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Clinical trial of deglycyrrhizinized liquorice in gastric ulcer

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In the past twenty years evidence has accumulated that liquorice and related compounds accelerate the rate of healing of gastric ulcers.

Powdered succus liquiritiae (Revers, 1948) and glycyrrhiza extract (Schulze, Franke, and Keller, 1954; Ferenbach, 1954; Ohrt, 1955) were shown to be beneficial in patients with gastric ulcer but adequately controlled clinical trials of liquorice extracts were not available until 1962 with the result that little attention was paid to this form of treatment.

Interest in liquorice as a therapeutic agent was revived with the synthesis of carbenoxolone sodium from glycyrrhizinic acid, a glycoside extracted from liquorice. Carbenoxolone sodium has been shown in a number of controlled clinical trials (Doll, Hill, Hutton, and Underwood, 1962; Doll, 1964; Doll, Hill, and Hutton, 1965; Doll, Langman, and Shawdon, 1968; Horwich and Galloway, 1965; Bank, Marks, Palmer, Groll, and Van Eldick, 1967) to promote the healing of gastric ulcers. However, treatment with either carbenoxolone sodium or succus liquiritiae was often complicated by retention of water and electrolyte imbalance. The frequency and severity of side effects occurring in patients receiving carbenoxolone sodium have been emphasized by many authors (Doll *et al*, 1962; Turpie and Thomson, 1965; Mohamed, Chapman, and Crooks, 1966). The main side effects noted have included frank oedema, elevation of diastolic blood pressure, hypokalaemia, and paresis of muscles.

Langman (1968) stated that a variant of carbenoxolone which is devoid of side effects on fluid and electrolyte balance is clearly needed. Borst, Blomhert, Molhuysen, Gerbrandy, Turner, and de Vries (1950) found that the glycyrrhizinic acid moiety of liquorice was responsible for the fluid retention and electrolyte imbalance. This view was confirmed by Revers (1952). There is now available a preparation of liquorice which does not contain glycyrrhizinic acid; it is found in the proprietary preparation, Caved-(S)

Each tablet of Caved-(S) contains:

Deglycyrrhizinized powdered block liquorice	380 mg
Bismuth subnitrate	100 mg
Aluminium hydroxide gel	100mg
Light magnesium carbonate	200 mg
Sodium bicarbonate	100 mg
Powdered frangula bark	30 mg

The present study was carried out to determine whether deglycyrrhizinized liquorice was active in accelerating the rate of healing of gastric ulcers; also would it be devoid of the side effects which have been found with crude liquorice or with carbenoxolone sodium?

METHOD

PILOT STUDY A pilot study using Caved-(S) was made of 10 inpatients suffering from duodenal ulcer for evidence of overt toxicity. Each patient was given two tablets of Caved-(S) thrice daily (equivalent to 760 mg of deglycyrrhizinized liquorice thrice daily) for a period of four weeks. Weight, blood pressure, and the presence or absence of oedema were recorded daily. The levels of serum urea, sodium, chloride, and potassium were estimated before the start of treatment and at weekly intervals during the study. Electrocardiograms were performed before and after treatment. No restrictions were placed on the patients' activity while in the wards and antacid in the form of colloidal aluminium hydroxide was available to them as required.

No patient developed oedema; there was no excessive weight gain; the blood pressures remained constant and there was no evidence of electrolyte imbalance. The electrocardiograms after four weeks were unchanged.

DOUBLE-BLIND TRIAL A double-blind clinical trial of deglycyrrhizinized liquorice was then carried out in 33 patients with gastric ulcer. Only patients in whom the profile of the gastric ulcer niche on radiographs was greater than 10 sq mm in area were included in the trial. Consecutive patients referred to us for investigation were treated: 16 received the active drug in specially

prepared capsules, each containing 380 mg of deglycyrrhizinized liquorice; 17 patients received the placebo capsules which contained caramel-coloured lactose. The dose in each patient was two capsules three times a day after meals. For the most part the trial was conducted on an outpatient basis; four patients from either group were treated in hospital, remaining ambulant during the trial period.

The treatment continued for one month, after which the patients were reassessed clinically with special reference to weight, the presence of oedema, and other side effects; each was referred for a second barium meal examination. Assessment of the rate of healing of the gastric ulcer was expressed as a percentage reduction in the area of ulcer niche, as described by Doll *et al* (1962).

RESULTS

The comparability of the patients in the groups treated with the active principle and the placebo in respect of age, sex, and size of ulcer is shown in Table I.

TABLE I

COMPARABILITY OF PATIENTS IN THE TWO GROUPS

	Number of Patients	
	Active	*Placebo*
Sex		
Male	5	7
Female	11	10
Total	16	17
Age in Years		
Under 45	3	5
45-54	3	4
55-64	5	3
65+	5	5
Area of Ulcer (sq mm)		
10-49	8	9
50-100	2	4
Over 100	6	4

There is an unusual preponderance of females in both groups; this occurred by chance. The age distribution and the size of the ulcer in both groups are similar.

TABLE II

RESULTS OF TREATMENT

	Active	*Placebo*
Average percentage reduction in ulcer size	78	34
No. of ulcers 'healed' radiologically	7	1
No. of patients requiring operation	1	4

The average percentage reduction in ulcer size in each group is shown in Table II.

