailed probability).

Study 2—The findings in this study were similar to those in study 1. Significant improvement was associated with levamisole treatment but not with placebo, and all indices studied, apart from the monthly incidence of RAS outbreaks, showed intergroup differences that were significantly in favour of the active treatment (tables III and IV). The overall results could be assessed in only 13 patients (6 on placebo and 7 on levamisole): none of the controls showed any improvement, while all those on levamisole had improved at the end of the study. This difference was significant ($P < 0.05$, Fisher test, two-tailed).

FIG 2—Mean ($\pm$ SE) numbers of lesions per episode in each group in each study.

TABLE IV—Statistical evaluation of results

	No of episodes/month†	Duration of episodes†	No of lesions/episode‡	Diameter of lesions‡	Degree of pain of lesions‡
Study 1					
Levamisole*					
Month 1		0.002	NS	NS	NS
Month 2		NS	0.007	0.024	NS
Month 3		<0.001	<0.001	<0.001	NS
Month 4		<0.005	<0.001	<0.001	<0.001
Placebo*					
Month 1		NS	NS	NS	NS
Month 2		NS	NS	NS	NS
Month 3		NS	NS	NS	NS
Month 4		NS	NS	NS	0.023
Levamisole v placebo					
Month 1	NS	NS	NS	NS	NS
Month 2	NS	NS	0.02	<0.001	NS
Month 3	NS	0.024	<0.001	<0.001	NS
Month 4	0.029	0.003	<0.001	<0.001	0.03
Study 2					
Levamisole*					
Month 1		NS	NS	NS	NS
Month 2		NS	NS	0.004	NS
Month 3		NS	NS	0.002	0.016
Month 4		0.024	0.012	0.002	0.032
Placebo*					
Month 1		NS	NS	NS	NS
Month 2		NS	NS	NS	NS
Month 3		NS	NS	NS	NS
Month 4		NS	NS	NS	NS
Levamisole v placebo					
Month 1	NS	NS	NS	NS	NS
Month 2	NS	NS	NS	<0.001	NS
Month 3	NS	0.05	0.05	<0.001	NS
Month 4	NS	0.016	0.014	<0.001	<0.001
Study 3					
Levamisole v before treatment*					
Month 1		NS	NS	NS	NS
Month 2		<0.05	<0.001	NS	<0.001
Month 3		<0.001	<0.001	<0.001	<0.001
Month 4		<0.001	<0.001	<0.001	<0.001

*All comparisons with pretreatment values were performed by Wilcoxon matched-pairs signed-ranks test.

†Levamisole v placebo comparisons were performed by Mann-Whitney U test.

‡Levamisole v placebo comparisons were performed by Kolmogorov-Smirnov two-sample test.

Each test gave a two-tailed probability. NS = Not significant.

All intergroup differences were in favour of levamisole.

TABLE III—Results in each study. Numbers in italics indicate where the median values were

	Study 1										Study 2										Study 3									
	Before		Month 1		Month 2		Month 3		Month 4		Before		Month 1		Month 2		Month 3		Month 4		Before		Month 1		Month 2		Month 3		Month 4	
	L	P	L	P	L	P	L	P	L	P	L	P	L	P	L	P	L	P	L	P	Levamisole									
Episodes/month																														
0			0	0	0	1	1	1	5	2			0	0	0	0	0	0	1	0										
1			22	28	28	27	27	28	24	27			9	10	10	10	10	9	9	10										
2			9	4	3	5	4	4	2	5			0	0	0	0	0	1	0	0										
3			0	2	1	1	0	2	1	1			0	0	0	0	0	0	0	0										
>3			1	5	0	5	0	4	0	4			1	0	0	0	0	0	0	0										
Duration of episodes (days)																														
0	0	0	0	0	0	0	1	1	5	2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	4	1	2	1	4	5	3	6	3	1	3	1	3	1	3	1	3	2	3	1	8	8	3	16	23				
3	13	15	14	11	14	8	15	12	14	12	3	4	2	2	4	1	4	1	5	1	8	8	11	3	11	5				
4	10	7	10	15	12	16	9	13	7	12	3	0	2	2	1	4	5	3	2	2	13	13	13	3	1	1				
5	3	3	4	2	3	1	1	2	0	0	0	2	2	2	1	1	0	1	0	3	9	9	4	0	1	1				
>5	5	10	3	8	2	8	1	8	0	8	3	1	3	1	3	1	0	2	0	1	2	3	2	2	1	1				
No data	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No of lesions/episode																														
No data	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
1	0	3	0	4	0	4	1	4	3	3	1	0	1	0	2	0	5	1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	4	2	5	3	4	10	7	7	3	4	1	2	2	3	3	1	7	1	4	1	2	1	8	14					
3	6	8	6	7	10	6	8	4	7	6	3	6	4	7	4	4	1	5	0	1	4	3	11	15	13					
4	13	15	12	12	11	13	5	14	8	12	1	0	1	0	1	2	1	2	1	5	10	10	7	6	1	1				
5	8	4	8	2	5	2	6	2	2	3	2	0	3	1	1	1	0	1	1	2	3	4	4	1	1	1				
>5	5	5	4	8	3	8	1	7	0	6	0	0	0	0	0	0	0	0	0	1	15	0	8	1	1	1				
No episode	0	0	0	0	0	1	1	1	5	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Degree of pain																														
Cured	0	0	0	0	0	1	1	1	5	2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Not painful	0	2	1	1	0	2	5	3	9	3	0	0	6	7	1	0	5	1	5	0	0	0	12	21	37					
Moderately painful	26	26	25	25	26	21	19	22	12	21	4	4	3	6	7	5	6	2	5	29	3	11	12	2	0	0	0	0	0	0
Very painful	5	11	6	9	6	8	5	8	4	6	6	2	0	0	0	3	0	2	0	5	1	0	0	0	0	0	0	0	0	0
No data	1	0	0	4	0	7	2	5	2	7	0	0	0	0	0	0	0	1	2	0	1	0	0	0	0	0	0	0	0	0
Changes in diameter of lesions																														
Cured			0	0	0	1	1	1	5	2			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Smaller			0	2	9	2	19	4	16	3			0	0	9	0	10	0	10	0	0	0	6	29	32					
No change			28	35	21	34	11	32	11	34			10	10	1	10	0	10	0	10	32	21	4	1	1					
Larger			0	0	1	0	0	0	0	0			0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0
No data			0	2	1	2	1	2	0	0			0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0

