Treatment of Duodenal Ulcer with Glycyrrhizinic-acid-reduced Liquorice

A Multicentre Trial*

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Summary

A double-blind controlled therapeutic trial of glycyrrhizinic-acid-reduced liquorice 760 mg thrice daily for six weeks was carried out on 90 men with relapse of chronic duodenal ulcer. Effects of treatment were judged by the frequency and severity of pain, the amount of alkali consumed, and the doctors' and patients' rating of the clinical response. The results do not show any advantage for the active treatment when compared with the placebo.

Introduction

Preparations of glycyrrhizinic-acid-reduced liquorice have been reported to increase the rate of healing of gastric ulcer (Russell and Dickie, 1968; Turpie *et al.*, 1969) and to be effective in the treatment of duodenal ulcer (Tewari and Trembalowicz, 1968; Mills and Damrau, 1969). The purpose of the therapeutic trial reported here was further to determine whether treatment with glycyrrhizinic-acid-reduced liquorice has a beneficial effect on the symptoms of duodenal ulcer.

Patients and Methods

Patients referred to the seven hospitals, five of which are situated within the London Metropolitan area, participated in the trial.

SELECTION OF PATIENTS

Patients admitted to the trial were men with radiological evidence of duodenal ulcer crater or deformity of duodenal cap obtained within the previous two years who were judged to be suitable for outpatient management of their ulcer. They were all suffering from periodic attacks of upper abdominal pain in some way related to food and relieved by alkali; their pain was considered by the doctor to be typical of duodenal ulcer. All the patients included in the present series had their pain on three or more of the seven days immediately preceding admission into the trial. There were no restrictions with regard to age or the presence of conditions outside the gastrointestinal tract, but those suffering from other gastrointestinal ailments or from symptoms that might have been confused with those of duodenal ulcer were excluded. Those with atypical symptoms of duodenal ulcer, with known anaemia, and those currently treated with liquorice preparations were likewise excluded. Patients could also be excluded from the trial if the doctor thought that they were unlikely to complete the course of treatment.

CONDUCT OF TRIAL

Suitable patients were told that a medical treatment for duodenal ulcer was being tried and the procedures involved were explained to them. On gaining the patient's co-operation treatment was allocated in random fashion between active and placebo capsules of similar appearance, so that neither the doctor nor the patient knew the nature of the capsules dispensed by the hospital pharmacist. Randomization of the treatments was arranged in groups of 10. Each capsule in the active group contained 380 mg of glycyrrhizinic-acid-reduced liquorice, while the dummy capsules contained lactose coloured with caramel. The dose was two capsules thrice daily after meals for six weeks.

In addition to the treatment capsules, each patient was given an alkali (pulv. mag. trisil. co., tabs. mag. trisil. co., or tabs. Nulacin, according to personal preference) and advised to stop smoking; no specific instructions with regard to diet were issued, but, if asked, the doctors advised the patients to eat normal meals. Care was taken not to prescribe salicylates or anticholinergic drugs. A letter with details of the trial and a request to refrain from prescribing drugs that might vitiate the interpretation of results was sent to each patient's family doctor.

The patients were seen at two-weekly intervals. At the first and last attendance blood was taken for electrolytes and serum pepsinogen estimations. At each attendance the weight, blood pressure, and smoking habits were noted and the symptoms carefully recorded with the aid of a standard form. The doctor's and the patient's opinion of the overall effect of the treatment during each fortnight, in comparison with the preceding two weeks, was also recorded in standard terms as symptom-free, improved, unchanged, or worse. No specific inquiry was made with regard to side effects, but they were recorded if patients mentioned them.

At each visit the patient was issued with a diary card on which he recorded each day the presence or absence and the intensity (graded as severe, moderate, or mild) of his pain. The number of doses of alkali consumed and the number of treatment capsules actually taken were also recorded daily during the trial. The diary cards and the capsule containers were collected from the patients during each attendance at the clinic.

