RECURRENT MIKULICZ'S APHTHAE TREATED WITH TOPICAL HYDROCORTISONE HEMISUCCINATE SODIUM

DOUBLE-BLIND CONTROLLED CLINICAL TRIAL

BY

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The favourable report of the use of topical hydrocortisone hemisuccinate in recurrent aphthae by Truelove and Morris-Owen (1958) was thought to be encouraging enough to merit a controlled trial of this form of treatment.

Method and Material

A double-blind controlled clinical trial has therefore been undertaken to assess the relative value of tablets containing 2.5 mg. of hydrocortisone hemisuccinate with a lactose base, and an inert preparation of the lactose base alone, to patients suffering from these ulcers.

Patients were given four tablets a day to take when the ulcers were present and two tablets a day when they were not, and were asked to allow the tablets to dissolve in the region of the ulceration. This meant that most patients were, in fact, taking four tablets a day, apart from four patients who had complete remissions and who then took only two a day.

The trial involved 17 patients (8 male, 9 female) all with a long history of the same type of severe recurrent oral ulceration, often known as Mikulicz's aphthae (Prinz and Greenbaum, 1939). This type of ulceration is common, with the ulcer beginning clinically as a thickening of the non-keratinized mucosa, which within 24 hours breaks down into an ulcer without any vesicular stage. The site is determined largely by trauma, and is commonly the lower lip, commissures, buccal sulci, or the lateral margins of the tongue. It is unusual for more than four ulcers to be present at any one time, and most ulcers last from 8 to 12 days. Only long-standing ulcers heal with a scar. The ulcer is often 0.5-1 cm. in diameter, and has a punched-out, crater-like appearance with raised red rampart-like margins. In four patients a small ulcer was removed for histological examination, and in each case the diffuseness of the chronic inflammatory reaction in the corium and the absence of any change in the bordering epithelium suggest that the lesion may begin in the corium rather than in the epithelium.

In this type of ulceration natural remissions are common, and a good response is often given to any form of new treatment. Some patients known to have had these aphthae five years previously were recalled and were found to be free from ulcers. The trial was restricted to patients with almost continuous ulceration; those with multiple shallow herpetiform erosions were excluded. Two patients had a complete remission a

few weeks before the trial began and could not be included. None of the patients experienced ulceration in other parts of the body.

Each patient was given a specially designed form on which to keep a written record of the time each ulcer lasted, its site, and its relative size during the trial. At the start every patient kept the record for at least a month, and then was allotted tablets A or B from a list of random numbers. During the trial it was not known either to patients or to investigators which of the two tablets contained the hydrocortisone hemisuccinate. The patients were told that two preparations were being tested. The trial periods were of eight weeks, with an intervening period of two weeks without treatment. If during the first half of the trial patients were using tablets A, then they had tablets B during the second half, and vice versa.

Analysis and Results

Two figures lent themselves to accurate measurement—namely, the number of new ulcers and the number of ulcer days in a given period. By ulcer days is meant the sum of the duration of all ulcers during the period—for example, two ulcers occurring at the same time and each lasting a week are recorded as 14 ulcer days. This unit gives a measure of the amount of distress experienced by the patient. The results are shown in the Table and (for the mean number of ulcer days per week) in Fig. 1.

There was a much better clinical response to the drug than to the inert tablet, the difference being greater when the placebo was taken first. During treatment by the drug there is a reduction of about 50% in the number of ulcer days and in the number of new ulcers compared with the placebo. These differences are highly significant.

Results of Treatment

Order	No. of Patients	Placebo A	Drug B	Difference between Means, with Standard Error
<i>Ulcer days per 8-weeks period (mean values)</i>				
AB	8	83.8	23.1	60.6 } Difference (AB v. BA) 20.9 } = 39.7 ± 17.4*
BA	9	50.0	29.1	
Total	17	65.9	26.3	39.6 ± 9.8†
<i>Total ulcers per 8-weeks period (mean values)</i>				
AB	8	11.88	3.75	8.12 } Difference (AB v. BA) 2.00 } = 6.12 ± 2.77*
BA	9	6.44	4.44	
Total	17	9.00	4.12	4.88 ± 1.54†

* Significant at the 5% level. † Significant at the 1% level.