Statistical analysis of the percentage reduction in ulcer size in each patient using Wilcoxon's test reveals a significant difference in the reduction in ulcer size in favour of the treated group compared with the control group ($P<0.001$). In seven (44%) of the group treated with deglycyrrhizinized liquorice compared with one (6%) treated with the placebo, the ulcer niche disappeared radiologically.

It is of interest that a total of five patients was referred after the trial period for surgical treatment; one was from the 'active' group, four from the 'placebo' group.

The pattern of change in weight of the patients is shown in Table III.

TABLE III

CHANGE IN WEIGHT IN THE TWO GROUPS

	Active	*Placebo*
Average increase in weight (kg)	1·1	0·87
Maximum increase (kg)	3·5	6
Maximum loss (kg)	0·2	1·1

There is no statistical difference between the two groups. No patient developed oedema. The serum electrolytes and blood pressure were not measured routinely. No patient from either group made any spontaneous complaint.

DISCUSSION

Deglycyrrhizinized liquorice in the form of Caved-(S) has been widely used on the European continent for the treatment of peptic ulcer. Gassman and Forster (1963) found no evidence of salt and water retention in their patients receiving this drug. Tewari and Trembalowicz (1968) reported no electrolyte disturbance, pitting oedema, or rise in blood pressure in a small series of patients treated with Caved-(S). In a trial of Caved-(S) in patients with gastric and duodenal ulcers, Russell and Dickie (1968) found no evidence of fluid retention or electrolyte upset. We have found no sign of disturbance of fluid and electrolyte balance in the patients treated with deglycyrrhizinized liquorice or Caved-(S). This is in marked contrast to the high incidence of side effects reported with the use of crude liquorice or carbenoxolone sodium.

Healing of gastric ulcers was accelerated in the patients treated with deglycyrrhizinized liquorice to a statistically significant degree ($P<0.001$). Comparison of the average percentage reduction in the size of ulcer crater using deglycyrrhizinized liquorice with results of previously reported trials using carbenoxolone sodium is strikingly similar (Table IV).

The numbers of patients showing radiological 'healing' in the different series are also very similar (Table V).

The results obtained with pure deglycyrrhizinized liquorice in the present trial are also strikingly

TABLE IV

AVERAGE PERCENTAGE REDUCTION IN SIZE OF GASTRIC ULCER

	Active	*Placebo*
Present trial	78	34
Doll *et al* (1962)	72	34
Doll *et al* (1965)	78	39
Doll *et al* (1968)	91	—

TABLE V

RADIOLOGICAL 'HEALING' OF ULCER

	Active	*Placebo*
Present trial	7 (44%)	1 (6%)
Doll *et al* (1962)	11 (37%)	1 (5%)
Doll *et al* (1965)	10 (42%)	6 (27%)

TABLE VI

COMPARISON OF RESULTS OBTAINED WITH DEGLYCYRRHIZINIZED LIQUORICE AND CAVED-(S) IN GASTRIC ULCER

	Active	*Placebo*
No. of patients		
Present trial	16	17
Russell and Dickie (1968)	8	8
Average percentage reduction in size		
Present trial	78	34
Russell and Dickie (1968)	92	39
Radiological healing		
Present trial	7 (44%)	1 (6%)
Russell and Dickie (1968)	5 (62%)	0 (0%)

similar to those obtained with Caved-(S) in patients with gastric ulcer by Russell and Dickie (1968). The results in the two trials are shown in Table VI.

Deglycyrrhizinized liquorice has been shown in the present trial and in that of Russell and Dickie (1968) to give similar rates of reduction in ulcer size as carbenoxolone sodium but has the obvious advantage of not producing fluid retention or electrolyte imbalance.

Doll *et al* (1968) have shown in a recent study that the healing properties as well as the fluid-retaining properties of carbenoxolone sodium may be blocked by spironolactone whereas the fluid-retaining property only is blocked by thiazide diuretics. Carbenoxolone is a derivative of the glycyrrhizinic acid fraction of liquorice. We have shown that deglycyrrhizinized liquorice has a similar effect to that of carbenoxolone sodium causing reduction in the size of gastric ulcers but no evidence of fluid retention or electrolyte imbalance.

It must therefore be postulated that liquorice contains at least two active principles which promote the healing of gastric ulcers.

SUMMARY

In a double-blind clinical trial of deglycyrrhizinized liquorice 16 patients with gastric ulcer received the active drug for four weeks in a dose of 760 mg thrice daily and 17 the placebo. All patients, except four from each group who remained ambulant, were treated as outpatients. The results of the trial were assessed by the change in the size of the ulcer crater on barium meal before and after treatment.

Of the patients given the active drug, on average the size of the ulcer niche was reduced by 78%; in six patients (44%) the crater disappeared radiologically. In contrast the average reduction in size of the ulcer niche of the placebo group was 34% and in only one (6%) did the ulcer disappear. The difference in the reduction in ulcer size in favour of the treated group compared with the control group is statistically significant ($P<0.001$). None of the patients developed oedema and there was no excessive weight gain.

A pilot trial using Caved-(S) in a dose containing 760 mg of deglycyrrhizinized liquorice thrice daily for one month showed no toxic effects on fluid and electrolyte balance in 10 patients.

We are grateful to the physicians and surgeons who referred their patients to us for inclusion in this trial; to Dr S. Haase and members of the X-ray Department of Stobhill General Hospital for their willing cooperation. We are indebted to Tillotts Laboratories and to Cedona, Haarlem, Holland, for supplying the prepared capsules containing deglycyrrhizinized liquorice or the placebo.

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