Healing of Peptic Ulcers on Conventional Antacid Therapy with or without Butriptyline

I. N. MARKS

SUMMARY

A group of ulcer patients taking conventional doses of antacids were subjected to a double-blind randomized trial to examine the possible effect of butriptyline on ulcer healing.

The study failed to show any advantage of butriptyline over placebo, but this may well have been due to the very success of antacid therapy. The healing rates of gastric and duodenal ulcers in patients on conventional antacid therapy were found to be comparable to those reported with many of the newer ulcer preparations. This study also showed that larger ulcers tend to take longer to heal than small ones.


A wide range of anti-ulcer preparations has been developed in recent years. Most are directed against acid-pepsin aggression or impaired mucosal resistance, the two major factors responsible for peptic ulceration. A third factor mediated by corticohypothalamic pathways has also been invoked, and it is with this in mind that various tranquillizers and antidepressants have been tested for possible anti-ulcer effects.

This study was carried out on office patients to examine the possible effect of an antidepressant, butriptyline, on ulcer healing, by means of a double-blind, controlled, randomized trial. Reluctance to treat office patients with placebo prompted the use of a low-dose antacid regimen, which was considered acceptable in view of the nihilistic attitude towards the ulcer-healing effect of such a regimen. This provided an opportunity to assess ulcer healing on a conventional antacid regimen with or without butriptyline and, in addition, to consider the possible relationship between initial ulcer size and ulcer healing at 6 weeks.

PATIENTS AND METHODS

A series of 45 ambulant patients in whom endoscopy had revealed evidence of gastric or duodenal ulceration were admitted to the trial. Twenty-three patients had gastric ulceration, 19 had duodenal ulceration and the remaining 3 had combined gastric and duodenal ulceration. Two of the latter were arbitrarily assigned to the duodenal ulcer group and 1 to the gastric ulcer group. The trial number for each patient was taken sequentially from randomization tables for the duodenal and gastric ulcer groups. For the purposes of the present study, multiple gastric or duodenal ulcers were considered as a single ulcer, but the 3 patients with combined gastric and duodenal ulcers were each regarded as having 2 distinct ulcers. The series of 45 patients thus had 26 gastric and 22 duodenal ulcers.

The 45 patients represented a consecutive series of patients considered suitable for repeat endoscopic studies. A few were not included in the trial because of uncertainty regarding the precise visualization of a discrete measurable ulcer or because of technical difficulties encountered with the initial endoscopy. Of the 22 patients with duodenal ulcers who were admitted, 14 had ulcers situated on the anterior wall and 6 had ulcers on the floor of the cap; only 2 patients with posterior ulcers were admitted. Precise localization was also a problem in the occasional patient with a pyloroduodenal ulcer, and these patients were also excluded.

All the patients were given a coded 3-week supply of three 350-ml bottles of hydrated magnesium aluminate suspension (magaldrate — Riopone; Ayerst) (15 ml about 30 minutes after meals and at bedtime) and 96 tablets of this product (a total of 4 or 5 taken at intervals during the day) and of butriptyline or butriptyline placebo (2 tablets at bedtime). The dosage of antacid liquid and tablets was equivalent to a neutralizing capacity of about 175 mEq per day. Patients were advised to have regular meals and adequate rest, to avoid salicylates and other anti-inflammatory drugs, to curtail alcohol intake and to reduce smoking to after meals and tea. Patients were given a further 3-week supply of the coded medication after 3 weeks.

Endoscopy was carried out at 0 and 6 weeks and the ulcer size was estimated with a calibrated measuring device or the opened tip of a biopsy forceps. The surface area of the ulcer was calculated according to the formula $A = \pi (d_1 + d_2)^2 / 4$, with $d_1$ and $d_2$ representing the long and cross diameters of the ulcer. Only the largest ulcer was considered in those patients with multiple gastric or duodenal ulceration. Patients in whom the ulcer had not healed after 6 weeks were asked to continue with the antacid liquid and tablets for a further 6 weeks, and to report for repeat endoscopy at the end of this period.

