Effect of low dosage of carbenoxolone sodium on gastric ulcer healing and acid secretion

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Carbenoxolone sodium has been shown to cause significant healing of benign gastric ulcers in three short-term, double-blind clinical trials restricted to ambulant outpatients (Doll, Hill, Hutton, and Underwood, 1962; Doll, Hill, and Hutton, 1965; Doll, Langman, and Shawdon, 1968). The degree of healing in the treated groups was similar to that obtained with inpatient treatment, including bed rest, without carbenoxolone (Doll and Pygott, 1952, 1954; Doll, Jones, and Pygott, 1958). The drug does not appear to act satisfactorily when used in inpatients alone (Middleton, Cooke, Stephen, and Skyring, 1965). Most trials have established the efficacy of the drug in a dosage of 100 mg tds but significant side effects may arise (Turpie and Thompson, 1965) and the manufacturers now recommend a dose of 50 mg tds. This paper reports a double-blind trial of the drug in ambulant outpatients using a low dose regime. During the course of this work Doll *et al* (1968) concluded independently that fewer side effects occur using the lower dose, but less satisfactory healing results.

Healing in previous trials has usually been measured radiologically. The inherent inaccuracies of the barium meal examination can be minimized by the complementary use of endoscopy, and, therefore, in this study both methods were used to assess healing. Although endoscopy is often used in routine clinical practice in the management of gastric ulcers, only in the study of Bank, Marks, Palmer, Groll, and Van Eldick (1967) has it previously been used in a short-term trial. These authors also reported that acid secretion was reduced in all patients, with the greatest fall occurring in the carbenoxolone-treated group. Before this, little information had been available about the effect of the drug on gastric acid secretion and its relation to ulcer healing. The present study provides further data on this aspect. In addition a note has been made of the significant side effects of the drug, and healing has been correlated with symptoms, age, sex, initial ulcer size, gastric acidity, blood group, and secretor status.

MATERIAL AND METHODS

Fifty-six outpatients with a gastric ulcer who were under the age of 70, without evidence of serious disease of the heart, liver, or kidneys, with a resting diastolic blood pressure below 100 mm Hg, were reviewed with a further barium meal and endoscopy; an augmented histamine test was also performed. Thirteen were then excluded because the maximal profile of the ulcer measured less than 10 sq mm in area. Five more were excluded because of possible malignancy. Thirty-eight patients were entered for the trial and referred to a special gastric ulcer clinic, but one failed to attend for further investigation and one was found to have a malignant ulcer, leaving 36 patients completing the trial period.

Those selected for the trial were started on treatment within five days of the screening tests. They were then treated for five weeks with either carbenoxolone in a dosage of 100 mg tds for one week, followed by 50 mg tds for four weeks, or an indistinguishable placebo. Allocation was random according to a prearranged schedule known only to Biorex Laboratories. The patients were asked to lead a normal life, and to eat a normal diet if possible; they were prescribed unrestricted antacids for symptomatic relief. No advice was given about smoking. They were seen weekly, when they were supplied with prepacked tablets for the following week. At each visit, the frequency and severity of symptoms were noted, the patient was weighed, examined, and the blood pressure was recorded. In addition, the erythrocyte sedimentation rate, haemoglobin concentration, white cell count, packed cell volume, prothrombin time, serum concentrations of sodium, potassium, bicarbonate, and urea, and serum activity of glutamic-oxaloacetic and glutamic-pyruvic transaminases were estimated. At the end of the five-week trial period a second barium meal, endoscopy, and augmented histamine test were carried out. There were exactly six weeks between barium meal studies in each patient. The two groups have proved to be similar in respect of age, sex, ulcer size, length of history, blood group, and secretor status (Table I). The mean initial ulcer size was slightly greater in the control group, but this difference was not statistically significant.

The large standard deviation of the initial ulcer size reflects a positive skewness of the distribution.

BARIUM MEALS These were carried out at the beginning

TABLE I
CHARACTERISTICS OF THE TWO GROUPS OF PATIENTS

	Control Group	Carbenoxolone Group
Age (yr)		
Mean	49.7	49.0
Standard deviation	±11.7	±10.2
Sex		
Male	12	13
Female	5	6
Ulcer site		
Upper third	6	10
Middle third	8	8
Prepyloric	3	1
Initial ulcer size (sq mm)		
Mean	104.6	77.1
Standard deviation	±92.7	±72.4
Length of history		
Mean	7 years 6 months	7 years 2 months
Standard deviation	± 7.0	± 7.3
Blood group ^{1,2}	A O B AB	A O B AB
	7 8 - -	6 10 1 1
Secretors ^{1,2}	12	12
Non-secretors	3	6

¹Only 33 patients had these investigations carried out.

