Treatment of Gastric Ulceration with Carbenoxolone Sodium*: Clinical and Radiological Evaluation

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Gastric ulcers have a natural tendency towards healing, and a controlled therapeutic trial is the only reliable method for assessing the value of any method of treatment. This paper reports our experience with carbenoxolone, and confirms the studies of Doll *et al.* (1962).

Carefully controlled trials have shown the following treatments to be ineffective: cabbage juice (Doll and Pygott, 1954); Robaden, an extract of gastro-intestinal tissue (Doll and Pygott, 1954); an extract of brain (Brøchner-Mortensen *et al.*, 1955); alkalis and continuous milk (Doll *et al.*, 1956).

Doll and Pygott (1952) compared the effect of bed rest of in-patients with ambulant treatment of out-patients, and found that 56% of ulcers treated by bed rest healed by two-thirds or more. Doll *et al.* (1958) showed that stopping smoking helped to heal gastric ulcers.

In the trial of carbenoxolone reported by Doll *et al.* (1962), of 30 patients receiving the drug 70% healed by two-thirds or more, while of 20 patients receiving dummy tablets 20% healed by two-thirds or more. The figure for complete healing in their trial was 37%.

Revers (1946) undertook the first clinical trial of an extract of liquorice in the treatment of gastric ulceration. He demonstrated a beneficial effect, but a large number of patients developed oedema and interest waned. Liquorice extracts contain glycyrrhizic acid; from this may be prepared the triterpenoid glycyrrhetinic acid. The latter acid has a low solubility in body fluids, and a water-soluble derivative has been synthesized—that is, the disodium salt of glycyrrhetinic acid hydrogen succinate (carbenoxolone sodium). It differs from preparations containing liquorice extracts, where the action cannot be attributed to any one constituent.

Method

All in-patients and out-patients attending the medical clinics of the hospital in whom a gastric ulcer was demonstrated radiologically were admitted to the trial, provided there were no contraindications. A double-blind trial was adopted; the clinician and radiologist, as well as the patient, were unaware of the precise medication being administered for the first two weeks and sometimes four weeks of treatment.

Forty sets of tablets were prepared, only 35 of which were used. Half of the tablets contained 50 mg. of carbenoxolone, together with starch *B.P.*, lactose *B.P.*, and peppermint oil. The remaining, or "dummy," tablets were identical in appearance. The sets of tablets were intermingled and each set was given a trial number. The key to the trial tablets was kept in a sealed envelope, which was not opened until the trial was completed. When patients were admitted to the trial they were given the trial tablets by the dispensary in numerical order. In this way a random allocation of patients to the active-tablet and dummy-tablet groups was obtained.

Treatment was started with the trial tablets within five days of the barium-meal examination demonstrating the ulcer crater. The patient took the trial tablets for two weeks, the first week's dosage being two tablets thrice daily, the second week's one tablet three times daily. Patient's were asked to take a normal diet, alkalis were not routinely prescribed, and no instructions were given about smoking and drinking.

After two weeks' treatment the patient attended for a restricted barium-meal examination. If the ulcer showed signs of healing, as demonstrated by reduction in size, the trial tablets were continued, but if the ulcer was unchanged in size, or larger, the patient was given known carbenoxolone tablets 50 mg. three times daily until the ulcer was radiologically healed. Patients attended at two-weekly intervals for restricted barium-meal examinations until the ulcer crater was healed.

Clinical Assessment

In-patients were seen by one of us (L. H.) at least twice a week, and out-patients were seen weekly. All patients were invited to comment freely on their symptoms and progress, and were examined fully at weekly intervals. At the same time the weight and blood-pressure were recorded and blood was taken for estimation of the electrolytes, serum proteins, prothrombin, and cell count. An electrocardiogram was taken weekly.

The information obtained was not passed on to the radiologist, who reported the size of the ulcer every two weeks during the investigation.

General Condition.—In the patients receiving dummy tablets the general condition was unchanged. In the carbenoxolone-treated patients there was an overall feeling of well-being, occasionally amounting to euphoria. At first this was attributed to a possible steroid-like effect of carbenoxolone, but as it persisted after treatment it was presumably due to alleviation of symptoms.