Patients were assessed clinically at 0, 3, 6 and, if necessary, at 12 weeks. The psychological status of the patients was assessed at 0 and 6 weeks by means of an anxiety-depressive rating technique. Patients were not preselected in terms of their psychological score, but only if endoscopic examination had revealed an ulcer.
RESULTS

Butriptyline and Ulcer Healing

Patient profile with regard to age, sex and duration of symptoms was similar in the butriptyline and placebo subgroups. Butriptyline showed no advantage over placebo in the duodenal and gastric ulcer groups or in both ulcer groups considered together (Table I). Nine of 11 ulcers in the duodenal ulcer subgroup treated with butriptyline had healed completely at 6 weeks compared with 8 of 11 in the placebo subgroup. Seven of 12 of the gastric ulcers treated with butriptyline and 9 of 14 of the gastric ulcers treated with placebo had healed completely at 6 weeks.

<table>
<thead>
<tr>
<th>TABLE I. INCIDENCE OF COMPLETE HEALING OF ULCERS IN BUTRIPTYLINE AND PLACEBO GROUPS</th>
<th>Healed at 6 wks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>Butriptyline</td>
<td>82</td>
</tr>
<tr>
<td>Placebo</td>
<td>73</td>
</tr>
</tbody>
</table>

Butriptyline and Psychological Status

Analysis of the psychological data showed that only 24 of the 45 patients entered into the trial had an anxiety-depressive rating score in keeping with a depressive state. No statistical difference could be found between the butriptyline and placebo groups with regard to psychological improvement. However, both groups experienced a sense of psychological well-being which seemed to parallel the progressive healing of their ulcers.

Antacid and Ulcer Healing

The failure of butriptyline to influence ulcer healing permitted the butriptyline and placebo subgroups to be considered together in the assessment of the possible value of antacids for both duodenal and gastric ulcers (Table II).

Seventeen of the 22 duodenal ulcers had healed completely at 6 weeks, and 1 of the remaining 5 healed after a further 6 weeks. Only 16 of the 26 gastric ulcers had healed completely at 6 weeks, but 5 of the other 10 ulcers healed after a further 6 weeks. One of the patients with an unhealed duodenal ulcer and 1 of the patients with an unhealed gastric ulcer failed to attend the 12-week follow-up, and were excluded from the 12-week analysis.

| TABLE II. ULCER HEALING IN PATIENTS TREATED WITH ANTACIDS COMBINED WITH BUTRIPTYLINE OR PLACEBO |
|---------------------------------|----------------|----------------|
| Group                           | Number of patients | Mean initial ulcer size (mm²) | Complete healing |
|                                 |                      | 6 wks | 12 wks |
| Duodenal ulcer                  | 22                  | 40    | 17 (77%) |
| Gastric ulcer                   | 26                  | 114   | 16 (62%) |

* Excludes 1 patient lost to 12-week follow-up.

Initial Ulcer Size and Ulcer Healing

In Fig. 1 the calculated initial size of ulcers which had healed at 6 weeks is compared with that of those which had still not healed at this time. Some overlap in the initial size of both gastric and duodenal ulcers was noted between the healed and unhealed subgroups, but ulcers that had not healed at 6 weeks tended to have a larger initial size than those which had healed. The mean initial ulcer size of the unhealed gastric ulcers was 221 mm², significantly greater than the mean initial size of 47 mm² of the gastric ulcers which had healed at 6 weeks (P<0.001). Similar findings were noted in the duodenal ulcer group, the mean initial sizes of the unhealed and healed ulcers having been 104.0 and 20.9 mm² respectively.

Patient Profile and Ulcer Healing at 6 Weeks

There were no significant differences in sex, age, smoking and drinking habits and dental status between the groups with healed ulcers and that with unhealed ulcers (Table III). The history of dyspepsia and the duration of the
recent attack tended to be longer in patients whose ulcers remained unhealed at 6 weeks, and there was perhaps a higher incidence of double dentures in the group whose ulcers had not healed. The majority of patients heeded advice regarding regular meals, and the few heavy drinkers were able to renounce alcohol. The same applied to those patients whose ulcers appeared to have developed as a result of analgesic insult.