²Numbers of patients.

and end of the trial, if possible by the same radiologist. Similar profile views were obtained of the maximum ulcer niche. The areas of the ulcer outlines were traced onto paper and measured by superimposing a grid squared in millimetres (Cocking and MacCaig, 1968).

ENDOSCOPY A Hirschowitz gastroduodenal fibroscope was used for all endoscopic examinations and these were carried out on each patient within three days of a corresponding barium meal. The endoscopic appearances were recorded, described, and sometimes drawn, and at the time this was done the radiological report was not known. If the ulcer site could not be seen because of technical difficulties, this was recorded as a failed examination. There were seven such failures among the patients finally included in the trial, and the overall failure rate for the 56 patients reviewed was 16%. There were no complications.

ACID SECRETION This was estimated at the beginning and the end of the trial period, by the augmented histamine test (Kay, 1953). The tube was not sited fluoroscopically as this has been shown to be inessential (Johnston and Jepson, 1967). The results in three patients in the carbenoxolone-treated group were excluded; two patients had complete achlorhydria and the third could not tolerate the tube on the second occasion.

PEPSIN SECRETION This was estimated in a few patients by the method of Hunt (1948).

BLOOD ANALYSES The erythrocyte sedimentation rate was determined by the Westergren method; haemoglobin concentration photometrically by the cyanmethaemoglobin method of Crosby, Munn, and Furth (1954); white cell count on the EEL blood cell counter; packed cell volume by the Wintrobe method; prothrombin time by the one-stage method of Quick (1945); serum electrolytes and urea concentration on the Technicon AutoAnalyzer; serum transaminases by the method of King (1958); and blood group and secretor status by the methods described by Dunsford and Bowley (1967).

RESULTS

HEALING The barium meal assessment of healing is recorded in Table II. The difference between the two groups was not statistically significant though the trend was in favour of the treated group, in which more ulcers healed completely and fewer increased in size.

Endoscopic assessment was not sufficient accurately to determine partial degrees of healing but the presence or absence of complete healing could be accurately observed. Among the 13 ulcers thought to be healed radiologically, two were not visualized endoscopically (failed examination), seven were healed, and the remaining four were seen endoscopically not to be healed, three of the latter, including one which showed no evidence of healing at all, were in the control group. In contrast, two ulcers were shown endoscopically to be healed, though a small shadow persisted on barium meal. Hence radiological assessment of complete healing is liable to error, and this error can often be corrected by the additional use of endoscopy. Partial healing measured radiologically is similarly inaccurate, but correction by endoscopy is inappropriate in this group as endoscopy itself cannot assess small changes in ulcer size. Table II shows the results of combined assessment; the previous radiological assessment has been corrected for the presence or absence of complete healing as shown endoscopically. The difference between the control and treated groups was significant ($\chi^2_2 = 7.91$, $P < 0.025$), when those ulcers showing no evidence of healing were considered as a single group.

When the degree of healing was assessed by a simple scale (1 = healed, 2 = healing, 3 = no

TABLE II
ASSESSMENT OF HEALING

		Ulcer			
		Healed	Healing	No Change	Larger
Barium meal	Control	5	7	1	4
	Carbenoxolone	8	10	1	0
Combined	Control	2	9	2	4
	Carbenoxolone	9	9	1	0
					Total
					17
					19
					17
					19

TABLE III

COMPARATIVE RESULTS OF GASTRIC ULCER HEALING

Author	No. of Patients	Outpatient (O) or Inpatient (I)	Carbenoxolone	Average Percentage Reduction in Size of Ulcer Niche	Percentage of Patients with Healed Ulcers
Doll and Pygott (1952)	32	O	No	15	9
	32	I	No	59	16
Doll and Pygott (1954)	64	I	No	57	20
Doll <i>et al</i> (1958)	104	I	No	66	23
Doll <i>et al</i> (1962)	20	O	No	35	5
	30	O	Yes	72	37
Doll <i>et al</i> (1965)	22	O	No	39	27
	24	O	Yes	78	42
Middleton <i>et al</i> (1965)	16	I	No	72	31
	15	I	Yes	62	27
Present series	17	O	No	46	12
(corrected by endoscopy)	19	O	Yes	70	47

change, 4 = larger), and variability due to age and sex was removed, the average grading for the control group was 2.4 and for the treated group 1.6. The difference between the groups was again significant ($P < 0.01$).

