PAPERS AND ORIGINALS

Double-blind Trial of Carbenoxolone Sodium Capsules in Duodenal Ulcer Therapy, Based on Endoscopic Diagnosis and Follow-Up

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Summary

A high-dose double-blind trial of carbenoxolone sodium capsules (Duogastrone) in the treatment of duodenal ulceration was combined with endoscopic diagnosis and follow-up. Thirty-one ambulant patients with an endoscopically visible duodenal ulcer were allocated at random to a 12-week course of treatment with either carbenoxolone sodium 300 mg daily or a placebo. Symptomatic and endoscopic follow-up was performed at 2-4 weeks, 6-8 weeks, and 12-16 weeks. Carbenoxolone was shown to increase the rate of healing of duodenal ulcers in the early stages of treatment, but by 12 weeks there was no difference between the two groups. There was no significant difference in symptomatic improvement between the two groups at any stage of treatment. Side effects, especially hypokalaemia, were prominent in the patients treated with carbenoxolone. There was a poor relation between endoscopic and symptomatic improvement in patients on either form of treatment.

Introduction

Since the original report of its use in the treatment of peptic ulcer (Doll *et al.*, 1962) the value of carbenoxolone sodium tablets (Biogastrone) in the treatment of gastric ulcer has been well established (Doll *et al.*, 1965; Horwich and Galloway, 1965; Turpie and Thompson, 1965). The original study (Doll *et al.*, 1962) showed the tablet form of carbenoxolone to be ineffective in duodenal ulcer therapy, and more recently a positioned-release capsule (Duogastrone), which is said to prevent the release of the drug in the stomach, has been developed (Galloway, 1968).

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However, reports of its value in the treatment of duodenal ulcer based on radiological and symptomatic assessment have been conflicting. A number of trials have shown significant improvement with carbenoxolone (Craig *et al.*, 1967; Lawrence *et al.*, 1968; Amure, 1970), while in others reports have been equivocal or unfavourable (Colin-Jones *et al.*, 1968; Montgomery *et al.*, 1968; Cliff and Milton-Thompson, 1970).

These conflicting results may be partly due to the difficulties of radiological diagnosis in duodenal ulceration and subsequent radiological assessment of ulcer healing. Similarly, symptoms may provide an inaccurate guide to the presence of an ulcer or its subsequent course during treatment. Duodenoscopy is a safe and acceptable procedure for direct examination of the duodenal bulb (Salmon *et al.*, 1972), and we report a double-blind study of carbenoxolone sodium capsules in the treatment of duodenal ulcer, with patient selection and follow-up based on endoscopic examination of the duodenal bulb.

Method

Patients with clinical and radiological evidence of a duodenal ulcer were submitted to duodenoscopy. The examination technique has previously been described (Salmon *et al.*, 1972). The initial examination was always carried out with a forward viewing instrument so that the oesophagus and stomach could also be fully examined. After duodenal intubation 40 mg of hyoscine *N*-butylbromide was given intravenously to paralyse the duodenal bulb, which allows a more complete examination and facilitates photography. In some cases a complete view of all the bulb with the forward viewing instrument was not possible, and in these cases a lateral viewing instrument was also employed. In each patient the instrument which gave the better view was used at all subsequent examinations. At subsequent examinations endoscopic healing was recorded if there was a definite reduction in ulcer size or if duodenal inflammation or oedema was noticeably improved.

As the magnification produced by a fibreoptic system varies inversely with the distance between the object and the distal objective of the endoscope it was necessary to assess ulcer size at each examination. In most cases this could be done by comparison with an endoscopic landmark such as the superior

duodenal fold. If the ulcer was in a position where no such landmark was in view, then size was compared with the opened blades of the endoscopic biopsy forceps. The forceps were passed down the instrument, opened, and advanced on to the mucosa alongside the ulcer. At subsequent examinations any variation in ulcer size due to differences in magnification would be reflected in apparent changes in relevant size.