The results were analysed on the basis of the doctors' and the patients' own assessments of symptoms and also with regard to the frequency and intensity of the pain and the quantity of alkali consumed in the three successive two-weekly periods. Patients who omitted 20% or more of the treatment capsules or whose diary card was incomplete or uninterpretable in any fortnight were excluded from the analysis. Many patients took no antacids or had no pain in the later stages of the trial and therefore calculated averages were considered to be unhelpful because of abnormal distribution of the data. For this reason statistical analyses were performed by the χ^2 method between arbitrarily defined groups within each variable (see Table III).

Results

Of 130 men with active duodenal ulcer who were admitted to the trial, 40 had to be withdrawn for reasons listed in Table I, leaving 90 patients who completed the six-weeks course of treatment for analysis of the results. Approximately equal numbers were treated in each of the seven participating hospi-

*The following took part in the trial: Dr. J. J. Misiewicz (convener) and Dr. R. I. Russell, M.R.C. Gastroenterology Unit and Department of Gastroenterology, Central Middlesex Hospital; Dr. J. H. Baron and Mr. A. G. Cox, Prince of Wales's Hospital (J.H.B.) and Hammersmith Hospital and Royal Postgraduate Medical School (J.H.B. and A.G.C.); Dr. M. J. Grayson, Plymouth General Hospitals; Dr. J. Howel Jones, Hospital of St. Cross, Rugby; Dr. J. E. Lennard-Jones, Dr. D. G. Colin-Jones, and Dr. J. Temperley, University College Hospital; and Dr. P. Richardson, the London Hospital.

TABLE I—*Reasons for Withdrawal*

	Treatment	
	Active	Placebo
No. of patients admitted to trial	65	65
Pain worse, stopped treatment	4	3
⩾ 20% treatment capsules missed	6	4
Diary card incomplete	6	8
Defaulted	2	5
Other alimentary disease found	1	—
Intercurrent illness	1	—
Total No. withdrawn	20	20
No. Available for analysis	45	45

TABLE II—*Various Clinical Criteria of the Two Groups*

	Treatment	
	Active	Placebo
Mean age (range) (years)	41 (20-70)	39 (18-63)
Mean length of history (range) (years)	8·1 (1-30)	6·5 (1-22)
Mean No. of days with pain in week before trial	5·3	5·6
Mean No. of smokers at start (and end) of trial	32 (32)	29 (28)
Mean No. of daily cigarettes/smoker at start (and end) of trial	13 (12)	13 (12)

tals. The two treatment groups were comparable with respect to various clinical criteria (Table II). There were no meaningful changes in weight, blood pressure, or serum electrolytes in either group during the trial. Two patients (one on liquorice, the other on dummy capsules) complained of loose stools, but this was not severe enough to cause the drug to be discontinued.

The doctors' and patients' opinions of the effects of treatment on symptoms in each fortnightly period (Fig. 1) do not suggest any pronounced advantage for the active treatment group, while there is considerable similarity between the physicians' judgement of the patient and the patients' self-assessment. Analysis of the data culled from the diaries kept by the patients on the frequency and severity of the pain and with regard to the quantity of antacid consumed (Figs. 2, 3, and 4) shows no significant differences between the active and placebo treatments (Table III). Serum pepsinogen levels before and after treatment were available in 17 patients receiving the active and in 16 on the placebo capsules. The average level was the same in both groups before treatment (219 units) and remained unchanged after completion of the trial.

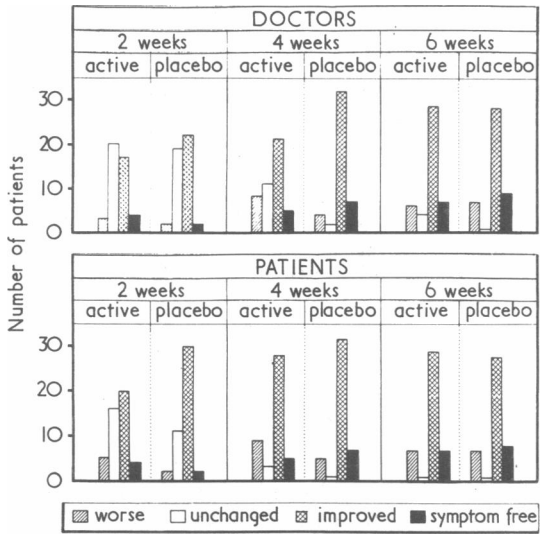

FIG. 1—Doctors' and patients' assessment of effect of treatment on symptoms in each two-weekly period of trial.

