

# Clinical trial of deglycyrrhizinised liquorice in gastric ulcer

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**SUMMARY** Ninety-six patients with gastric ulcer were randomly allocated to treatment either with deglycyrrhizinised liquorice or placebo. After four weeks no differences were found between the treatment groups in the proportions with complete healing, whether assessed by gastroscopy or radiology, or in the percentage reduction in ulcer area, or in clinical improvement.

Liquorice extract from which glycyrrhizic acid has been removed has been explored as a less toxic alternative to carbenoxolone sodium in the treatment of gastric ulcer. Authors of four papers published between 1968 and 1972 claimed acceleration of gastric ulcer healing comparable with that produced by carbenoxolone sodium and without side effects (Table 1), but the largest treatment group in any of these trials contained only 16 patients and not all trials were double blind. One rather larger trial failed to confirm a beneficial effect (Engqvist *et al.*, 1973).

## Method

All patients had a benign-looking gastric ulcer, verified by endoscopy on entry to the trial. Radiographs were taken showing the ulcer in maximum profile. Ulcer areas in mm<sup>2</sup> were standardised against

the apparent radiographic size of a one penny piece placed beneath the patient, thereby correcting for the variable magnification effect arising from the tube-film distance associated with the height of the image intensifier.

Physical examination and blood tests were done within 24 hours of the admission endoscopy. Patients were then randomly allocated under double-blind conditions, and stratifying for age, sex, and the presence or absence of either cardiovascular disease or hypertension, to take two capsules five times daily for four weeks, containing either 500 mg deglycyrrhizinised liquorice<sup>2</sup> (DGL) or 200 mg sucrose.

Measured amounts of antacid tablets<sup>3</sup> and mix-

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<sup>2</sup>Ulcedal, prepared by Cedona of Holland and marketed by Boehringer Ingelheim.

<sup>3</sup>Neutralactis, Wander: dried aluminium hydroxide gel BP 140 mg, magnesium trisilicate BP 200 mg, calcium carbonate BP 280 mg, high protein milk solids 1.5 g.

Table 1 Cumulative experience in five previous trials

Treatment group	Radiological assessment	Number of patients				
		Tewari and Trembalowicz (1968)	Russell and Dickie (1968)	Turpie et al. (1969)	Montgomery and Cookson (1972)	Engqvist et al. (1973)*
Deglycyrrhizinised liquorice	Healed	5	5	7	6	4
	Not healed	1	3	9	10	16
	Total	6	8	16	16	20
Placebo	Healed	0	0	1	4	4†
	Not healed	3‡	8	16	12	14
	Total	3	8	17	16	18

\*Results only for first four-week period shown; results similar for second (crossed-over) period.

†First period of a cross-over trial, so these patients included, during second period, in the six DGL patients.

‡Text says five patients, but their last row of Table IV indicates only four.

ture<sup>4</sup> were supplied and patients recorded daily their consumption of each type, and any pain experienced. They otherwise continued with normal domestic, dietary, and smoking habits.

At the end of four weeks, the physical examination, blood testing, gastroscopy, and (in most cases) barium meal were repeated, usually all within a 24-hour period. Residual capsules and antacid supplies were collected, having been issued in excess of required amounts so that compliance could be checked.

Ulcer healing on gastroscopy was defined as re-epithelialisation with or without a scar; the radiological definition was disappearance of the crater.

## Results

Of the total 96 patients, 59 had a single ulcer of at least 10 mm<sup>2</sup> seen on barium meal; these form the main study and are presented separately in Tables 2, 3, and 4. The remaining 37 had smaller or multiple ulcers or, in a few cases, no initial radiology.

The 48 patients on DGL were similar in age distribution, proportion of males, site of ulcer, and cigarette smoking habits to the 48 on placebo (Table 2). The groups also had similar durations of symptoms and of proportions with epigastric tenderness and with congestive failure or ischaemic heart disease.

<sup>4</sup>Aluminium hydroxide gel BP 280 mg, magnesium trisilicate BP 200 mg, calcium carbonate 280 mg.

However, those on DGL included a smaller proportion of patients with either very large or very small ulcers initially than those on the placebo.

