Controlled trial of Duogastrone in duodenal ulcer

W. A. DAVIES AND P. I. REED¹

From the Departments of Medicine, Wexham Park Hospital, Slough, Berkshire and Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY A double-blind placebo-controlled trial of carbenoxolone, as 50 mg Duogastrone capsules, and in a dose of 200 mg daily for 12 weeks, was carried out in 40 ambulant subjects with endoscopically diagnosed duodenal ulceration, of whom 34 were available for final analysis. Each patient was seen every two weeks and endoscoped at four, eight and 12 weeks. Serum carbenoxolone was measured at each visit. Complete ulcer healing occurred in a significantly greater number of patients receiving Duogastrone than placebo, the significance being greater after four and eight weeks treatment ($P < 0.01$) than at 12 weeks ($P < 0.02$). While significant symptomatic improvement also was achieved ($P < 0.05$), but only after 12 weeks on Duogastrone, there was much closer correlation between ulcer healing and symptom relief, 69% on Duogastrone returning to normal, compared with 22% of controls ($P < 0.02$). Rise of systolic blood pressure and reduction in serum potassium levels, especially during the last four treatment weeks, were the most common effects noted in patients taking Duogastrone, and five patients required thiazide diuretics and potassium supplements. Higher serum carbenoxolone levels were found in patients with healed ulcers as well as in those with more marked side-effects.

While several trials have shown that carbenoxolone sodium, in capsule form (Duogastrone), improves the rate of healing of duodenal ulcers (Hunt, 1968; Brown *et al.*, 1972; Archambault *et al.*, 1975; Gheorghiu *et al.*, 1975), others have given equivocal results (Colin-Jones *et al.*, 1968; Cliff and Milton-Thompson, 1970). Symptomatic improvement has correlated poorly with duodenal ulcer healing (Brown *et al.*, 1972) resulting in a difference of opinion about the value of Duogastrone for symptom relief, only Cliff (1968) and Hunt (1970) reporting a beneficial response.

However, as all these studies have certain shortcomings, the need for a carefully controlled trial avoiding these was evident. This report presents the results of a prolonged double-blind placebo-controlled trial, based on endoscopic assessment, of carbenoxolone sodium (Duogastrone) in the treatment of duodenal ulcers.

Methods

Patients under the age of 75 years and without

cardiac, renal, or hepatic disease qualified for entry into the trial if they had symptoms of peptic ulcer disease for at least one month and if a duodenal ulcer was seen at endoscopy. Patients were excluded if there was evidence of oesophagitis, gastric ulcer, carcinoma, or gall bladder disease.

All patients were examined with a forward-viewing GIF-D Olympus fibrescope, and, in one patient in whom this did not enable adequate inspection of the duodenum, a side-viewing JF-B Olympus duodenoscope was also used. Informed consent was obtained.

Every patient was questioned, weighed, examined, and had blood drawn for haematological and biochemical investigations, which included measurement of serum electrolytes and enzymes. Each patient had an electrocardiograph, radiograph of the chest, and urinalysis. Those who had not been examined radiologically within the preceding month had a barium meal and, if gall bladder disease was suspected, a cholecystogram. Blood was drawn at each visit for measurement of serum carbenoxolone (Rhodes and Wright, 1974).

The capsules were of identical appearance and contained either 50 mg carbenoxolone sodium (Duogastrone) or inert ingredients (placebo). Patients were instructed to swallow whole one capsule 30

¹Address for communications: Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London, W12 0HS.

Received for publication 1 September 1976

minutes before each of three meals and before retiring at night, taking a total of 200 mg carbenoxolone sodium daily. Treatment was allocated randomly, according to a code known only to the hospital pharmacist and Biorex Laboratories. Each patient was also given magnesium trisilicate compound tablets (BPC) to be taken as necessary for relief of symptoms.

Medication was started within seven days of panendoscopy and was taken for 12 consecutive weeks. Assessments were made every two weeks and duodenoscopy repeated at four, eight, and 12 weeks. Patients were asked to remain ambulant and not to modify their daily habits except to take regular meals. Consistent capsule taking was emphasised; those who missed more than the equivalent of two days of medication in each week were excluded from the final analysis. At every visit patients were questioned about dietary and smoking habits, symptoms, and antacids used; they were examined, weighed, and blood pressure recorded. Symptomatic response was determined according to a grading system outlined in Table 1.