**Reduction in Ulcer Size in Unhealed Groups**

The extent of ulcer healing in those ulcers which were unhealed at 6 weeks was of the order of 90%. In 9 of the 10 unhealed gastric ulcers there was a 90-99% reduction in initial ulcer size, with a mean value of 96%. In the remaining one, a chronic high posterior wall ulcer with an initial size of 19.6 mm², there was a reduction of only 50%. Similarly, in 4 of the 5 unhealed duodenal ulcers there was an 85-98% reduction in the initial ulcer size, with a mean value of 93%. The initial ulcer in the 5th patient had disappeared after 6 weeks, but was adjudged 'non-healed' because of the development of multiple small, shallow ulcers in the cap. The latter and 5 of the unhealed gastric ulcers had healed at 12 weeks (see Fig. 1).

**Features Revealed by Endoscopic Examination of Patients with Healed Ulcers after 6 Weeks**

In the vast majority of patients the ulcers healed with the formation of a pinpoint scar with radiating folds, a linear scar or, indeed, no visible scar at all. Significant gastric changes were noted in the region of previous ulceration in 3 patients, and a 4th developed a small erosion in a different site of the stomach. Persistent duodenitic changes were noted in 4 of the patients with healed duodenal ulcers, and a 5th was found to have a small prepyloric erosion.

**Patient Compliance and Side-Effects**

Patient compliance was good, with the exception of 5 patients who found it necessary to reduce the dose of butriptyline from 2 tablets to 1 tablet at night because the larger dose caused morning drowsiness. Three of the patients on placebo reduced the dose to 1 tablet at night because of drowsiness in the morning, 1 stopped the tablets because of bad dreams and another because he thought they kept him awake. Of interest was the fact that 7 of 23 patients slept very well on placebo, and that 3 of these 7 felt 'doped' in the morning. On the other hand, 4 of 22 patients slept badly on butriptyline. There was excellent compliance from the patients taking antacids, none of whom complained of constipation or diarrhoea. Palatability of the antacid liquid was excellent, but a few patients thought the antacid tablets a 'bit sweet'.

**DISCUSSION**

The study failed to show any advantage of butriptyline over placebo with regard to ulcer healing or, indeed, psychological improvement. This was hardly surprising. The administration of conventional doses of antacids to all patients considerably reduced the chances of demonstrating any possible ulcer-healing effect of butriptyline, and the fact that only about half the patients entered into the trial had a depressive rating militated against the finding of a significant psychological improvement on butriptyline. Moreover, both the butriptyline and placebo groups experienced a sense of psychological well-being which seemed to parallel ulcer healing. The apparent failure of butriptyline may well have been due to the very success of antacid therapy.

Conventional antacid therapy is based largely on tradition and clinical experience, but its value has been questioned in recent years by the results of a number of seemingly objective clinical trials. Doll et al." and Butler and Gersh7 failed to show any advantage of antacids over placebo in the treatment of hospitalized gastric ulcer patients, and Baume and Hunt8 reported no difference in healing rates in a group of gastric ulcer patients who were randomly allocated to therapy with either calcium

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**TABLE III. INITIAL ULCER SIZE, PATIENT PROFILE AND CLINICAL AND OTHER FEATURES IN HEALED AND UNHEALED ULCERS AT 6 WEEKS**

<table>
<thead>
<tr>
<th></th>
<th>Healed</th>
<th>Unhealed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of ulcers</strong></td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td><strong>Initial ulcer size (mm²) (mean and SE)</strong></td>
<td>47 ± 10</td>
<td>221 ± 51</td>
</tr>
<tr>
<td><strong>Male/female ratio</strong></td>
<td>9:7</td>
<td>7:3</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>49.9 (25-71)</td>
<td>47.9 (23-66)</td>
</tr>
<tr>
<td><strong>Dyspepsia (yrs)</strong></td>
<td>5.1 (1/12 - 15)</td>
<td>8.2 (1/12 - 23)</td>
</tr>
<tr>
<td><strong>Recent attack (wks)</strong></td>
<td>5.6 (1 - 24)</td>
<td>7.2 (3 - 12)</td>
</tr>
<tr>
<td><strong>Symptom relief on treatment days</strong></td>
<td>7.4 (2 - 21)</td>
<td>8.7 (1 - 21)</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
<td>0</td>
<td>5→0</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>12→9</td>
<td>8</td>
</tr>
<tr>
<td><strong>Alcohol — Mild/ moderate</strong></td>
<td>8→6</td>
<td>6→5</td>
</tr>
<tr>
<td><strong>Dentures</strong></td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td><strong>Regular meals</strong></td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td><strong>Sick leave for 2 weeks</strong></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Mean and range.
† Before and during trial.
carbonate or token doses of aluminium hydroxide tablets. Hollander and Harlan and Littman et al., on the other hand, found antacids to be more effective than placebo in gastric ulcer healing.

