Clinical trial of a new carbenoxolone analogue (BX24), zinc sulphate, and vitamin A in the treatment of gastric ulcer

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SUMMARY The effects of a new carbenoxolone analogue (BX24), zinc sulphate, and vitamin A on the healing of gastric ulcer have been assessed in a multifactorial clinical trial conducted in out-patients treated for four weeks.

Forty-eight patients completed the trial. Three groups of eight patients were given respectively 300, 600, and 1 200 mg of BX24 daily and were compared with 24 patients who were given 300 mg of carbenoxolone sodium daily. The size of the ulcer niche was reduced on average by 14.6% in the eight patients given BX24 300 mg daily, by 47.6% in the patients given 600 mg daily, and by 51.0% in the patients given 1 200 mg daily. In the patients given carbenoxolone the size of the niche was reduced by 68.9%. These results were compared with those obtained previously with carbenoxolone and inert tablets and it was concluded that BX24 is without clinically useful effect in the doses used.

Eleven of the 24 patients (46%) treated with carbenoxolone sodium developed side effects due to fluid retention and electrolyte disturbances. None of the patients given BX24 experienced such effects.

In addition to carbenoxolone or BX24, 24 patients were given zinc sulphate, 660 mg daily, and in 24 patients these tablets were withheld. Among the patients given carbenoxolone the reduction in the size of the niche was much the same irrespective of whether or not the patients received zinc sulphate. Among the 12 patients given BX24 with zinc sulphate the ulcer healed completely in four and, on average, the size of the niche was reduced by 53.5%, compared with 21.9% in the 12 patients given BX24 alone. This difference is not statistically significant but the possibility of a beneficial effect from zinc is not excluded. No side effects attributable to zinc were observed.

Twenty-four patients were also given vitamin A, 50 000 units daily, and in 24 patients the vitamin was withheld. No evidence was obtained to suggest that vitamin A had any beneficial effect on the healing of gastric ulcer.

The original observation that carbenoxolone sodium promotes the healing of gastric ulcer (Doll, Hill, Hutton, and Underwood, 1962) has been confirmed many times (Sullivan, 1970). In a dose of 300 mg daily carbenoxolone sodium may cause sodium and water retention and a decrease in serum potassium, so that some patients rapidly gain weight with oedema, hypertension, and hypokalaemia. Although

such side effects can be reversed with thiazide diuretics (Doll, Langman, and Shawdon, 1968) and potassium supplements, treatment of gastric ulcer with this dose of carbenoxolone sodium in elderly patients and those with hypertension and heart disease is inadvisable. Reduction in dosage below 300 mg daily diminishes the incidence of side effects but with some decrease in efficacy as well (Doll *et al.*, 1968). Preliminary animal studies and a limited open clinical investigation in man suggested that BX24 (lauroyl glycyrrhetic acid), a substance closely related to carbenoxolone, lacked its fluid- and sodium-retaining effects but had, weight for weight,

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at least equal anti-inflammatory properties.

We have, therefore, compared the effects of BX24 and carbenoxolone sodium on the rate of healing of gastric ulcer in a controlled trial. The conduct of such a trial, however, takes a long time and we preferred to use a multifactorial design so that we could assess the value of two ancillary treatments with zinc sulphate (ZnSO_4) and vitamin A at the same time.

In 1967 Pories, Henzel, Rob, and Strain reported that oral zinc sulphate accelerated the healing of wounds caused by excision of pilonidal sinus and there have been several publications suggesting that this substance may accelerate the healing of chronic leg ulceration (Husain, 1969; Greaves and Skillen, 1970; Serjeant, Galloway, and Gueri, 1970). Zinc is concentrated in healing tissues where it is probably incorporated in enzyme systems (Savlov, 1962). The use of vitamin A had been suggested by a colleague on theoretical grounds and its value had been tested on a small group of patients with gastric ulcer. The results of this pilot trial were so encouraging (Doll, unpublished) that it seemed desirable to subject vitamin A to further investigation.