Complete healing when assessed by radiology combined with endoscopy could be measured with the greatest accuracy. The difference between the proportion of ulcers showing complete healing in the control and treated groups was statistically significant (one-sided Fisher exact test, $P = 0.023$), and the results are compared with other figures in Table III.

Healing in ulcers can only be measured by changes in true ulcer size which is not itself accurately represented by profile views obtained at a barium meal. It follows that accurate measurement of ulcer profiles and their conversion into percentage healing will not always represent true ulcer healing. This has been borne out by the endoscopic findings. Although the figures for percentage healing are given for comparison with other trials in Table III, in the present study this method of assessment had little value.

ACID SECRETION Baron (1963) has shown that peak acid output is the most reproducible assessment of gastric acidity. According to Kay (1967), the augmented histamine response (AHR) correlates well with the peak acid output, and the one-hour maximal acid output. Therefore, the acid secretion during the 30-minute period beginning 15 minutes after a histamine injection was the basis of the results in Table IV. Mean levels for the augmented histamine response for both groups lie in the lower normal range (Kay, 1967). The initial augmented histamine response in the carbenoxolone-treated group was lower than in the control group, but the difference was not statistically significant. Mean levels fell after treatment in both groups.

Acid secretion was also correlated with the degree

TABLE IV

ACID SECRETION

		Mean Augmented Histamine Response (m-equiv/30 min)	Standard Deviation	Mean Percentage Reduction
Control (17)	Before treatment	9.6	± 6.5	12.8
	After treatment	6.3	± 5.1	
Carbenoxolone (16)	Before treatment	5.8	± 6.5	15.6
	After treatment	3.9	± 4.9	

of ulcer healing. The groups of control patients showed similar mean percentage reductions of acid secretion of 9 to 16%, irrespective of whether their ulcers healed completely, partially, or showed no response to treatment. Patients showing partial healing on carbenoxolone had 11% reduction, but those whose ulcers healed completely had a mean percentage reduction of 34%.

The degree of healing bore no relation to the initial gastric acidity.

Two patients had complete achlorhydria. One of these had two tests, and at operation a benign ulcer was removed. The other had three test meals, each at six weeks' interval, and nine months after his ulcer healed he remains well. In none of these tests could any free acid be titrated, and at no time did the pH fall by more than half a unit or below a level of 6.5. In the third test on one patient, pepsin was also estimated, and a low output of pepsin (1,200 Hunt units in 30 minutes) was detected. The presence of pepsin in this test, and the absence of bile from all but one of the tests, confirm that the tube was probably situated in the stomach. These two achlorhydric patients were excluded from the above results;

a third patient was excluded who could not tolerate the second test. All these excluded patients were in the carbenoxolone group.

PEPSIN SECRETION Pepsin estimations were carried out in a number of patients, but only in seven was a full series of results obtained before and after treatment. In all cases, the pepsin secretion tended to follow acid secretion, but there was no difference between the studies in the three patients on placebo compared with the four taking carbenoxolone.

SIDE EFFECTS The common side effects noted in the past have been weight gain, heartburn, oedema, hypertension, and hypokalaemia. The side effects occurring in the present study are recorded in Table V. Mean weight gain was significantly greater in the carbenoxolone-treated group (*t* test, 34 degrees of freedom, $t = 2.09$, $P < 0.05$), but the other individual side effects and the side effects considered as a whole were not significantly greater in the treated group.