FIG. 1.—Mean ulcer days per week. Because a few patients forgot to give themselves a two-weeks "no treatment" period between the two halves of the trial period, this has been omitted from the chart.

Four patients experienced complete remissions, three while being treated with the drug and one while on the placebo. Seven other patients had only 7 to 10 ulcer days during the whole eight-weeks period while taking the active tablets.

Apart from the relief of pain given by the reduction of ulceration, the impression was not gained that the individual ulcers were any the less painful while the active tablets were being taken. Figures relating to the size of the ulcers were too subjective for accurate evaluation, but in almost every case the ulcers were smaller while the active tablets were being taken.

Progress

After the trial was over, all the patients, apart from one who did better on the placebo, were told that the tablets that had given them the greatest benefit contained 2.5 mg. of hydrocortisone hemisuccinate and that they were marketed under the trade name of "corlan." Thereafter, corlan tablets were prescribed in varying maintenance doses. The patient who had a complete remission on the placebo has maintained the remission on the placebo tablets for four months. Of the other three patients in whom the active tablets were thought to have produced a complete remission, in two the remission has been maintained for three months without treatment, and in the other the remission has been maintained for three months on corlan tablets.

Nine patients had a period of about a month without treatment after the trial: in six of them the ulcers quickly returned to their normal severity, in two the ulceration was less severe, and one had a complete remission. Thereafter the patients have been three months on varying maintenance doses of two, three, and four corlan tablets a day with effect similar to that achieved on the trial. The response to maintenance therapy varied from patient to patient, and even four tablets a day did not prevent exacerbations.

The varying response in three patients is of interest.

Case 1.—A woman of 21 gave a seven-years history of severe recurrent ulceration. This continued at the same severity through the trial period without treatment and on the placebo (Fig. 2), but while on the drug she suffered only a third as much. Then followed a seven-weeks period without treatment, during which time the ulceration returned to its former severity. She was then told that she was to

FIG. 2.—Ulcer chart of Case 1.

be put on the active preparation—namely, corlan tablets, four a day—and the effect for a month was exactly the same as during the period when, unknowingly, she had been receiving the same treatment. On smaller doses the treatment was less effective, but, even so, there was still a marked reduction of about 50% in ulcer days.

Case 2.—A man aged 29 gave a 16-years history of severe recurrent ulceration. After his preliminary period without treatment he was placed on the active preparation with about 25% relief of the ulceration, but while on the placebo he had a severe exacerbation of the ulcers (Fig. 3).

FIG. 3.—Ulcer chart of Case 2.

Then he was given corlan tablets twice a day for eight weeks with the same effect as when he was receiving four a day on the trial. Then followed two months with corlan tablets three times a day, the effect being almost the same as with two a day. Finally he was given corlan tablets four times a day, and the amount of ulceration experienced almost returned to the pre-trial level without treatment.

Case 3.—A woman aged 27 gave a seven-years history of severe recurrent ulceration. Her ulceration was so severe that after only a three-weeks instead of the usual four-weeks preliminary period without treatment she was placed on the trial, receiving, as it happened, the active preparation first (Fig. 4). The relief was remarkable, the ulceration being only a fifth as severe as it was before. Then during the following fortnight without treatment, the ulceration

FIG. 4.—Ulcer chart of Case 3.

returned with a severe exacerbation. There followed a period on the placebo, the relief being just as great as when she had been taking the drug. The day she began taking the placebo coincided with the achievement of her life's ambition, for she began her medical studies, having previously been a nurse. She soon stopped having ulcers, and had a complete remission. This continued for six months, whether or not she was taking corlan tablets.

Discussion

The advantage of drug over placebo has clearly been demonstrated in 16 out of 17 patients serving as their own controls. When considering all the patients together the degree of ulceration was reduced by about 50%, and the reduction could often be maintained for three to six months. It is interesting to note that in Figs. 2 and 3 the effect of the drug was almost the same when the patients knew they were receiving the active preparation as when they were unaware of the nature of the tablets. Nevertheless, any complete remissions were probably the result of the natural history of the disease rather than the result of the drug, since one occurred with the placebo and two others have been maintained for three months without treatment.