Method

Patients with gastric ulcer, who were thought suitable for outpatient treatment, were seen in a special clinic three days after a barium meal and entered the trial unless (1) the ulcer had healed or was less than

10 sq mm in area when measured in maximum profile; (2) a second gastric ulcer or duodenal ulcer, scar, or deformity was also present; (3) the patient was over 70 years of age; (4) there were clinical reasons such as hypertension, heart disease, or a suspicion of malignancy, which made inclusion in the trial undesirable.

All patients in the trial were advised to continue at work if possible, take a normal diet with frequent meals, limit alcohol intake, and to stop smoking (Doll, 1964). Antacids were given when necessary for the relief of pain.

Allocation of the treatments was random but restricted so that each successive group of eight patients received each of the eight possible combinations (Table I). The treatments were given for four weeks, during which the patients were seen at weekly

Combination	Treatment		
	Carbenoxolone Sodium or BX24	Zinc Sulphate	Vitamin A
1	Carbenoxolone	+	+
2	Carbenoxolone	+	0
3	Carbenoxolone	0	+
4	Carbenoxolone	0	0
5	BX24	+	+
6	BX24	+	0
7	BX24	0	+
8	BX24	0	0

Table I Combinations used in assessing the individual effects of three treatments given concurrently

Characteristic	No. of Patients					
	Carbenoxolone	BX24	Zinc Sulphate	No Zinc Sulphate	Vitamin A	No Vitamin A
<i>Sex</i>						
Male	16	19	16	19	17	18
Female	8	5	8	5	7	6
<i>Age</i>						
Under 40 years	2	3	1	4	3	2
40-49 years	6	3	7	2	5	4
50-59 years	10	10	8	12	11	9
60-69 years	6	8	8	6	5	9
<i>Duration of ulcer history</i>						
Less than 1 year	9	4	4	9	7	6
1-4 years	7	9	8	8	7	9
5 years or more	8	11	12	7	10	9
<i>Size of ulcer niche</i>						
Less than 25 sq mm	4	4	4	4	4	4
25-49 sq mm	4	4	4	4	4	4
50-99 sq mm	5	8	7	6	8	5
100 sq mm or more	11	8	9	10	8	11
<i>Response to advice about smoking</i>						
Stopped or almost stopped	1	4	2	3	1	4
Reduced by more than half	6	9	5	10	8	7
Other response	11	11	14	8	12	10
Not applicable (non-smoker)	6	0	3	3	3	3

Table II Comparability of patients in different treatment groups

intervals. At each visit clinical details, including weight, blood pressure, and the presence of side effects, were recorded. Plasma electrolytes were measured at the start and the end of the trial. A further barium meal examination was carried out four days after the end of treatment. The area of the ulcer niche was measured in maximum profile using a millimetre grid viewed through a lens, and the effect of treatment was assessed in terms of the percentage change in the size of the ulcer.

Results

Altogether 54 patients were admitted to the trial. Three patients unexpectedly left the area and therefore failed to attend (one treated with carbenoxolone, one with BX24 and ZnSO₄ and one with carbonoxolone, ZnSO₄, and vitamin A). Two other patients (treated with BX24, ZnSO₄ and vitamin A, and with BX24 and ZnSO₄ respectively) were subsequently shown to have carcinoma of the stomach. One other patient (on carbenoxolone, ZnSO₄, and vitamin A) required admission to hospital for clinical and social reasons. The remaining 48 patients completed the treatment as planned.

The comparability of patients in the different treatment groups is examined in Table II; there were no great differences between the patients in any of the groups.

CARBENOXOLONE SODIUM AND BX24

Change in size of ulcer

The results of treatment with carbenoxolone sodium and BX24 assessed by change in size of the ulcer niche are shown in Table III. The first 16 patients received either carbenoxolone sodium or BX24 in a dose of 300 mg daily. In four of the eight patients receiving carbenoxolone the ulcer healed radiologically and the average reduction in ulcer size was 76.9%. The ulcer healed in only one patient receiving BX24, and the average reduction in ulcer size was

14.6%, two of the eight ulcers having actually increased in size. This difference in the effect of the two drugs is clearly significant ($P < 0.05$), and in view of the ineffectiveness of this dose of BX24 and the absence of side effects, it was decided to increase the dose to 600 mg daily for subsequent patients prescribed BX24.