Patients with an endoscopically visible duodenal ulcer without evidence of gastric ulceration were admitted to the trial, but those over 70 years of age and those with cardiac or renal disease or receiving hypotensive treatment were excluded. Patients were allocated at random to a 12-week course of treatment with carbenoxolone sodium (Duogastrone) 300 mg daily in 75 mg capsules or identical capsules containing a placebo (lactose) to be taken four times daily 15-30 minutes before meals. Magnesium trisilicate tablets were supplied and patients asked to use them as their sole antacid and to record the number of tablets used. No dietary change was advised and patients were encouraged, so far as their symptoms would allow, to continue their normal daily routine.

Progress was assessed symptomatically and endoscopy repeated at 2-4 weeks, 6-8 weeks, and 12-14 weeks. Symptomatic assessment was based on frequency and severity of pain and consumption of antacid.

Results

Of 31 patients admitted to the trial 17 were in the active group and 14 in the placebo group (Table I). Twenty-six patients presented with dyspepsia alone and five with a haematemesis. Only five of the patients were women. In 11 cases (35%) barium-meal examination failed to show an ulcer crater and in two of these the duodenum was radiologically normal.

TABLE I—*Comparison of the Two Groups of Patients*

Carbenoxolone Group (n = 17)			Placebo Group (n = 14)		
Sex	Age (Years)	History (Years)	Sex	Age (Years)	History (Years)
M.	38	15	M.	35	5
M.	42	8	M.	59	25
M.	37	10	M.	66	7
M.	45	8	M.	59	5
M.	64	5	M.	46	10
M.	44	0	M.	33	3
M.	44	10	M.	33	2
M.	20	4	M.	26	5
M.	45	15	M.	58	1½
M.	23	1	M.	54	2
M.	59	20	M.	65	0
M.	64	25	M.	21	½
M.	43	25	F.	60	10
M.	41	2	F.	68	25
F.	38	1			
F.	31	3			
F.	44	4			
Mean	42·5	9·2		48·7	7·2

Forward and lateral viewing instruments were employed in 13 initial examinations. In four of these, duodenal intubation failed with the forward viewing instrument but was successful with the narrower, more flexible, lateral viewing instrument. In the other nine cases only limited views of the duodenal bulb were obtained with the forward viewing instrument.

One patient on carbenoxolone failed to attend for any further follow-up, and two other patients (1 from each treatment group) withdrew after the first follow-up. Two patients on carbenoxolone had treatment stopped but had a final assessment at 12 weeks. Only 8 out of a possible 68 (11·7%) endoscopic examinations in the active group and 7 out of 56 (12·5%) in the placebo group were missed.

Symptomatic Assessment.—Two patients, one in each treatment group, presented initially with a haematemesis and had no dyspeptic symptoms at any time. There was a small but statistically insignificant difference in the number of patients noting improvement in symptoms at two to four weeks in the carbenoxolone group (12/15) compared with the placebo group (7/13) (Table II). There was no difference in numbers noting symptomatic improvement in the two groups in the later stages of treatment, but at the final assessment 7 out of 14 patients in the active group compared with 3 out of 13 patients in the placebo group were free of pain ($P > 0.05$).

TABLE II—*Number of Patients showing Symptomatic Improvement during Treatment*

Stage of Treatment	Treatment Group		P
	Carbenoxolone	Placebo	
2-4 Weeks ..	12/15 (80%)	7/13 (54%)	N.S.
6-8 Weeks ..	11/13 (85%)	9/11 (82%)	N.S.
12-16 Weeks ..	12/14 (86%)	9/12 (75%)	N.S.
No pain ..	1	1	

N.S. = Not significant.

Endoscopic Assessment.—There was a statistically significant difference ($P < 0.01$) in the number of patients with endoscopic evidence of ulcer healing at 2-4 weeks in the carbenoxolone group (13/16) compared with the placebo group (4/13) (Table III). The difference was still significant ($P < 0.05$) at 6-8 weeks, but there was no difference between the two groups at the final assessment. In three patients on carbenoxolone there was a recurrence of ulceration at 12 weeks, following initial healing. At 12-16 weeks there was complete healing of the ulcer, with no visible duodenal inflammation in 8 out of 15 patients in the carbenoxolone group and 2 out of 12 patients in the placebo group ($P > 0.05$).