Of the 29 patients on DGL in the main study, six showed healing radiologically at the end of the trial (Table 3); 27 were assessed gastroscopically and 14 showed healing. Similar healing rates by the respective techniques were found among the 30 patients on placebo in the main study. The extent of concordance between the gastroscopic and radiological assessment of healing is the subject of a separate paper (Bardhan *et al.* (in preparation)). The median percentage change in the ulcer area was again comparable for the two treatment groups; the mean percentage change in ulcer area is shown only for comparison with previous ulcer healing studies. Among the patients not in the main study, few were assessed radiologically at the end of therapy, but gastroscopies were done for most: the proportions healed gastroscopically were the same in those on DGL as in those on placebo.

For each treatment group, healing rates appeared to be higher for ulcers in the body and/or fundus than for other sites (Table 3). For the main study, combining the treatment groups, the difference among the three sites shown was not quite significant at the 5% level ( $\chi^2 = 4.2$  with Yates' correction; 2 df), while the difference between the body and/or fundus compared with the other two sites combined was significant at this level ( $\chi^2 = 4.7$ ; 1 df). Similar conclusions obtain if the data for all 95 patients for whom the site was known are used.

Table 2 Comparability of treatment groups on admission

	Initially seen both by radiology and gastroscopy				All patients*	
	Single ulcers initially $\geq 10$ mm <sup>2</sup>		Small ulcers initially $< 10$ mm <sup>2</sup> , and/or multiple ulcers		DGL	Placebo
	DGL	Placebo	DGL	Placebo		
Sex						
Males	20	17	9	10	33	28
Females	9	13	3	4	15	20
Age (yr)						
Mean	54.1	53.4	51.8	53.7	54.3	54.3
Ulcer area						
Median ulcer area (mm <sup>2</sup> )	26.5	35.6	10.1	7.1	21.3	22.1
No. with small ulcers ( $< 10$ mm <sup>2</sup> )	—	—	6	12	10	14
No. with large ulcers ( $\geq 100$ mm <sup>2</sup> )	1	7	—	—	1	7
Multiple	—	—	6	2	6	2
Ulcer site						
Pre-pyloric/antrum	4	6	2	3	8	10
$\leq 2$ cm from incisura	9	5	1	1	11	6
Body and/or fundus	16	19	9	10	29	30
Not recorded	—	—	—	—	—	2
Smoking						
10 or more cigarettes daily	19	14	5	9	29	24
Total no. of patients	29	30	12	14	48	48

Numbers of patients unless otherwise stated.

\*Including 11 patients assessed gastroscopically only, or for whom initial ulcer size not known.

A similar proportion in each treatment group experienced improvement in dyspepsia/abdominal pain and in epigastric tenderness (Table 4). As some patients failed to complete their daily records, results are shown only for those patients who entered positive or negative data on at least 24 days, for day-time pain, antacid tablets, and antacid mixture respectively; the treatment groups did not differ significantly in any of these items (Wilcoxon's rank sum tests), for the main study or for the remaining patients.

On the basis of the pharmacists' count of returned capsules, mean total consumption among 46 patients on DGL returning their bottles was 262 (SD 23) and among 44 patients on placebo was also 262 (SD 27): consumption over 28 days should have been 280. Smoking and drinking habits during treatment as determined from the daily records continued much as before treatment.

A possible side-effect was noted in only one patient who became oedematous and developed hypokalaemia while taking DGL, although her weight

Table 3 Ulcer healing at end of trial therapy

	Initially seen both by radiology and gastroscopy				All patients	
	Single ulcers initially $\geq 10$ mm <sup>2</sup>		Small ulcers initially $< 10$ mm <sup>2</sup> and/or multiple ulcers		DGL	Placebo
	DGL	Placebo	DGL	Placebo		
<b>Gastroscopy:</b>						
Replacement of ulcer by scar/mucosa:						
Any site	14/27*	10/28*	3/10*	4/13*	20/42*	17/44*
Pre-pyloric/antrum	(1/4)	(1/6)	(1/2)	(1/3)	(3/7)	3/10
$\leq 2$ cm from incisura	(3/9)	(1/5)	(-/1)	(1/1)	3/11	(2/6)
Body and/or fundus	10/14	8/17	(2/7)	(2/9)	14/24	11/27
Site not known	—	—	—	—	—	(1/1)
<b>Radiology (excluding ulcers initially <math>&lt; 10</math> mm<sup>2</sup>):</b>						
Both pre- and post-treatment x-rays done	29	30	7	2	36	32
Healed	6	6	(-)	(1)	6	7
Increase in size	2	4	(4)	(-)	6	4
% change in ulcer area†:						
Mean (for comparison with other studies only)	-47	-54	(+159)	(-78)	-7	-56
Median	-62	-66	(+7)	(-79)	-60	-66
Total number of patients	29	30	12	14	48	48

Number of patients, unless stated; indices based on fewer than 10 patients shown in parentheses.