Abdominal Pain.—Relief of pain was not invariable in the early stages of healing but was always present in the later stages. On the other hand, symptomatic relief did not occur without reduction in the ulcer size on the subsequent radiological examination.

Tenderness was usually present in the smaller and more acute gastric ulcers and usually disappeared early in healing cases. Patients with large chronic ulcers seldom had much abdominal tenderness.

Weight.—In the carbenoxolone-treated patients a gain was usual, mainly due to fluid retention. Where the outcome of the treatment was satisfactory the appetite improved, and this contributed to the gain in weight, especially as there was no dietary modification or restriction.

Radiological Assessment

The barium-meal examinations were carried out on all patients with an image intensifier and closed-circuit television. Strict precautions were taken to reduce the radiation received

* Carbenoxolone sodium is available under the branded name of Biogastrone and is abbreviated to carbenoxolone throughout this paper.

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by the patients. The restricted barium-meal examination consisted of one or two pictures of the site of the ulcer crater, the radiographs being "coned down" to this site. The maximum diameter and depth of the ulcer crater were recorded at each examination, and the presence of other lesions such as duodenal ulcer and hiatus hernia was noted. Patients in the trial had a routine postero-anterior radiograph of the chest at the time of the first barium-meal examination, and this was repeated later in the trial if the patient complained of dyspnoea or showed clinical evidence of oedema.

Results

Thirty-five patients were admitted to the trial. One absconded and abandoned the treatment; he was subsequently found to have been taking dummy tablets. Later he responded satisfactorily to carbenoxolone but was not included in the final assessment.

The patients were divided into three groups according to their clinical progress: group A, who were free from pain and tenderness and showed a tendency to gain weight, which was maintained after treatment ceased; group B, who showed marked relief of symptoms and resolution of abdominal tenderness; and group C, who had no relief of symptoms and in whom tenderness persisted when present.

The radiological assessment was based on the size of the ulcer, the maximum diameter of the crater being used: in group 1 complete radiological healing had occurred, the ulcer crater being no longer visible; in group 2 the ulcer crater had decreased in size as shown by a reduction of the maximum diameter by 25% or more; and in group 3 there was no decrease in the maximum diameter of the ulcer crater.

The results after two weeks are shown in Table I. No clinical assessment was made for one patient on dummy tablets after two weeks, and no radiological assessment was made for one patient receiving carbenoxolone for two weeks, as these patients were unable to attend for assessment at the times indicated.

TABLE I.—*Results After Two Weeks on Double-blind Trial*

Clinical Assessment			Radiological Assessment		
Group	Carbenoxolone	Dummy	Group	Carbenoxolone	Dummy
A. Relieved	8	5	1. Healed	9	6
B. Improved	5	4	2. Improved	8	3
C. No relief	6	5	3. Unchanged	1	6
Total	19	14	Total	18	15

Analysis of Radiological Assessment Results

The numbers in each group are too small to allow a valid calculation of the significance of the difference between the two treatment groups in the three categories. Table II shows the results when the "healed" and "improved" categories are combined together. This demonstrates that healing in the patients treated with carbenoxolone is significantly greater than in those given dummy tablets ($P=0.023$, Fisher's test).

TABLE II

	Carbenoxolone	Dummy
Healed or improved (groups 1 and 2)	17	9
Unchanged (group 3)	1	6

Effect of Treatment on Ulcer Size

After two weeks' treatment the reduction in size of the ulcer craters was computed by measuring the diameter of the craters and comparing it with that found before treatment, and assuming the square of the diameter to be the best available index of the actual ulcer area.

The average healing in the two groups (plus or minus standard error) was dummy, $50\% \pm 13$; carbenoxolone, $88\% \pm 5$. The difference is again very significant ($P<0.01$) with the Aspin-Welch test for small samples with unequal variances (one tailed).

Complete Healing

After two weeks' treatment those patients who were not showing radiological improvement on the randomized treatments were given known carbenoxolone tablets as previously described. The patients were then radiologically examined at two-weekly intervals until healed.

Of the 34 patients in the trial eight were healed on dummy tablets alone—six after two weeks, one after four weeks, and one after six weeks. The remaining 26 received carbenoxolone tablets, either from the beginning or after the initial two-week double-blind period. The numbers of patients healed after various times on carbenoxolone therapy are shown in Table III. It will be seen that 92.3% of patients were eventually healed while on carbenoxolone therapy, 81% of these after six weeks' treatment.

