A double-blind trial of carbenoxolone sodium capsules in the treatment of duodenal ulcer

J. M. CLIFF AND G. J. MILTON-THOMPSON

From the Royal Naval Hospitals at Haslar and Plymouth

SUMMARY A controlled trial of carbenoxolone sodium positioned-release capsules (Duogastrone) was carried out on a randomized series of 100 unselected male Service personnel with symptoms of active duodenal ulceration and supporting radiological evidence. Fifty-seven patients completed the trial, 29 in the carbenoxolone group and 28 in the control group. The carbenoxolone group was given capsules containing 50 mg carbenoxolone four times a day for 12 weeks while the controls received a capsule identical in every respect except that it did not contain carbenoxolone. All patients were assessed at fortnightly intervals and had clinical and radiological reassessments three and six months after commencing treatment.

Review at three months and at six months revealed a slight but clinically insignificant trend in favour of the carbenoxolone group.

As a corollary to this controlled trial, those patients (38 in all) who did not have an early remission of symptoms were removed from the trial and placed on capsules known to contain carbenoxolone. Subsequently these patients did not show an advantage for carbenoxolone.

Carbonoxolone sodium has been shown in several controlled trials to increase the rate of healing of chronic gastric ulcers in the ambulant patient (Doll, Hill, Hutton, and Underwood, 1962; Doll, Hill, and Hutton, 1965; Horwich and Galloway, 1965; Turpie and Thomson, 1965; Bank, Marks, Palmer, Groll, and Van Eldik, 1967). When administered orally in tablet form it does not affect the natural course of duodenal ulceration and therefore a positioned-release capsule (Duogastrone) has been developed, the intention being to release 50 mg carbenoxolone sodium into the duodenum.

A pilot trial was carried out in 1967 in which the clinical results of the treatment (with Duogastrone) of Servicemen with duodenal ulceration were compared with a similar group of patients treated with propantheline bromide tablets (Cliff, 1968); the response to carbenoxolone sodium capsules was so satisfactory and confirmed by other preliminary studies (Craig, Hunt, Kimerling, and Parke, 1967; Hunt, 1968; Lawrence, Manton, Mendl, and Montgomery, 1968) that a double-blind controlled trial against placebo was set up.

We now report our findings in 100 patients who have been followed up for six months.

Material and Methods

One hundred unselected male Service personnel with symptoms of an ulcer dyspepsia and radiological evidence of deformity of the duodenum were accepted into the trial. Patients with a history of recent haemorrhage or perforation were excluded although there were included in the trial four patients with a previous history of haemorrhage and two who had had previous conservative surgery for perforated duodenal ulcer.
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The ages of the group ranged between 16 and 59 years, the majority being aged 20 to 24 years. Thirty gave a history of symptoms for less than a year, 53 had had symptoms for one to five years, and 17 for more than five years. Forty-six subjects had not been absent from duty on account of dyspeptic symptoms during the previous year while 37 had been sick for up to one month and 17 for an even longer period. There was a positive family history of duodenal ulceration in 52, no such history being obtained from the other 48. Thirteen subjects were regarded as having an anxious and polysymptomatic personality. There were no cases of cardiac or renal disease, as might be expected in an active service population.

Initial investigations included a barium meal, augmented histamine or pentagastrin test, haematological and biochemical studies including haemoglobin estimation, packed cell volume, blood urea, serum bilirubin, alkaline phosphatase, serum aspartate transaminase (SGOT), serum alanine transaminase (SGPT), serum electrolytes and blood grouping.

None of the preliminary haematological or biochemical investigations revealed any significant abnormality.

The augmented histamine or pentagastrin test showed a stimulated secretory rate of more than 40-0 m-equiv/hour in 42, the remaining 58 giving rates below this figure.

Blood grouping demonstrated that 46 belonged to group O, 44 to group A, 6 to group B, and 4 to group AB.

The cigarette smoking habits of the group were that seven were non-smokers, four smoked occasionally, 35 smoked up to 10 cigarettes a day, 43 smoked up to 20 cigarettes a day, and 11 smoked more than 20 cigarettes daily.

Ten subjects were teetotal, 47 took alcohol occasionally, 39 drank an average of one to two pints of beer daily and four consumed larger quantities of alcohol.