TABLE III—*Number of Patients showing Endoscopic Improvement during Treatment*

Stage of Treatment	Treatment Group		P
	Carbenoxolone	Placebo	
2-4 Weeks ..	13/16 (81%)	4/13 (31%)	<0·01
6-8 Weeks ..	9/12 (75%)	3/10 (30%)	<0·05
12-16 Weeks ..	10/15 (66%)	7/12 (58%)	N.S.

N.S. = Not significant.

Side Effects.—There were statistically significant changes in the mean plasma potassium ($P < 0.001$) and mean systolic blood pressure ($P < 0.025$) after only two weeks of treatment with carbenoxolone. There were less important changes in the mean diastolic pressure and weight, although the weight of three patients increased between 10 and 14 lb (4·5 and 6·5 kg) while on active drug. Five patients required potassium supplements and two required a thiazide diuretic. One patient developed symptoms of hypokalaemia despite potassium supplements, and treatment was stopped at 10 weeks. This patient had no symptoms and an apparently normal duodenal bulb at her final assessment. Another patient had treatment stopped inadvertantly at six weeks because of ankle oedema, but as her symptoms had improved and the ulcer had virtually healed treatment was not reinstituted and she had a normal duodenal bulb at 12 weeks. These were the only two women on carbenoxolone for longer than four weeks.

TABLE IV—*Mean Change (±S.D.) in Blood Values and in Weight Before and Two Weeks After starting Treatment*

	Treatment Group			
	Carbenoxolone		Placebo	
	Pre-treatment	Two Weeks	Pre-treatment	Two Weeks
Plasma potassium (mEq/l.) ..	3·94 (±0·21)	3·34 (±0·47)	3·98 (±0·28)	3·97 (±0·28)
Systolic B.P. (mm Hg)	115 (±11)	130 (±20)	120 (±13)	121 (±13)
Diastolic B.P. (mm Hg)	83 (±9)	86 (±10)	80 (±10)	81 (±11)
Weight lb	156 (±20)	160 (±16)	140 (±27)	140 (±24)
Weight kg	70·8 (±9·1)	72·6 (7·3)	63·5 (12·2)	63·5 (10·9)

Discussion

Previous trials of duodenal ulcer therapy have all been based on symptomatic and radiological assessment. Duodenoscopy provides a third and possibly more accurate method of diagnosis and follow-up of duodenal ulcers. In an early trial of carbenoxolone in duodenal ulcer therapy (Colin-Jones *et al.*, 1968) 142 patients were referred for inclusion in the trial but 82 were unsuitable on radiological grounds. In the present study no patient entered into the trial had to be excluded because of unsatisfactory follow-up examinations. In a retrospective survey of 400 duodenoscopies, endoscopic and radiological findings were compared in those cases in which the two procedures had been performed within six weeks of each other, and in 60% the interval was less than two weeks. Twenty-one endoscopic findings in the duodenum were not diagnosed by radiology, and conversely duodenal lesions were diagnosed radiologically but not by endoscopy in nine cases, representing 28% disagreement between the two procedures in the diagnosis of duodenal morbidity alone. The commonest finding in the endoscopic group which was not diagnosed radiologically was a duodenal ulcer crater, and in five of the 17 cases the barium-meal picture was normal and the patient would otherwise have been labelled as *x*-ray-negative dyspepsia. It also represents a group of patients who would have been missed in any previous trial of duodenal ulcer therapy.

If endoscopic assessment is to be used in the evaluation of ulcer therapy, then the procedure must be acceptable to the patient. Only 15 out of 124 scheduled examinations were missed in this study, and so far as we could ascertain none of these were missed because of the discomfort of the endoscopic procedure. Fifty other patients who had had only one endoscopic examination were sent a postal questionnaire, and endoscopy appeared as acceptable as a barium-meal examination and far more acceptable than the passage of a nasogastric tube (Brown *et al.*, 1972).