Table 1 *Symptom grading*

Grade	
0	Asymptomatic
1	Mild symptoms: mild epigastric pain readily relieved by antacid occurring more than once daily
2	Moderate symptoms: epigastric pain more than once daily, which may be associated with other dyspeptic symptoms such as anorexia, nausea, vomiting, but relieved by antacid
3	Severe symptoms: disabling prolonged epigastric pain not relieved by antacid; and/or acute ulcer bleeding

Forty patients were admitted to the study, 34 fulfilling the trial criteria for assessment and the remainder excluded as shown in Table 3. The treatment groups were comparable, though there were more smokers among the controls, who also had a longer history of dyspepsia (Table 2). However, these differences were not significant. Nor was there correlation between smoking and length of dyspepsia.

The statistical analyses that were used were the χ^2 test and the Mann-Whitney U test (1947), the latter being used to make a cross-comparison between the treatment groups to determine whether the patients studied originated from the same population.

ENDOSCOPIC ASSESSMENT (Figure)

A highly significant difference in healing rate, favouring Duogastrone, was already present at four weeks and was maintained throughout the trial period.

Table 2 *Comparison of treatment groups*

	Duogastrone	Placebo
Number		
Total	16	18
Male	13	15
Female	3	3
Age (yr) Mean (range)	51 (21-73)	49 (18-67)
Length of ulcer history (yr)		
Mean (range)	5.9 (0.1-20)	12.5 (2-30)
Other factors		
Family history	6	7
Analgesics	3	3
Smoking	10	17
Alcohol	6	8
Barium meal diagnosis		
Duodenal ulcer	6	9
Duodenal deformity	6	5

Table 3 *Patients excluded from trial*

<i>Duogastrone</i>	
1	Male: age 59. Missed nearly half capsules. Unreliable about appointments. DU present at 4, 8 and 12 w
2	Male: age 36. Excellent symptomatic improvement first 4 w and took half of remaining capsules. DU at 4, 8 and 12 w
3	Male: age 39. Apprehensive man could not understand instructions (took antacid instead of capsule). Missed half of capsules. Healed ulcer at 4 w but recurrence at 8 and 12 w
4	Male: age 26. Totally unreliable patient who missed over half of capsules and failed to attend 2 endoscopies. Ulcer healed after 4 m
<i>Placebo</i>	
1	Male: age 62. Unremitting symptoms. Emergency operation at 5 w for ulcer bleeding
2	Female: age 44. Persistent symptoms. Remained in bed final 6 w and required sedation for control. Ulcer healed at 12 w

Duogastrone group

Only five patients had unhealed ulcers after four weeks' treatment. In three the ulcers were smaller with marked lessening in duodenal inflammation and they healed completely after eight weeks. In the remaining two patients ulceration persisted throughout the trial. One developed a milk-alkali syndrome with hypercalcaemia and rise in urea. After the trial was completed a further four weeks on Duogastrone and a calcium-free diet resulted in ulcer healing and a return to normocalcaemia and normal renal function. The other patient had a large ulcer and severely inflamed duodenum. At four weeks multiple small shallow ulcers had replaced the solitary ulcer. Subsequently, he took the medication irregularly (just avoiding elimination from assessment) and three small erosions were still present at 12 weeks. Complete healing occurred after another four weeks' treatment.

Duodenal ulceration recurred in two patients during the trial: a 36-year-old man, whose ulcer healed at four weeks, developed multiple shallow ulcers at eight weeks, still present at 12 weeks; a 51-year-old woman, whose symptoms improved and ulcers healed within four weeks, developed a small shallow ulcer at 12 weeks.

Figure Ulcer healing rate significantly favouring Duogastrone treatment ($p < 0.01$ < 0.01 < 0.02).

Placebo group

Four of 18 patients (22%) had healed duodenal ulcers at four weeks but only two of these continued ulcer-free for the rest of the trial. One recurred at 12 weeks and another at eight weeks, only to heal again by the final endoscopy. Six of the remaining 14 patients had persistent ulcers throughout the trial. Four others healed only at 12 weeks and four more, whose ulcers had healed by eight weeks, had recurrences by the end of the trial.

SYMPTOMATIC RESPONSE

Fourteen of 16 (88%) patients on Duogastrone and 12 of 18 (67%) on placebo had severe symptoms at the start of the trial. The respective mean symptom grades were 2.9 and 2.6 and both groups were similar when compared using the Mann-Whitney U test.