Patients were placed on treatment with carbenoxolone capsules or placebo capsules according to a randomized series and given instructions to take their capsules four times a day, half an hour before their main meals; the placebo capsules were identical in appearance to those containing the active drug. In addition all patients were supplied with tablets of magnesium trisilicate to be used as required for the relief of symptoms and they recorded the number of tablets used each day.

All patients remained at full duty on either a normal Service diet or their usual home diet if they happened to be employed ashore and living at home. They were advised to take regular meals, avoid spicy foods and moderate their alcohol and tobacco consumption (where this was applicable).

Each patient was reviewed at fortnightly intervals when the weight and blood pressure were recorded, and the presence or absence of pain and epigastric tenderness noted with the number of tablets of magnesium trisilicate taken each week.

Haematological and biochemical examinations were repeated after one month and at the end of three months continuous treatment with one capsule four times a day, radiological reassessment being carried out at the end of three months treatment. A final clinical and radiological appraisal was made at the end of six months.

As a corollary to this controlled trial, those patients who did not have an early remission of symptoms were transferred to capsules known to contain carbenoxolone sodium and either received a full course of this preparation or were withdrawn on account of persisting symptoms. The results from those who completed the double-blind trial (57 patients) and the rest will be dealt with separately.

Clinical assessment was based on the severity of pain (1-3 points), the degree of epigastric tenderness (1-3 points) and the radiological findings (1-3 points) (Table I). Total scores of 8 to 9 points would therefore indicate considerable improvement or a clinical remission.

Results

Fifty-seven patients completed the controlled trial as planned. Thirty-eight patients were removed from the controlled trial on account of persisting symptoms and placed on known carbenoxolone; in this way 20 patients were transferred from placebo and 18 patients from coded carbenoxolone to known carbenoxolone. This latter group will be considered separately.

Five patients were withdrawn: two patients taking placebo (one with a perforated duodenal ulcer and one with a haematemesis), one patient on coded carbenoxolone with increasingly severe symptoms, one patient on coded carbenoxolone who left the United Kingdom, and one patient who defaulted.

Results of the Controlled Trial

There were 57 patients, 29 taking carbenoxolone and 28 taking placebo. The total clinical assessment scores at three months and at six months did not show a significant advantage for carbenoxolone (Table II). Seventeen patients on carbenoxolone achieved scores of 8 or 9 points compared with 12 patients on placebo. Since pain is commonly the presenting symptom, the scores for pain in the two groups are shown separately in Table III; there is no significant difference in the response to carbenoxolone or placebo.

The radiological assessment of the two groups (Table IV) was made by applying the scoring
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Pain Tenderness Radiograph

<table>
<thead>
<tr>
<th>Pain</th>
<th>Tenderness</th>
<th>Radiograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on four or more days each week</td>
<td>Marked 1</td>
<td>Ulcer present 1</td>
</tr>
<tr>
<td>Pain on less than four days each week</td>
<td>Minimal 2</td>
<td>Ulcer 'healing' or deformity present 2</td>
</tr>
<tr>
<td>No pain or pain on one day each week</td>
<td>Absent 3</td>
<td>Ulcer 'healed' with or without deformity 3</td>
</tr>
</tbody>
</table>

Table I Scoring system for clinical assessment of pain, epigastric tenderness, and radiological findings

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Total scores</th>
<th>Initially</th>
<th>After Three Months</th>
<th>After Six Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbenoxolone</td>
<td>29</td>
<td>115</td>
<td>217</td>
<td>199†</td>
</tr>
<tr>
<td>Controls</td>
<td>28</td>
<td>116</td>
<td>201</td>
<td>183*</td>
</tr>
</tbody>
</table>

Table II Total clinical assessment scores (pain, tenderness, and radiological findings) in the controlled trial

1Incomplete data for three cases
2Incomplete data for two cases

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Total Scores</th>
<th>Initially</th>
<th>After Three Months</th>
<th>After Six Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbenoxolone</td>
<td>29</td>
<td>40</td>
<td>84</td>
<td>71†</td>
</tr>
<tr>
<td>Controls</td>
<td>28</td>
<td>42</td>
<td>79</td>
<td>69*</td>
</tr>
</tbody>
</table>

Table III Clinical assessment scores for pain in the controlled trial

1Incomplete data for three cases
2Incomplete data for two cases

<table>
<thead>
<tr>
<th>After three months</th>
<th>After six months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbenoxolone (29 cases)</td>
<td>Controls (28 cases)</td>
</tr>
<tr>
<td>'Healed' with or without deformity</td>
<td>9</td>
</tr>
<tr>
<td>'Healing' with or without deformity</td>
<td>5</td>
</tr>
<tr>
<td>Unchanged</td>
<td>14</td>
</tr>
<tr>
<td>Worse</td>
<td>1</td>
</tr>
</tbody>
</table>