TABLE V

SIDE EFFECTS

	Mean Weight Gain (kg)	No. Patients with			
		Heart-burn	Oedema	Hypertension ¹	Hypokalaemia
Control	0.3	4	0	1	1
Carbenoxolone	1.8	2	3	3	3
Significance	$P < 0.05$	NS	NS	NS	NS

¹Diastolic blood pressure of 100 mg Hg or more

Hypokalaemia was reversed by adding potassium supplements; only one patient with oedema and another with hypertension required treatment with oral diuretics, because in the remainder these side effects did not persist for more than one visit. In one patient in the carbenoxolone group, the serum sodium level rose from 148 to 161 m-equiv/litre. There was a transient rise of the serum glutamic-oxaloacetic transaminase in one control patient, and of the serum glutamic-pyruvic transaminase in one carbenoxolone-treated patient. The only other change found among the investigations carried out was in the packed cell volume (Table VI). This fell to a highly significant degree (paired *t* test, 16 degrees of freedom, $t = 5.06$, $P < 0.001$) in the treated group at the end of the first week during which a dosage of 100 mg tds was used. There was no significant change in the packed cell volume in the control group during the same period. The difference between the two groups at the end of the first week of treatment was again highly significant (*t* test, 34 degrees of freedom, $t = 4.58$, $P < 0.001$).

TABLE VI

CHANGES IN PCV

	Mean Initial PCV (%)	Mean PCV at End of First Week of Treatment with 100 mg tds (%)	Mean PCV at End of Fifth Week of Treatment with 50 mg tds (%)
Control	43.8	44.3	44.1
Carbenoxolone	45.1	42.3	45.2

During the next four weeks, on the lower dose of carbenoxolone, the packed cell volume returned to its original level in the treated group, whereas no change occurred in the control group.

CORRELATION WITH HEALING

SYMPTOMS There was no significant relationship in either the control or carbenoxolone groups between the symptomatic response and the presence or absence of healing of the ulcer. When the two groups were compared as a whole (Table VII) there was significantly greater symptomatic improvement in the treated groups, if the patients with no symptoms throughout were disregarded ($\chi^2_2 = 6.19$, $P < 0.05$). In any individual patient, however, symptoms were not a guide to healing of the ulcer.

TABLE VII

SYMPTOMS

Symptoms					
	Improved Completely	Improved Partially	Unchanged	Worse	No Dyspepsia Throughout
Control (17)	0	3	12	1	1
Carbenoxolone (19)	5	3	8	0	3

AGE AND SEX When the degree of healing was assessed by a simple score (1 = healed, 2 = healing, 3 = no change, 4 = larger) and related to age the patients under the age of 50 obtained a score of 2.2 whereas over this age the score was 1.8. The ulcers of the older patients, therefore, tended to heal better. The elderly males appeared to fare best, the scores for the control and treated groups of elderly males being 2.4 and 1.3 respectively. The numbers, however, were too small to attach statistical significance to these findings.

INITIAL ULCER SIZE The initial mean ulcer size in the carbenoxolone group was slightly less than in the control group. When only those patients with larger ulcers (> 90 sq mm in area) in both groups were considered, those in the carbenoxolone group again showed greater healing. The slight difference in initial mean ulcer size did not account for the

different behaviour of the carbenoxolone and control groups as a whole. Nor did response to treatment depend on initial ulcer size in either group.

BLOOD GROUP AND SECRETOR STATUS In 33 patients the blood group and secretor status were determined. The distribution of the blood groups and secretor status was similar in the control and treated groups. When acid secretion and response to treatment were related to secretor status of the patients no difference was found between the secretors and the non-secretors. Similarly, no difference in healing was noted between the patients of blood group A and those of blood group B.

DISCUSSION

This trial has shown that carbenoxolone is effective in healing gastric ulcers in ambulant outpatients using a low dosage regime. Healing was most accurately assessed using a combination of radiology and endoscopy. The limitations of radiology used alone and the value of the complementary use of endoscopy in assessing ulcer healing have been more fully discussed elsewhere (Cocking and MacCaig, 1968).

The present results using a low dosage regime for five weeks do not differ greatly from previous results obtained using a dose of 100 mg tds for four weeks. However, another recent trial over four weeks (Doll *et al.*, 1968), in which both high and low dose regimes were compared, has concluded that less healing results from the lower dosage. In numerous controlled trials reported since 1952 (Table III) varying proportions of 16 to 31% of ulcers have healed on treatment with bed rest in hospital, with or without the additional use of carbenoxolone. In outpatients treated with carbenoxolone 37 to 47% of ulcers have healed completely. Carbenoxolone appears to exert its maximum effect in ambulant outpatients. One explanation of this is that when used on inpatients, the therapeutic advantage of the drug may be masked by healing resulting from bed rest alone (Jones, 1966). Alternatively, carbenoxolone may actually act optimally in ambulant patients. The drug is largely excreted conjugated in the bile and biliary reflux through the pylorus is greatest in ambulant patients (Kilby, 1967). However, it is not known if the biliary conjugated form of the drug has a local healing action on gastric ulcers.