TABLE III.—*Patients Healed on Carbenoxolone*

	Weeks on Carbenoxolone Therapy					
	2	4	6	8	10	12
No. healed	9	6	6	0	2	1
Cumulative No. healed	9	15	21	21	23	24
Per cent. healed	34·6	57·7	80·8	80·8	88·5	92·3

Side-effects

Salt-and-water Retention was the most frequent and important side-effect, and occurred in 31% of patients treated with carbenoxolone. It appeared within a week in three cases, but in others was not apparent for several weeks. Oedema of the ankles and pretibial area predominated in women, with only occasional rise in blood-pressure. Men showed much greater tendency to hypertension and seldom developed oedema. These features were soon reversed on discontinuing carbenoxolone for two or three days or by giving thiazide or mercurial diuretics. These side-effects sometimes caused breathlessness on exertion, and in several cases radiological changes appeared in the lungs. One male patient with mitral incompetence developed nocturnal dyspnoea, which cleared in under 48 hours after the tablets were stopped.

A female patient developed a severe "bursting" early-morning headache at the same time as she developed oedema of the legs. There were no fundal or E.E.G. changes, and these untoward features cleared up within four days of stopping the carbenoxolone.

A 72-year-old man showed a rise in blood-pressure during the second week of treatment, and this was followed by an epileptic fit lasting three minutes. The next day there was a slight left-sided facial weakness which lasted 24 hours. His E.E.G. taken 16 hours after the fit showed an excess of low-amplitude slow activity and spikes arising from the right fronto-temporal region. A week later the second E.E.G. had improved considerably, but there were changes consistent with generalized cerebrovascular disease.

In both these cases relief of abdominal pain and discomfort occurred in two or three days. Both ulcers showed rapid healing radiologically, although each had less than two weeks' treatment. It has been our impression that ulcers in patients who show obvious salt-and-water retention heal quickly.

Potassium Deficiency.—A slight fall in serum potassium occurred in patients on prolonged treatment but never produced clinical effects. Very low potassium levels, the lowest being

2.5 mEq/l., were found in four patients who were given chlorothiazide with a small amount of potassium in a combined tablet to prevent or reverse salt-and-water retention. These patients developed frequent extrasystoles and E.C.G. changes such as a prolonged Q–T interval with flat T waves, especially in the chest leads.

Increased Abdominal Pain occurred in three cases despite radiological reduction in the size of the ulcer. It was present only during the first two weeks of carbenoxolone treatment and then cleared up.

Heartburn often occurred in the first few cases but not when the tablets were taken during the course of a meal or when they were followed by a glass of milk. When they were swallowed under radiological control spasm of the lower oesophagus was found to be the explanation.

Cushingoid appearance presented in one patient. He gained weight, his face became round, and he developed a high facial colour. This subsided after treatment. There was no rise in blood-pressure, the glucose tolerance was normal, and the 17-ketogenic and 17-ketosteroid excretions were normal.

There was no fall in haemoglobin or alteration in the white-cell count in any of the cases during the period of the trial. Normal prothrombin levels were maintained in all cases.

Discussion

The period of only two weeks of trial tablets before a change of treatment was considered may be thought to be relatively short, but it was justified for two main reasons. First, the effects of salt-and-water retention could occur in two weeks, and it was felt that carbenoxolone must be shown to be significantly better than dummy treatment in this time. At this point the analysis of results shows carbenoxolone to be effective in reducing the ulcer size. Secondly, it was necessary to establish how often carbenoxolone would be preferred in known form during the second fortnight to carbenoxolone in unknown form during the first fortnight. In fact this occurred only once in 18 cases.

Principally the effectiveness of the drug was assessed for the purpose of this trial on the radiological evidence of reduction in the ulcer size. Healing was not regarded as complete if there was still a small dimple or niche at the site of the previously demonstrated ulcer crater. The final clinical assessment showed symptomatic relief to run parallel with radiological improvement, though this was not so in the first two weeks. During this period increased pain occasionally occurred, and in these cases the radiological findings were reassuring to both patient and physician.