RELATION BETWEEN ENDOSCOPIC AND SYMPTOMATIC ASSESSMENTS

The mechanism of duodenal ulcer pain and the anatomical site from which it is referred are still unknown. Most theories incriminate gastric acid, abnormal intestinal motility, duodenal inflammation, or a combination of these as the basic causative factor, and the oesophagus, stomach, and duodenum have all been claimed to be the site from which pain is referred. The problem has been reviewed in detail (Ivy *et al.*, 1950; Bockus, 1963).

Hurst (1911) postulated that dyspeptic symptoms were due to altered motility and increased tone in the stomach. Radiological and pressure studies have shown that the pain of duodenal ulcer occurred at the same time as increasing motility and contraction of the duodenal bulb (Wilson, 1928; Patterson and Sandweiss, 1942). Pain has also been related to increased gastric contractions (Ruffin *et al.*, 1953).

The production of epigastric pain by the application of acid to the gastric or duodenal mucosa of normal subjects and patients with a peptic ulcer has been extensively studied (Talma, 1884; Palmer, 1926; Smith, 1955). Epigastric pain has also been produced by distention of the lower oesophagus (Polland and Bloomfield, 1931) and by application of acid to the lower oesophagus in patients with oesophagitis (Bernstein and Baker, 1958) or a duodenal ulcer (Earlam, 1970). In ulcer patients with pain localized to the epigastrium perfusion of the lower oesophagus with dilute acid produced identical pain in most patients. The same procedure failed to produce pain in those with ill-localized dyspepsia.

As the activity of a duodenal ulcer can be accurately assessed by duodenoscopy the natural history of the disease and especially the relation of symptoms to the presence or absence of an ulcer crater can now be studied in more detail. A comparison of endoscopic findings with symptomatic assessment at each stage of treatment is given in Table V. Endoscopic and symptomatic improvement were not synchronous. In those patients with no endoscopic improvement, in both treatment groups, the majority claimed symptomatic improvement. This may have been due to a placebo effect in the early stages, but the disparity was still marked at 12 weeks. Some patients with endoscopic evidence of ulcer healing noted no improvement in symptoms. Of the 10 patients who had a normal duodenal bulb at 12 weeks, two had had no dyspeptic symptoms at any time. The remaining eight noted some symptomatic improvement but only three were free from pain. The poor correlation between ulcer healing and symptomatic improvement suggests that, at least in a proportion of cases, the pain of a duodenal ulcer is not caused by the ulcer itself.

TABLE V—*Comparison of Symptoms and Endoscopic Findings in the Two Groups of Patients*

Stage of Treatment	Carbenoxolone Group				Placebo Group			
Endoscopy:	Healing		No Change		Healing		No Change	
Symptoms:	I.	N.C.	I.	N.C.	I.	N.C.	I.	N.C.
2-4 Weeks ..	9	3	3	0	3	1	4	4
6-8 Weeks ..	7	1	2	1	2	0	6	1
12-16 Weeks ..	8	1	4	1	5	1	4	1

I. = Improved. N.C. = No change.

CARBENOXOLONE AND DUODENAL ULCER

The results of the present study show that carbenoxolone sodium increased the rate of healing of duodenal ulcers in the early stages of treatment. Because of the accuracy of endoscopic follow-up this is the first time that any drug has been shown to affect the actual rate of duodenal ulcer healing. By 12 weeks, however, there was no difference between the carbenoxolone or placebo treated groups, mainly because ulcers treated with placebo healed more slowly, reflecting the natural tendency of duodenal ulcers to remit, but also because ulcers recurred in three patients on carbenoxolone, in whom there had been initial healing. In those patients with endoscopic improvement at 12 weeks there was complete healing of the ulcer in eight of the carbenoxolone group and only two of the placebo group, but this difference just failed to reach statistical significance. Complete healing may be important in the long-term prognosis of duodenal ulcer, but a larger study for a much longer time would be required to assess subsequent relapse rate and occurrence of duodenal ulcer complications. As there was no significant difference in ulcer healing between the two groups at 12 weeks, symptoms remain, especially from the patient's point of view, an important criterion in assessing the value of the drug. Although carbenoxolone increased early ulcer healing, there was no significant difference in symptomatic improvement between the two groups at any stage of treatment. This difference was, however, never to the detriment of carbonoxolone sodium.