TABLE III—*Comparison of the Two Groups*

Variable	Basis for Comparison	χ^2 at			Significance
		2 wk	4 wk	6 wk	
Instances of pain	5 or less instances of pain *v.* all others	0·12	2·41	2·84	None
Intensity of pain	Pain score of 10 or less *v.* all others	1·55	2·20	0·76	None
Antacids consumed	Taking no antacids *v.* all others	0·62	0·56	2·86	None

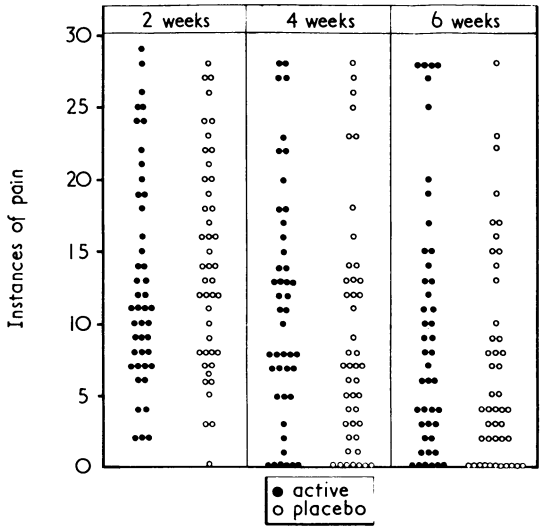

FIG. 2—Instances of pain in individual patients in each fortnight of trial. Each point represents the number of days with pain experienced by one patient in the trial.

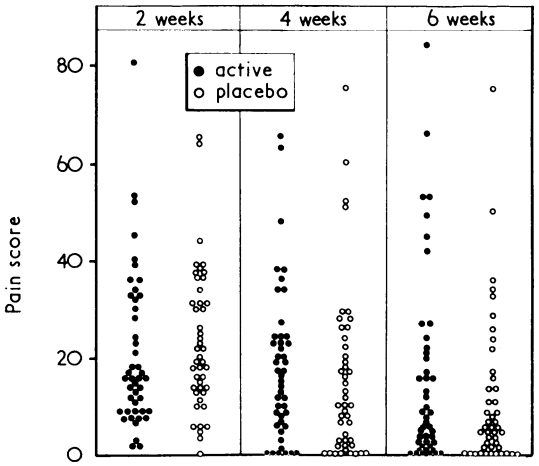

FIG. 3—Severity of pain in individual patients in each fortnight of trial, symptoms scored as severe = 3, Moderate = 2, mild = 1, none = 0 for each day. Each point represents the total score of one patient in the trial.

Discussion

Results of this trial suggest that glycyrrhizinic-acid-reduced liquorice 760 mg three times a day for six weeks has no better effect than a placebo on the course of an acute relapse of chronic duodenal ulcer in men, as judged by the frequency and severity of the pain, the amount of antacid consumed, or the doctors' and patients' assessments of the clinical state. In both comparable groups of patients the symptoms declined progressively during the course of treatment, indicating that the observations