There was considerable symptomatic improvement in both groups at four and eight weeks (Table 4). Greater reduction in symptoms occurred in those on Duogastrone but a significant difference was seen only after 12 weeks. While there was continued improvement in the Duogastrone group throughout the trial period, the controls showed a slight deterioration over the last four weeks. Eight patients

Table 4 Symptomatic response

Length of treatment (weeks)	Mean grade (% reduction)		P	U
	Duogastrone group	Placebo group		
Pre-treatment	2.9	2.6	NS	112
4	0.8 (72%)	1.2 (54%)	NS	108
8	0.6 (79%)	0.8 (69%)	NS	125
12	0.4 (86%)	0.9 (65%)	$P < 0.05$	85

(50%) taking Duogastrone became symptom-free within the first four weeks and 13 (81%) at 12 weeks. Only 28% of controls had complete relief at four weeks and 56% at 12 weeks, but these differences are not significant. Symptoms remained severe in one patient in each treatment group throughout the trial. All other patients on Duogastrone continued to improve, but two on placebo had a severe relapse by 12 weeks and a third redeveloped moderate symptoms.

Use of antacids

Four patients on Duogastrone and four on placebo took antacids even when they were completely free of pain. Five on Duogastrone and seven control subjects took more than two antacid tablets daily during the whole trial. Two on Duogastrone and four on placebo had a higher antacid intake during the last four weeks compared with the first four weeks.

Correlation between ulcer healing and symptom relief (Table 5): there was a positive association in

Table 5 Correlation between ulcer healing and symptom relief

Correlation	Duogastrone (n = 16)			Placebo (n = 18)		
	Weeks of treatment					
	4	8	12	4	8	12
I. Positive						
Ulcer healed and symptom free	6	10	11*	1	5	4*
Ulcer and symptoms present	3	2	2	10	6	5
II. Negative						
Ulcer present but symptom free	2	1	2	4	5	6
Ulcer healed but symptoms present	5	3	1	3	2	3

* $P < 0.02$.

at least half the patients. In those treated with Duogastrone the correlation became more pronounced with increasing length of treatment, being most marked at 12 weeks when 11 of 16 patients (69%) had a healed ulcer and were symptom-free. In contrast only four of 18 controls (22%) had a similar response ($p < 0.02$).

Table 6 Side-effects

Treatment group			Blood pressure rise (mmHg)		Sodium retention			Potassium loss				Hepatic enzyme rise	Additional treatment
Duogastrone			Diastolic pressure >90 mmHg	Diastolic rise >15 mmHg	Na ⁺ >145 mmol/l	Oedema	Wt. gain >5%	K ⁺ <3.7 mmol/l	HCO ₃ >29 mmol/l	CPK >130 IU/l	Myo-pathy	SGT >35 IU/l	potassium diuretic
No.	Sex	Age (yr)											
1	M	73	155/92		147	+		1.6	49	786	+		+
2	M	71	190/96	+				2.5					
3	M	69	190/98					3.1					+
4	M	61	170/105	+		+		2.9	32				
5	M	61	170/100	+				2.2	40	690	+		+
6	F	60	200/100		147	+	9%	2.5				61	+
7	M	54	170/110*					3.4					
8	M	54						2.6	35	222			+
9	F	53			146	+	6%	3.6					
10	F	51				+	14%		30				
11	M	47						3.3†					
12	M	43						3.4					
13	M	36	140/100	+	146		5%					43	
14	M	36											
15	M	21	150/92					3.6	30	182			
Total			9	4	4	5	4	12	6	4	2	2	5
Placebo													
1	M	67						3.4†					
2	M	64		+					30				
3	M	59	150/100	+									
4	M	51							32				
5	F	49	190/110*			+		3.5					
6	M	47		+									
7	M	40					6%	3.4					
8	M	18	130/105	+		+	12%	3.4†					+
Total			3	4		2	2	4	2				1

*Initial diastolic pressure 90 mmHg.

†Initial serum potassium <3.7 mmol/l.

SIDE-EFFECTS

The side-effects in both groups are tabulated in Table 6.

Blood pressure changes

The mean rise in blood pressure in patients taking Duogastrone was 15/9, 18/7 and 21/8 mmHg at four, eight, and 12 weeks, significantly higher than the mean rise 2/3, 3/2, 3/0 mmHg in the control patients ($P < 0.05$ < 0.05 < 0.01 systolic pressure; $P < 0.05$ at 12 weeks diastolic pressure). The mean diastolic pressure remained within normal limits in both groups throughout the trial period, but the mean systolic pressure was raised on Duogastrone though not in the controls, at four, eight and 12 weeks.