That the response to the drug over a period of time was not as constant as in Fig. 3 does not necessarily mean that the drug is no longer effective, but may rather reflect the periodicity of the severity of the ulceration, as is also shown by the difference between the ulceration at the beginning of the trial and while on the placebo.

That psychological factors play an important part is suggested not only by the difference between the effect when the active preparation preceded the placebo and vice versa, but in the history in Case 3, illustrated by Fig. 4, when the remission is plainly not the result of any therapy but perhaps the personal satisfaction of beginning medical studies. The smaller effect of the active preparation over the inactive one when the former was given first can also be accounted for by the feeling of well-being that these patients experience when at last they obtain some relief, even though only partial, from their severe ulceration.

No side-effects have been noted in patients treated in this way, but it has been my experience, so far, that only the Mikulicz type of ulceration responds in this manner, and that the type of recurrent ulceration with multiple shallow erosions of herpetiform type is made worse, not better, by local hydrocortisone therapy.

Thus in the treatment of the Mikulicz type of recurrent ulceration, tablets containing 2.5 mg. of hydrocortisone hemisuccinate given four times a day are of value in reducing by half the degree of ulceration, especially during acute exacerbations. Remissions are not induced nor are they maintained by the treatment in the type of case that is severe enough to warrant this therapy. Since it in no way cures or prevents these troublesome ulcers, four tablets a day for eight weeks would appear to be enough to help a patient during a particularly severe bout of ulceration. The resultant relief from pain may induce such a feeling of well-being that the ulceration may remain at a less severe level for a month or two, after which another period of therapy could then be tried if desired.

Summary

Assessment of the value of topical hydrocortisone hemisuccinate in the treatment of patients suffering from recurrent Mikulicz's aphthae has been undertaken by a

double-blind controlled clinical trial. The results show that, compared with the placebo, the drug reduces by about 50% the number of ulcer days and of new ulcers per patient, per eight-weeks period.

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BACTERIAL FLORA OF THE SMALL INTESTINE IN ACUTE INTESTINAL OBSTRUCTION

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In acute obstruction of the small intestine the bowel above the site of obstruction soon becomes filled with fluid which is feculent, both in colour and in odour. When appropriate treatment is deferred, fluid of this nature may eventually be vomited.

It has usually been assumed that the flora of this fluid is closely akin to that of normal faeces. Moreover, it has generally been believed that the small intestine is inoculated with organisms by retrograde spread from the large bowel. A search of the literature of the past 60 years has not revealed any detailed investigation of the bacterial flora in intestinal obstruction in man.

In the work reported here, samples of intestinal content were taken at operation from many levels of the small bowel by aspiration of its content through hypodermic-needle punctures of the bowel wall. The specimens were then examined bacteriologically.

The results show that the small intestine above an obstruction contains a profuse flora of faecal type. This is abnormal. In contrast, the small intestine below the obstruction is either sterile or yields only a scanty growth. This is normal (Cregan and Hayward, 1953; Cook, Elliott, Elliot-Smith, Frisby, and Gardner, 1957). This leads to the conclusion that the profuse flora of faecal type present above an obstruction of the small intestine is acquired by ingestion.

Materials and Methods

Patients Studied.—Twenty-seven patients with intestinal obstruction were examined (Table I). Twenty-three obstructions were of the small intestine and were caused by herniae (9), bands or adhesions (10), obturation (2), volvulus (1), paralytic ileus (1). The bowel was considered to be gangrenous in two patients with strangulated herniae. The remaining four obstructions were in the large intestine, and were caused by diverticulitis (2) or carcinoma (2). The duration of the obstructions ranged from 6 hours to 10 days. No patient was accepted for study if any chemotherapy had been used.

Collection of Specimens.—Samples were taken in the following order: (a) stomach contents aspirated by