The side effects of carbenoxolone include oedema, hypertension, and hypokalaemia, probably due to an aldosterone-like effect of the drug (Baron and Nabarro, 1968; Hausmann and Tarnoky, 1968). Rarely, the hypokalaemia may cause a myopathy and nephropathy (Mitchell, 1971). The dose of carbenoxolone used in this study was higher than has previously been recommended for duodenal ulcer therapy, and side effects might therefore be expected to be more prominent. The changes in mean plasma potassium and mean systolic blood pressure are shown in Table IV. Of the 17 patients in the carbenoxolone group, three gained between 10 and 14 lb (4·5 and 6·4 kg) in weight and five required potassium supplements because of a plasma potassium below 3·0 mEq/l. One patient developed symptoms of hypokalaemia with a plasma potassium of 1·8 mEq/l. despite potassium supplements of 32 mEq/day.

In this study of a high dose of carbenoxolone sodium capsules in duodenal ulcer therapy we have shown that the drug increases

the early healing of duodenal ulcers without significantly affecting symptoms but produces frequent severe side effects. On the evidence of this trial the use of such a high dose cannot be recommended, but if its effect on ulcer healing is still apparent at a reduced (the normal) dose with the likelihood of less pronounced side effects, then carbenoxolone may have a place in duodenal ulcer therapy.

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Effects of Haemodialysis on Bone in Chronic Renal Failure

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Summary

Quantitative histological studies have been done on 80 sequential bone biopsies taken at yearly intervals from 37 patients with chronic renal failure on long-term haemodialysis treatment. Twenty-three patients were studied at the start of dialysis, and in about half the bone was abnormal. During dialysis mean osteoid area and the maximum number of unmineralized osteoid lamellae increased, and mineralized bone area decreased. The loss of bone during dialysis was also reflected in reduction of the width of individual trabeculae. These trends were less obvious in patients already established on dialysis at the time of the initial biopsy. The course of osteitis fibrosa appeared to be unaffected by dialysis.

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Introduction

Bone disease is a common complication of chronic renal failure and is not always cured by long-term haemodialysis (Pendras and Erickson, 1966; Harrison, 1968; Katz *et al.*, 1969; Kaye *et al.*, 1969; Kleeman *et al.*, 1970; Siddiqui and Kerr, 1971). Before dialysis bone disease rarely causes symptoms. Radiographic appearances and plasma biochemistry are poor indices of renal osteodystrophy, particularly in dialysed patients, and diagnosis is imprecise without bone biopsy (Katz *et al.*, 1969; Bishop, *et al.*, 1971). Histologically there may be a combination of osteomalacia, osteitis fibrosa, and osteosclerosis (Follis and Jackson, 1943). Osteoporosis is rare (Garner and Ball, 1966; Kyle, 1969; Stanbury, 1969).

After dialysis treatment has been started the bone disorder may be similar to that affecting non-dialysed patients (Pendras, 1969). However, dialysed patients can develop a different form of disease attributed to dialysis itself (Harrison, 1968; Siddiqui and Kerr, 1971; Woods *et al.*, 1972). In this disorder pain and unhealed pathological fractures are common; there is periarticular osteoporosis on radiography and histological examination shows a reduced volume of mineralized bone, increased osteoid, and little osteitis fibrosa (Siddiqui and Kerr, 1971). In Oxford florid bone disease in dialysed patients is rare. Histological abnormalities are more frequent (Woods *et al.*, 1972) but less often defined by measurement of plasma calcium, phosphate, and alkaline phosphatase than in non-dialysed patients.

We have studied the histological changes in sequential bone biopsy specimens from dialysed patients from the beginning of treatment to decide whether the natural history of bone disease due to chronic renal failure hitherto described (Stanbury and Lumb, 1966) is altered by prolonged haemodialysis.