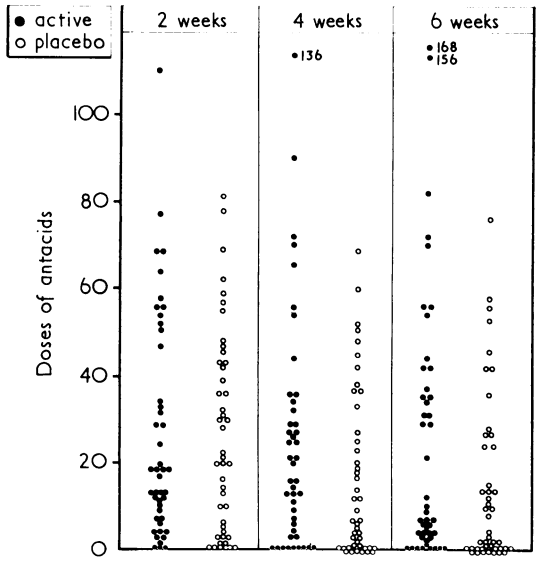

FIG. 4—Number of doses of antacid consumed by each patient during each fortnight of the trial.

probably document the natural evolution of an attack of duodenal ulcer under outpatient management.

The present data are in agreement with those of Feldman and Gilat (1971), but do not confirm the beneficial effect on symptoms of duodenal ulcer reported by others on the basis of controlled observations on a total of 70 patients treated for two or four weeks (Tewari and Trembalowicz, 1968; Mills and Mamrau, 1969). The dose used by these workers was the same as in the present series, but a commercially available tablet (Caved-S) was prescribed which, in addition to 380 mg of glycyrrhizinic-acid-reduced liquorice, contained bismuth subnitrate 100 mg, colloidal aluminium hydroxide 100 mg, magnesium carbonate 200 mg, sodium bicarbonate 100 mg, and frangula 30 mg. It is possible, though unlikely, that the small quantity of antacid and laxative contained in the commercial tablet or its physical properties are responsible for the difference in the respective results. If the peak acidity in gastric juice of men with duodenal ulcer is taken to be 125 mEq/l. (Baron, 1963), in-vitro tests have shown that two tablets of the commercial preparation would raise the pH of 45 ml of gastric juice to 3·0, which would account for about seven minutes of secretion at the peak histamine-stimulated rate. Moreover our patients were encouraged to consume sufficient alkali to relieve their symptoms. In other trials the rate of healing of gastric ulcers was significantly accelerated by capsules of glycyrrhizinic-acid-reduced liquorice without alkali or frangula, similar to those used in the present investigation (Turpie *et al.*, 1969).

It is, however, generally accepted that in the absence of unequivocal radiological criteria the assessment of results of treatment in duodenal ulcer is difficult, based as it is on subjective variables such as pain or on indirect measures such as quantity of alkali consumed. Further clinical trials are needed if the usefulness of glycyrrhizinic-acid-reduced liquorice for the treatment of duodenal ulcer is to be established.

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Effects of Externally Applied Pressure on the Haemodynamics of the Lower Limb

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Summary

The effects of externally applied pressure of 5-150 mm Hg on the haemodynamics of the leg of dog and man were investigated. The criteria used for the assessments included femoral arterial and venous blood flow as well as vascular hydraulic conductance. The results indicated that external pressure of 5 mm Hg results in a very small non-significant increase in the femoral arterial and venous flow. Higher external pressure of 15 mm Hg or more significantly reduces the femoral arterial and venous flows as well as the vascular conductance. It therefore seems that compression produced by bandaging in horizontal supine subjects has little or no haemodynamic value and may prove to be harmful unless carefully controlled.

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Introduction

Venous stasis in the lower limb of resting recumbent patients (McLachlin *et al.*, 1960) is probably an important cause of thrombosis in the deep veins of the calf (Hadfield, 1950). Radiographic and anatomical studies have shown that venous blood stagnates in the thin-walled soleal sinuses, which may have a diameter of up to 1 cm (Gibbs, 1957) and a length of up to 5 cm (Cotton and Clark, 1965). Induction of anaesthesia and associated inactivity of the calf muscles remarkably aggravates the stagnation in these sinuses (Cotton and Clark, 1965; Clark and Cotton, 1968).

Compression of the lower limb to prevent venous stasis and subsequent venous thrombosis was first suggested by Piere