Johnson *et al.* (1964), in a study of 4,201 cases of gastric ulcer, divided them into three types and recorded the percentage of patients in each type. We analysed our gastric ulcers similarly and found 53% of type I, 26% of type II, and 20% of type III. From the similarity of the percentages with those of Johnson *et al.* we conclude we have a representative group of ulcers.

The average ulcer diameter in the trial group was 1.2 cm., the largest being 4.2 cm. and the smallest 0.2 cm.

Of the 26 patients who received carbenoxolone for periods of from 10 days to 12 weeks nine (35%) had side-effects attributable to the drug. No patient had side-effects while receiving the dummy tablets. Salt-and-water retention was the most frequent finding, and was more obvious in the elderly and in those patients with cardiac or respiratory disease. The patient referred to earlier, with mitral incompetence, showed radiological features of pulmonary venous hypertension with oedema of the intralobular septa.

We have had the opportunity of seeing two patients with severe chronic bronchitis who had previously received carbenoxolone. In both cases congestive cardiac failure had developed ; such patients should therefore receive carbenoxolone only under strict supervision.

In the first few cases of fluid retention and rising blood-pressure 50 mg. of hydrochlorothiazide combined with 1 g. of potassium chloride was used three times a week. This diuretic regimen proved effective, but after some weeks it resulted in low levels of serum potassium in several patients. Mild cases of oedema could be corrected simply by omitting carbenoxolone for two or three days, and, furthermore, prolonged treatment without a diuretic resulted in only slight falls in the serum potassium level. Spironolactone proved inadequate as a diuretic by itself. After these findings a five- or six-day regime was used rather than prescribing large doses of potassium salts. Those at risk from salt-and-water retention took carbenoxolone in the usual dosage, but not on one or both days at the week-end. So long as the patients took three meals a day potassium supplements did not prove necessary.

The mode of action of carbenoxolone is not as yet understood. It is thought that the drug is rapidly absorbed in the stomach and effects healing by a direct action on the gastric mucosa. Recent work has shown that carbenoxolone is absent from the duodenal aspirate in the rat (Parke, 1964) and from the duodenal aspirate in man (Tarnoky, 1964). Carbenoxolone has been shown to be present in the blood, bile, and urine in man (Parke, 1964). This would also explain the ineffectiveness of the drug, in its present form, on duodenal ulcers.

That the recurrence rate of gastric ulcer is high is clear from previously reported long-term studies. Swynnerton and Tanner (1953) found that only 23.6% were without recurrence. Malmros and Hiertonn (1949) found only 21.9% symptom-free after 10 years. Qvigstad and Römcke (1946) found only 22% of patients symptom-free after an average follow-up of eight years, excluding pyloric ulcers, which they considered separately.

Since the trial was completed 24 patients have been followed up for periods from 6 to 12 months after the ulcer had healed. Of 18 patients treated with carbenoxolone the ulcer has recurred in eight, and of six patients who healed on dummy tablets one has had a recurrence, all at the site of the original ulcer. A subsequent analysis showed that the largest ulcer to heal on dummy tablets had a diameter of 0.9 cm., and the average diameter of this group was 0.4 cm.

In an attempt to prevent recurrence a maintenance dose of 25 mg. of carbenoxolone twice daily is at present being used.

It is emphasized that the healing of a gastric ulcer is only one aspect of the management of the condition. The gastric mucosa remains unstable, and recurrence at the same or other sites is always possible. The possibility of malignant changes must be borne in mind, though there is much controversy on how often this occurs. Martin and Lewis (1949) noted that 3% of their gastric-ulcer patients died from gastric carcinoma, but Swynnerton and Tanner (1953) concluded that if there is an association between gastric carcinoma and gastric ulcer it is due to a preference of both for the same type of degenerate mucosa. It would seem reasonable to hope that where a gastric ulcer heals and remains healed the risk of gastric carcinoma developing at this site is reduced, but it may, of course, develop in the gastric mucosa at another site.

Summary

A controlled double-blind trial of carbenoxolone in the treatment of radiologically confirmed gastric ulcer is reported. Radiological examination at two weeks showed a reduction in the ulcer area of 88% in the carbenoxolone group compared with 50% in those receiving dummy tablets ($P=0.01$). These results show that carbenoxolone is very effective in reducing the size of the ulcer.