The present study suggests that there is a tendency for acid secretion to fall in patients with active gastric ulcers. Acid secretion has been said to rise as gastric ulcers heal (Capper, 1967) but surprisingly there is little evidence to support this. Watkinson (1951) found conflicting results in nocturnal acid

secretion studies in five patients whose ulcers healed, as in two the secretion rose, but in the remainder it was difficult to draw any conclusion. Marks and Shay (1959) reported a rise of acid secretion occurring with ulcer healing in two patients. Bank *et al.* (1967) reported on 19 patients in whom there was a tendency for acid secretion to fall during a two- or four-week treatment period; there was a greater fall in the carbenoxolone-treated group, but changes in acid secretion were not correlated with the degree of healing.

The relationship between acid secretion and histological appearance of gastric mucosa is well documented (Joske, Finckh, and Wood, 1965; Bock, Richards, and Witts, 1963), less acid being secreted in the presence of atrophic gastritis. The fall in acid secretion that occurred in the present study and that of Bank *et al.* (1967) is compatible with the theory of increasing atrophic gastritis due to reflux of duodenal contents, with subsequent ulceration (Du Plessis, 1965; Capper, Butler, Buckler, and Hallet, 1966). The present study has not ascertained if gastric acidity rises to normal after the ulcer is completely healed. Should this be so, it would suggest that reversal of the atrophic epithelium to normal parietal-cell containing epithelium also lags behind ulcer healing. Hurst and Venables (1929), using fractional test meals, showed that gastric acidity rose in each of 13 patients after gastric ulcers had healed. The changes in acid secretion in relation to gastric ulcer healing require reappraisal.

Two patients in this study had histamine-fast achlorhydria though one was able to secrete pepsin. This finding indicates that a benign gastric ulcer can arise and persist in the absence of free hydrochloric acid contrary to previous beliefs (Watkinson, 1951; Doll, 1964). We would, however, agree with Johnson and Jepson (1967) that achlorhydria in the presence of a gastric ulcer should always arouse the suspicion of malignancy.

Despite the significant degree of healing found in the present study, the side effects encountered were few and not serious. Oedema, hypertension, and hypokalaemia each occurred in 16% of patients and this compares favourably with previous reports in which an incidence of up to 30% was recorded (Doll *et al.*, 1962, 1965, and 1968; Horwich and Galloway, 1965; Turpie and Thomson, 1965; Bank *et al.*, 1967; Montgomery, 1967). A most interesting observation was the fall in packed cell volume which occurred in the carbenoxolone-treated patients during the first week of treatment on a dose of 100 mg tds, and the subsequent return to the original value over the remaining weeks on the lower dose. This implies that fluid retention is a more likely phenomenon on the higher dose, and this tendency

was confirmed by the finding that weight rose significantly in the carbenoxolone-treated group. The fall in packed cell volume suggests that haemodilution was occurring and supports those who postulate that carbenoxolone may have an aldosterone-like action causing sodium retention (Hausmann and Tarnoky, 1968; Baron, Nabarro, Guercen, and Jackson, 1968). Further studies by Doll *et al* (1968) have shown that the action of carbenoxolone is inhibited by the concurrent use of spironolactone but not by thiazide diuretics. The aldosterone-like activity and healing properties of carbenoxolone appear to be closely related though not necessarily the same.

Attempts to correlate healing with symptoms, initial ulcer size, initial gastric acidity, blood group, and secretor status have given negative results. This trial has again shown that symptoms bear no relation to healing in the individual patient. There is the suggestion, however, that the drug may have its greatest value among older patients, and possibly more in men than in women.

SUMMARY

A double-blind trial of low doses of carbenoxolone sodium has been carried out on 36 ambulant out-patients with benign gastric ulcers. Significantly, more ulcers healed in the treated group. The degree of healing was similar to that in previous trials which used a high dose regime over a slightly shorter period. The incidence of side effects was low. The use of endoscopy has illustrated the imperfections of radiological interpretation alone, and the combined assessment of complete healing is considered to be the most reliable measure of healing of gastric ulcers. There was a tendency for acid secretion to fall over the trial period both in control and treated groups. The implications of this are discussed. Two patients with benign ulcers had histamine-fast achlorhydria. Some evidence in support of an aldosterone-like action is offered.

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