In the second group of 16 patients four ulcers healed completely, two in patients receiving 300 mg of carbenoxolone sodium daily and two in patients receiving 600 mg of BX24, and the average reduction in ulcer size was 61.7% and 47.6% respectively. This difference is not statistically significant (Table III).

In the third group of 16 patients the dose of BX24 was increased yet again to 1200 mg daily. In this group only one ulcer in a patient receiving carbenoxolone healed radiologically, but two healed in patients on BX24. The average reduction in ulcer size was 67.9% in patients receiving carbenoxolone and 51.0% in those receiving BX24, and again this difference is not statistically significant (Table III).

Side effects

Eleven of 24 patients (46%) treated with carbenoxolone sodium 300 mg daily experienced side effects due principally to sodium and water retention. Six patients became oedematous; four complained of severe headache; and four experienced muscle pains, which were associated with a hypokalaemic alkalosis in three of them. None of the patients receiving BX24 reported any side effects.

In patients receiving carbenoxolone blood pressure tended to rise during treatment and the mean maximum increase of systolic pressure over the pre-treatment level was 23 mm Hg; by contrast the increase averaged 7 mm Hg in patients given BX24. Changes in diastolic pressure tended to be similar but less marked, the increase averaging 11 mm Hg for patients treated with carbenoxolone and 5 mm Hg for those on BX24. That some increase would be observed, even if the treatment had no effect, is only

Patient No.	Treatment (mg/day)	No. of Patients Showing Ulcer Healed	Reduction in Size of Ulcer by (%)			Average Reduction in Size of Ulcer (%)	Significance (Wilcoxon's Rank Sum Test)
			67-99	34-66	33 or less		
1-16	Carbenoxolone (300)	4	1	2	1 (1+) ¹	76.9	P > 0.05
	BX24 (300)	1	0	3	4 (2+)	14.6	
17-32	Carbenoxolone (300)	2	4	0	2 (1+)	61.7	P > 0.05
	BX24 (600)	2	2	1	3 (2+)	47.6	
33-48	Carbenoxolone (300)	1	4	2	1 (0+)	67.9	P > 0.05
	BX24 (1200)	2	2	1	3 (1+)	51.0	

Table III Results of treatment with carbenoxolone and BX24 assessed by change in size of ulcer

¹ + = Number of ulcers increased in size.

to be expected when it is recalled that the pressure was measured at weekly intervals and that 'the mean maximum increase' is the mean of the maximum difference between the initial measurement and any subsequent one. The small changes in blood pressure in patients receiving BX24 in this study are similar to those recorded in patients given dummy tablets in an earlier trial (Doll, Hill, and Hutton, 1965).

Patients receiving carbenoxolone gained almost twice as much weight as those on BX24. The mean maximum weight gain was 2.2 kg (4.8 lb) and 1.2 kg (2.6 lb) respectively. This difference must be attributed mainly to fluid retention rather than to a true increase in weight for 11 out of the 24 patients receiving carbenoxolone sodium who were given a thiazide diuretic rapidly lost their excess weight. None of the patients receiving BX24 required such treatment.

Patients treated with carbenoxolone showed an average decrease in plasma potassium of 1.2 m-equiv/l in spite of additional potassium supplements in 10 patients. The plasma chloride decreased on average by 3.4 m-equiv/l and the bicarbonate rose by 4.6 m-equiv/l. Altogether 13 patients became hypokalaemic ($K^+ < 3.8$ m-equiv/l) and four of them were alkalotic ($HCO_3^- > 32$ m-equiv/l and $Cl^- < 95$ m-equiv/l). There was, however, no consistent change in the plasma sodium concentration. Patients treated with BX24 showed no significant alteration in any of their plasma electrolyte levels.