The ulcer crater disappeared completely in 81% of the cases after six weeks and in 92% after 12 weeks of carbenoxolone.

The dose used in the trial was 100 mg. thrice daily for the first week and 50 mg. thrice daily for the second and subsequent weeks. Treatment should be continued until the ulcer has been shown radiologically to have healed. After complete healing a maintenance dose should be prescribed to prevent recurrence.

Attention is also drawn to the drug's side-effects, which occurred in 35% of patients, and of which salt-and-water retention is the most important. The side-effects led to the introduction of a five- or six-day regime in which carbenoxolone was omitted on one or both days at the week-end in those at risk. Since the introduction of this regime side-effects have been much less marked and less frequent.

Carbenoxolone has a specific effect, facilitating the healing of gastric ulcer, and is not merely yet another symptomatic measure.

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Clinical Comparison of Frusemide with Bendrofluazide, Mersalyl, and Ethacrynic Acid

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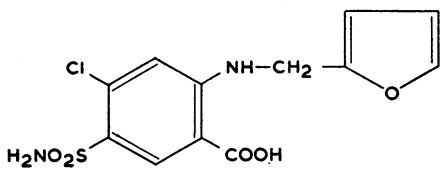
Frusemide (4 - chloro - *N* - (2 - furylmethyl) - 5 - sulphamoyl - anthranilic acid; Lasix) is a newly introduced diuretic agent which differs from all other such drugs at present in clinical use. Though a sulphonamide derivative (see Formula), frusemide does not closely resemble chlorthalidone or the benzothiadiazine drugs chemically or pharmacologically (Stewart, 1965). Frusemide may be given orally or parenterally; by either route it produces a rapid, short-lived diuresis due to inhibition of salt-and-water reabsorption in both proximal and distal portions of the renal tubule (Suzuki, Klütsch, and Heidland, 1964).



FRUSEMIDE

Several clinical trials in oedematous patients have shown that frusemide causes a greater natriuresis than other commonly used diuretic drugs. In doses ranging from 25 to 100 mg. it is superior to an equal dose of hydrochlorothiazide (Kleinfelder, 1963; Stokes and Nunn, 1964; Verel, Stentiford, Rahman, and Saynor, 1964). Stokes and Nunn (1964) found that 50 mg. of frusemide was more potent than 5 mg. of bendrofluazide or 200 mg. of chlorthalidone, and Verel *et al.* (1964) that 80 mg. of frusemide was more potent than mersalyl 2 ml., triamterene 200 mg., cyclopenthiazide 1 mg., or chlorthalidone 200 mg. Rosenkranz (1964) obtained a greater natriuretic response to frusemide, 1 mg./kg./day, than to 10 times this dose of acetazolamide.

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In the present trial frusemide was compared with ethacrynic acid, a very potent new diuretic, and with representative examples of the two commonly used types of diuretic drug, a benzothiadiazine and an organic mercurial. Frusemide was more efficacious than the benzothiadiazine or mercurial, and, in relation to natriuretic activity, caused little excess potassium loss.

Clinical Material and Methods

Eleven patients were studied. Each had been admitted to hospital for the treatment of oedema which had failed to improve with ordinary diuretic therapy. Relevant clinical data on these patients are shown in Table I. Of the 11 patients, one had portal hypertension, two had the nephrotic syndrome, and eight had congestive heart failure due to various causes. All but four patients had some impairment of renal function.

Each patient was weighed daily at 8 a.m., and accurate 8 a.m. to 8 a.m. fluid-balance charts were kept. The volume and sodium, potassium, and chloride content of each 24-hour collection of urine were measured. Serum and urinary electrolytes and serum urea nitrogen concentrations were determined on the Technicon AutoAnalyzer, and creatinine was measured by the method of Edwards and Whyte (1958).

Design of Clinical Trials

All patients were given a diet containing 3 g. of salt (approximately 50 mEq of Na) and allowed 1 litre of drinking-fluids each day. The diuretic drugs were given daily at 10 a.m. in a single oral dose unless otherwise stated, except spironolactone, which was given in four equal doses daily. In trials A, B, and C only one diuretic drug was given each day.

Trial A.—Three patients were given each of four different treatments in two-day periods for 32 days. The treatments