L = Levamisole. P = Placebo.

Study 3—At the end of this four-month uncontrolled study the length of the RAS episodes had been halved while the median number of ulcers per outbreak had dropped from five to two (table III). The diameter of the lesions had decreased in 32 of the 33 patients, and only two patients still had (moderately) painful ulcers during the last month of the study. All indices studied showed a significant improvement from the second month onwards (table IV).

Discussion and conclusions

Our studies have confirmed earlier reports which suggested that levamisole had a beneficial effect in preventing new episodes of RAS. This prophylactic effect is not the result of a placebo influence. Improvement seemed to occur earlier in study 3, which strongly suggests that the flexible regimen used in the last trial is better than the more rigid one used in studies 1 and 2. Other investigators have since confirmed our study 3 findings in a placebo-controlled experiment.⁸

We thank Dr J Bresseleers, Dr R Loncke, Dr G Mattelin, Dr R

Mertens, Dr J Morias, Dr J Sleenckx, and Dr K Van de Put for their highly appreciated co-operation with these trials. Thanks are also due to Janssen Pharmaceutica, B-2340 Beerse, for supplying the samples for this series of studies.

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(Accepted 31 December 1976)

Cholestyramine in treatment of postvagotomy diarrhoea—double-blind controlled trial

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British Medical Journal, 1977, **1**, 674-676

Summary

A double-blind controlled trial was performed to assess the effectiveness of cholestyramine in treating severe continuous postvagotomy diarrhoea. Each patient and a clinician assessed the results, and those treated with cholestyramine showed a considerable improvement over those given placebo. There were no significant side effects or changes in laboratory values in the cholestyramine group. Although the numbers were too small for statistical analysis, these results suggest that cholestyramine may be of value in the management of some patients with severe continuous postvagotomy diarrhoea who are unresponsive to other forms of treatment.

Introduction

Truncal vagotomy and drainage is at present the most common operation for duodenal ulcer. Continuous diarrhoea, which produces considerable upset in working and social life,^{1,2} is a major side effect in about 1% of patients. Treatment of the diarrhoea with diphenoxylate or mebeverine is usually disappointing.^{3,4}

We have previously shown that patients with severe, continuous postvagotomy diarrhoea excrete excessive amounts of

bile acids in the faeces, the principal bile acid present being chenodexychoic acid.⁵ The cathartic action of these bile acids on the colon may be a major factor in causing the diarrhoea. Continuous postvagotomy diarrhoea may therefore be similar to the "cholerheic" diarrhoea that follows ileal resection or severe Crohn's disease of the terminal ileum.⁶ Cholerheic diarrhoea may respond satisfactorily to treatment with cholestyramine.⁷

This paper reports the results of a double-blind controlled trial of cholestyramine in the management of patients with severe continuous postvagotomy diarrhoea.

Patients and methods

Sixteen patients, nine women and seven men, who had had continuous postvagotomy diarrhoea for at least two years were studied. In all patients the diarrhoea had started immediately after the operation. All had been unresponsive to dietary and other non-specific treatment. Each patient passed at least three watery, unformed, urgent stools a day.

Eight of the patients were given cholestyramine, 4 g three times a day, and eight were given a placebo three times a day. The placebo consisted of 3.8 g of sucrose and 1.2 g of inert excipient. Both the active preparation and the placebo were supplied in packets containing propylene glycol alginate and sucrose flavouring. The patients were allowed an unrestricted diet but stopped all non-essential treatment during the trial. No vitamin supplements were given and the patients were allowed to take the medication mixed with milk, fruit juice, or any liquid of their own choosing.

The drugs were given by one doctor, and another made an independent clinical assessment at the start of the treatment, after four weeks, and after eight weeks. The assessing clinician was unaware of the treatment given to each patient. The patients were asked to record on a specially designed card the number of stools passed a day, the time of defaecation, the consistency of the stool, and the degree of urgency. They also reported any feeling of distention or abdominal cramp. Blood was taken before the trial and at each visit for estimation of haemoglobin, white cell count, platelets, and concentrations of serum

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