ZINC SULPHATE

Change in size of ulcer

The results of treatment with oral zinc sulphate in a dose of 220 mg tds throughout the trial are shown in Table IV. Among the patients treated with carben-

oxolone sodium the addition of zinc sulphate did not confer any advantage. The average reduction in ulcer size was 70.2 % for those taking zinc, 67.5 % for those not prescribed the drug, and the number of ulcers healed radiologically was three and four respectively. However, ulcer size was reduced on average by 53.5 % in those who received both BX24 and zinc sulphate, compared with only 21.9 % in those who received BX24 alone. With the small numbers of patients involved even this apparently large difference falls short of the usual level statistical significance ($P > 0.1$, Wilcoxon's Rank Sum Test).

Side effects

No side effects attributable to zinc were observed.

VITAMIN A

The results of treatment with vitamin A in a dose of 50 000 units daily throughout the trial are shown in Table V. No evidence is provided to suggest that the vitamin has any beneficial effect on the healing of gastric ulcer. No side effects were observed.

Discussion

The healing effect observed with carbenoxolone sodium was similar to that recorded previously (Doll *et al*, 1962, 1965, 1968), the mean reduction in ulcer size after treatment with 300 mg daily for four weeks being 69 % (Table VI). Side effects due to fluid retention and electrolyte disturbance were seen in 11 out of the 24 patients (46 %), which is high when it is recalled that the trial was restricted to patients under 70 years of age in whom there was no appreciable hypertension and no evidence of heart disease.

Patients treated with BX24 did not show any side

Treatment	Patients Treated with Carbenoxolone			Patients Treated with BX24			All Patients		
	No. of Patients	Ulcer Healed	Average Reduction (%)	No. of Patients	Ulcer Healed	Average Reduction (%)	No. of Patients	Ulcer Healed	Average Reduction (%)
Zinc sulphate	12	3	70.2	12	4	53.5	24	7	61.9
No zinc sulphate	12	4	67.5	12	1	21.9	24	5	44.7

Table IV. Results of treatment with zinc sulphate assessed by change in size of ulcer

Treatment	Patients Treated with Carbenoxolone			Patients Treated with BX24			All Patients		
	No. of Patients	Ulcer Healed	Average Reduction (%)	No. of Patients	Ulcer Healed	Average Reduction (%)	No. of Patients	Ulcer Healed	Average Reduction (%)
Vitamin A	12	2	62.7	12	3	27.8	24	5	45.2
No vitamin A	12	5	74.9	12	2	47.7	24	7	61.3

Table V Results of treatment with vitamin A assessed by change in size of ulcer

effects that could be attributed to the drug, but the results were less satisfactory and similar to those obtained with inert tablets in previous studies (Table VI). The results with the two larger doses (600 and

Trial	Treatment	No. of Patients	Ulcer Healed	Average Reduction (%)
Doll <i>et al</i> (1962)	Carbenoxolone	30	11	72
	Inert tablets	20	1	35
Doll <i>et al</i> (1965)	Carbenoxolone	24	10	78
	Inert tablets	22	6	39
Doll <i>et al</i> (1968)	Carbenoxolone	22	9	82
Present trial	Carbenoxolone	24	7	69
	BX24	24	5	38

Table VI Results of treatment assessed by change in size of ulcer in four clinical trials

1 200 mg a day) were somewhat better than had been obtained with inert tablets, but the difference between these results and those obtained with the smallest dose (300 mg a day) was principally due to the unusually bad response of the patients in the latter group (average healing 14.6%). There was very little evidence of any further benefit with the largest dose (51.0% against 47.6% for the intermediate group) and even the patients given the largest dose did not do as well as those patients given carbenoxolone (average healing for all 24 patients, 68.9%). In the absence of other evidence to the contrary, we conclude that BX24 is without a clinically useful effect in the doses used in this study.

The somewhat greater healing observed in those patients who received zinc in comparison with those who did not may have been a chance effect. It will be noted, however, that the difference was almost

entirely confined to the patients who were given BX24. It may be, therefore, that maximum rate of healing was already being achieved in the patients who were given carbenoxolone and that a beneficial effect from zinc could be detected only in those who were not. Even in these patients the difference was not statistically significant, but the possibility that zinc may produce some minor benefit cannot be excluded.

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