Table IV Radiological assessment of the two groups

1One radiological assessment not available

RESULTS IN CASES TRANSFERRED FROM THE CONTROLLED TRIAL TO KNOWN CARBENOXOLONE

As indicated in the protocol, those patients who did not have an early remission of symptoms were removed from the controlled trial and given capsules known to contain carbenoxolone; then, unless they were withdrawn on account of persisting symptoms, they received a full 12 week course of this preparation. The transfer to known carbenoxolones usually occurred after six weeks in the controlled trial, the time varying between three weeks and 10 weeks.

In this way 20 patients were transferred from placebo to known carbenoxolone, of whom four were withdrawn with persisting symptoms. After six months the final review showed that five of the remainder had achieved 8-9 points, seven a score of 7 points and four showed little or no improvement. Eighteen cases were transferred from coded carbenoxolone to known carbenoxolone. Six were withdrawn with continuing symptoms and one was discarded as an unreliable witness; of the remaining eleven cases, six attained scores of 8-9 points and the remaining five showed some improvement.

These groups are too small for analysis but they certainly do not show a true trend in favour of carbenoxolone.

SIDE EFFECTS

One patient on carbenoxolone complained that the capsules made him vomit while another experienced depression while taking these capsules; on the other hand one subject attributed pain to swallowing placebo capsules and another felt that the placebo caused extrasystoles.

Fluid retention, hypertension, potassium loss, and heartburn can occur during the administration of carbenoxolone tablets (Biogastrene), especially in the presence of overt cardiac and renal disease (Turpie and Thomson, 1965) but the positioned-release capsules (Duogastrone) produced no such side effects in a group of 32 patients (Craig et al, 1967); in another series of 22 patients mild hypokalaemia and fluid retention was noted on two occasions (Montgomery,
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Lawrence, Manton, Mendl, and Rowe, 1968) and one example of hypokalaemia with muscle paresis has been reported in a patient taking carbenoxolone 200 mg daily in the form of Duogastrone for a period of six weeks (Forshaw, 1969).

If a gain in weight of more than 7 lb (3.2 kg) during the three months’ course of treatment should be accepted as evidence of fluid retention, there were eight such patients in this series, seven of whom were taking carbenoxolone and one the placebo; their ages ranged between 18 and 37 years. The only patient to develop minimal pitting oedema during his course of carbenoxolone was aged 37 and he gained 12 lb (5.4 kg) in weight; at the same time his blood pressure rose from 130/70 to 160/100 mm of mercury.

In this series no subject showed clinical evidence of hypokalaemia and analysis of the serum potassium and sodium levels showed no difference between those taking carbenoxolone or placebo.

An elevation of the serum transaminase levels has been reported during the metabolic studies of a single patient (Baron, Naborro, Slater, and Tuffley, 1969). In this group of 100 patients, either the SGOT or the SGPT was raised above 30 units/ml in 10 subjects for a short period during their course of treatment; six had been taking carbenoxolone while four had been receiving placebo.

Discussion

The clinical assessment of the progress of duodenal ulceration must be based on the presence or absence of pain and epigastric tenderness as well as the radiological findings. Although no single aspect can be considered in isolation, the presence of pain is certainly the feature which will undoubtedly lead to further morbidity. Particular attention was therefore paid to the relief of pain in this controlled trial but no difference was noted between those taking carbenoxolone or placebo.

Preliminary trials of carbenoxolone positioned-release capsules in Servicemen at duty on a normal Service diet (Cliff, 1968) indicated that the course of treatment should last for 12 weeks rather than six weeks and this view was also advanced by Montgomery et al (1968). In the present controlled trial, treatment was continued for 12 weeks but no clinical advantage for carbenoxolone was revealed.

We wish to thank Surgeon Captain F. A. F. Mackenzie and Surgeon Commander J. A. B. Harrison for carrying out the radiological studies and Surgeon Commander P. J. Preston for carrying out some of the final reviews. We are also indebted to Dr S. Gottfried of Biorex Laboratories and Dr M. J. S. Langman of the Department of Medicine, General Hospital, Nottingham, for their assistance.

References


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