Sodium retention

In four patients on Duogastrone serum sodium levels just above the upper normal range were recorded, associated either with ankle oedema or a significant weight gain. Four on Duogastrone and two on placebo had a weight gain of more than 5%. Mild oedema developed in five Duogastrone healed patients, four requiring diuretics. Two controls also developed oedema, one receiving a

diuretic. There was no difference in the mean weight change in either group

Potassium loss

In the Duogastrone group the mean serum potassium level fell to 3.6 mmol/l at four and eight weeks and 3.0 mmol/l at 12 weeks. It was below 3.7 mmol/l in 12 Duogastrone patients during the trial (falling below 3.0 mmol/l in six), compared with only three in the placebo group. Serum bicarbonate levels rose in six patients on Duogastrone and in two controls. Four Duogastrone patients also had muscle enzyme abnormalities with elevated creatine phosphokinase (CPK) levels, of whom two had clinical muscle weakness, one requiring hospital admission at 12 weeks to correct severe hypokalaemia (1.6 mmol/l). Potassium supplement, in the form of Slow-K tablets, was given to five patients taking Duogastrone—two during the first four weeks, two during the second four weeks and one during the last four-week period of the trial.

Hepatic enzyme abnormalities

Transient small rises in the serum alanine amino-transferase (SGPT) level occurred in two patients

on Duogastrone. Other liver function tests were all normal in every patient.

SERUM CARBENOXOLONE LEVELS

There was a wide range of serum carbenoxolone concentration (1-140 $\mu\text{g/ml}$), as well as considerable individual variation among the 16 Duogastrone patients throughout the 12-week trial (means 6-82 $\mu\text{g/ml}$). Though there were too few patients for statistical analysis, a pattern did emerge. Higher carbenoxolone levels, especially in the later weeks of treatment, were noted in patients with healed ulcers, in all of whom blood levels exceeded 20 $\mu\text{g/ml}$. Higher levels were also obtained in patients over the age of 60 years, in none of whom were they below 20 $\mu\text{g/ml}$.

The most severe side-effects were seen in the three patients with the highest carbenoxolone blood levels (means of 82, 82, and 55 $\mu\text{g/ml}$). They all required diuretic and potassium supplements, up to 96 mmol daily for several weeks, and had raised CPK and bicarbonate levels; two patients developed muscle weakness and diastolic hypertension and the third, systolic hypertension. Each was also taking other drugs; one chlorpropamide, another ibuprofen, and the third indomethacin. The next highest mean carbenoxolone blood level was only 36 $\mu\text{g/ml}$ and the side-effects noted in other patients were minimal.

Discussion

The natural history of duodenal ulcer is characterised by spontaneous remission and intermittent pain, which makes for difficulty in evaluating specific drug treatment, especially if the study period is a short one. Furthermore, as duodenoscopy is more accurate than radiology in demonstrating duodenal ulcers, trials not employing endoscopy for diagnosis are also more likely to produce questionable results. Gheorghiu *et al.* (1975) relied exclusively on radiographic evidence of healing, yet Brown *et al.* (1972) found 28% disagreement between endoscopic and radiological findings. In our study the discrepancy was even greater, the initial radiograph failing to demonstrate 19 (58%) of the ulcers; in 11 others there was pyloroduodenal deformity and eight appeared normal radiologically.

In the published reports on Duogastrone most of the patients were treated for only four to six weeks. In the present study, however, maximum ulcer healing was achieved after eight weeks and symptom relief after 12 weeks on Duogastrone, a positive correlation between the two being most pronounced at the end of the trial period. Therefore, for maximum

efficacy Duogastrone treatment should be maintained for at least eight and preferably 12 weeks.

SIDE-EFFECTS

Side-effects including electrolyte disturbances, muscle weakness, weight gain, oedema, or hypertension due to hypokalaemia and sodium retention have been noted in all previous trials with carbenoxolone but have generally been less frequent and severe with Duogastrone than with Biogastrone, used in the treatment of gastric ulcers. The side-effects noted in this study were no different. The mean serum potassium level dropped progressively during treatment with Duogastrone, below normal levels being recorded in 75% of patients, a higher percentage than in other reports. However, the five patients who required potassium supplementation were also taking thiazide diuretics because of oedema or hypertension, which probably further increased potassium loss.