\*No. with both pre- and post-treatment assessments by gastroscopy.

†In calculating mean % change and median % change, increases are counted as positive, reductions as negative.

Table 4 Symptomatic changes and antacid consumption

	Initially seen both by radiology and gastroscopy				All patients	
	Single ulcers initially $\geq 10$ mm <sup>2</sup>		Small ulcers initially $< 10$ mm <sup>2</sup> and/or multiple ulcers		DGL	Placebo
	DGL	Placebo	DGL	Placebo		
<b>No. of patients with clinical improvement at end in:</b>						
Dyspepsia/abdominal pain	25	26	9	13	40	42
Epigastric tenderness	12/14*	11/17*	5/7*	4/5*	20/25*	16/23*
<b>Diaries:</b>						
No. of days with pain in day time recorded:						
Mean	13.5	11.8	8.4	14.5	11.8	12.3
SD	9.5	9.3	7.8	8.7	9.1	9.1
No. with missing data	(2)	(6)	(2)	(1)	(6)	(9)
<b>Antacid tablets (total count):</b>						
Mean	49	41	23	50	39	43
SD	53	46	46	54	50	47
No. with missing data	(1)	(6)	(-)	(-)	(3)	(7)
<b>Antacid mixture (ml):</b>						
Mean	178	242	114	198	153	222
SD	152	219	112	201	139	212
No. with missing data	(2)	(7)	(-)	(-)	(4)	(8)
Total no. of patients	29	30	12	14	48	48

\*No. with epigastric tenderness initially.

gain was only 0.3 kg. The same patient had previously become oedematous while taking carbenoxolone sodium. With this exception, no abnormality occurred in any of the biochemical and haematological indices measured; in particular, hypokalaemia was not recorded.

### Discussion

Previously published trials of DGL have used radiological criteria alone in determining ulcer healing. In this trial both methods of assessment agreed in their failure to demonstrate therapeutic benefit, although there was substantial disagreement in their assessment of ulcer healing in individual cases. Treatment and placebo groups were similar in all respects that might be expected to influence healing, most particularly in smoking habits. Engqvist *et al.* (1973) have suggested that ulcers at the angulus heal less well than those at other sites. Our results show poorer healing of ulcers either at or distal to the angulus, but it is clear from Table 4 that there is no difference in healing rates between the treatment groups, even when the site of ulcer is taken into account.

The previous trials claiming benefit need careful scrutiny to explain their different conclusion. The two trials reported in 1968 are inadequate in size and in data on comparability (Table 1). The placebo group of Turpie *et al.* (1969) is remarkable as only one of 17 ulcers healed, and the advantage of DGL in the trial of Montgomery and Cookson (1972) was not statistically significant. None refers to how ulcers which increase in size were dealt with.

All DGL used in our own and previous trials was prepared by the same manufacturer and, although in all other trials the DGL was in the form of Caved-S, a preparation which also contains bismuth subnitrate and other antacids, we think it unlikely that any difference in formulation explains the apparent therapeutic failure in the present trial.

Can we firmly conclude that deglycyrrhizinised liquorice has no therapeutic activity? This trial was

designed to be capable of detecting a doubling of the assumed placebo healing rate of around 30%. Between 40 and 45 patients per treatment group were required to have only 20% chance of failing to detect any such doubling of healing rate, which would be significant at the 5% level (Clark and Downie, 1966); to reduce to 5% the chance of failing to detect it around 70 patients per treatment group would be required. The total study here had 48 patients per treatment group and it is therefore unlikely that DGL produces the doubling of the placebo healing rate which would justify its continuing place in clinical practice.

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