It is noteworthy that the most severe side-effects, with the highest recorded serum carbenoxolone levels, were seen in the three patients taking other drugs concurrently. One was a newly diagnosed diabetic receiving chlorpropamide, in whom glycosuria may also have increased potassium excretion, the other two were taking anti-inflammatory drugs, ibuprofen and indomethacin respectively. Both of these and also chlorpropamide, like carbenoxolone, are protein bound and excreted through the bile, though to a varying extent. It is possible that by competitive protein binding they may have affected the absorption of carbenoxolone, raising its serum concentration and thereby increasing the severity of side-effects.

This study has confirmed the significant therapeutic benefits of carbenoxolone sodium (Duogastrone), both in relieving the symptoms and influencing the healing of duodenal ulcers. While side-effects were observed in a number of patients receiving Duogastrone, these were significant mainly in the elderly or when other drugs were used concurrently. The majority required neither additional treatment nor alteration in the trial protocol. It is concluded that Duogastrone is highly effective in healing duodenal ulcers.

We wish to thank the Reabilities Trust for providing financial support for one of us (W.A.D.) and for the purchase of the GIF-D Olympus Panendoscope; Dr W. G. Morson, of Richardson-Merrill Inc., for financial support throughout the study; Dr S. Gottfried and Miss L. Baxendale, of Biorex Laboratories Ltd, for providing the Duogastrone and placebo capsules; Miss P. A. Wright and Mr P. C. Thornton (both of Biorex Laboratories Ltd) for

carrying out carbenoxolone assays and the statistical analysis respectively; and our endoscopy nurse/technicians, Mrs D. Wheeler and Mrs B. Turnbull, for expert assistance throughout the trial.

References

- Archambault, A., Farley, A., Gosselin, D., and Martin, F. (1975). Multicentre double-blind study of Duogastrone in the treatment of duodenal ulcers, In *Fourth Symposium on Carbenoxolone*, pp. 251-255. Edited by F. Avery Jones and D. V. Parke. Butterworths: London.
- Brown, P., Salmon, P. R., Htut, T., and Read, A. E. (1972). A double-blind trial of carbenoxolone sodium in duodenal ulcer therapy based on endoscopic diagnosis and follow-up. *British Medical Journal*, 3, 661-664.
- Cliff, J. M. (1968). A trial of carbenoxolone capsules in the Royal Navy. In *Symposium on Carbenoxolone Sodium*, pp. 239-244. Edited by J. M. Robson and F. M. Sullivan. Butterworths: London.
- Cliff, J. M., and Milton-Thompson, G. J. (1970). A double-blind trial of carbenoxolone sodium capsules in the treatment of duodenal ulcer. *Gut*, 11, 167-170.
- Colin-Jones, D. G., Lennard-Jones, J. E., Howel-Jones, J., Misiewicz, J. J., and Langman, M. J. S. (1968). Carbenoxolone capsules (Duogastrone) in duodenal ulcer: preliminary results. In *Symposium on Carbenoxolone Sodium*, pp. 209-216. Edited by J. M. Robson and F. M. Sullivan. Butterworths: London.
- Gheorghiu, Th., Frotz, H., and Dole, A. (1975). The therapeutic effect of carbenoxolone in duodenal ulcer. Preliminary analysis of a multi-centre double-blind trial. In *Fourth Symposium on Carbenoxolone*, pp. 257-265. Edited by F. Avery Jones and D. V. Parke. Butterworths: London.
- Hunt, T. C. (1968). Clinical experience with carbenoxolone capsules (Duogastrone) in duodenal ulcer. In *Symposium on Carbenoxolone Sodium*, pp. 195-201. Edited by J. M. Robson and F. M. Sullivan. Butterworths: London.
- Hunt, T. C. (1970). Multi-centre Duogastrone trial in duodenal ulcer (interim report). In *Carbenoxolone Sodium*, pp. 143-147. Edited by J. H. Baron and F. M. Sullivan. Butterworths: London.
- Mann, H. B., and Whitney, D. R. (1947). On a test of whether one or two random variables is stochastically larger than the other. *Annals of Mathematical Statistics*, 18, 50-60.
- Rhodes, C., and Wright, P. A. (1974). A gas chromatographic determination of carbenoxolone in human serum. *Journal of Pharmacy and Pharmacology*, 26, 894-898.