Experimental data on antacids and duodenal ulcer healing are even less impressive, and clinical truisms such as those about the value of antacids in easing duodenal ulcer pain have come under fire. The UCLA group, in a double-blind, controlled, randomized trial found that 'antacid and placebo produced similar pain relief in ten duodenal ulcer patients', although they conceded that antacids were 'arithmetically', albeit not 'statistically', more effective than placebo in a slightly larger group. Petersen et al., however, have recently found a large-dose antacid regimen to be significantly better than placebo in healing duodenal ulcers. Their regimen, designed to markedly reduce postprandial gastric acidity, consisted of 30-ml doses of a magnesium and aluminium hydroxide liquid 1 and 3 hours after meals and at bedtime — a total of 210 ml per day for 4 weeks. This dosage was equivalent to a neutralizing capacity of 1 010 mEq a day, approximately 6 times the dosage used in the present study. Complete ulcer healing was noted in 78% of their treated patients compared with 45% in their placebo group. This single study has gone a long way towards vindicating the time-honoured use of antacids in the treatment of duodenal ulcer. It leaves unanswered the question of whether the cumbersome large-dose regimen, tailored according to an impeccable theoretic rationale, is in fact necessary for the healing of the majority of duodenal ulcers. This study, despite shortcomings inherent in an antacid trial without a placebo antacid group, suggests that conventional doses of antacid may well suffice.

The antacid regimen used in the present study consisted of magaldrate liquid 15 ml about 30 minutes after meals and at bedtime, and 4 or 5 magaldrate tablets chewed at intervals during the day and evening. About one-half of the patients in the study took a bedtime dose of butriptyline. Patients were advised to avoid ulcerogenic drugs, to reduce heavy smoking and excessive alcohol intake and, of course, to take regular meals and adequate rest. Six patients in the series were given sick leave for 2 weeks, but none was hospitalized. Under these conditions, healing rates comparable to those attained with many of the newer preparations for ulcer therapy and with the large-dose antacid regimen were achieved. Complete ulcer healing occurred in 77% of duodenal ulcer patients at 6 weeks and in 86% at 12 weeks, and healing of gastric ulcers occurred in 62% of patients at 6 weeks and in 84% at 12 weeks.

The problem of objective evaluation of ulcer trials is highlighted by the results obtained by the Swiss group who studied the healing of gastric and duodenal ulcers with placebo treatment. Only patients whose most recent attack had started less than 4 weeks previously were selected, and those with symptoms were allowed a liquid antacid in token doses of 1 teaspoonful after meals. All patients were advised to take a bland diet and to moderate their smoking habits. Fifty-three per cent of the duodenal ulcers healed within 3 weeks and 73% within 6 weeks, and no fewer than 83% of the gastric ulcers healed within 6 weeks. The healing-time course for both types of ulcers appeared to follow an exponential function and, as in other trials, larger ulcers tended to take longer to heal than small ones. These thought-provoking results with 'placebo therapy' underline the extreme difficulties in drug assessment although, in truth, they may have been influenced by patient selection, inclusion of a large number of relatively small ulcers and consideration of each ulcer in patients with two gastric or duodenal ulcers. Their mean initial gastric ulcer size was about two-thirds of that in the present study, and their mean initial duodenal ulcer size was also somewhat smaller.

The present study supports the view of these and other workers regarding the relationship between initial ulcer size and healing. The mean initial size of ulcers which healed at 6 weeks was significantly smaller than that of ulcers which were unhealed at 6 weeks, and this applied to both gastric and duodenal ulcers. We agree with Littman et al. that initial ulcer size should be considered in all studies in which complete, as opposed to percentage, healing is the sole parameter of the effectiveness of therapy.

The present study also illustrates a disturbing aspect of endoscopic trials, the definition of ulcer healing. Although the majority of duodenal ulcers healed with the formation of a pin-point scar with radiating folds, a linear scar or, indeed, without trace, about 25% of patients with healed ulcers still had persistent and sometimes marked duodenitic changes. These ulcers were undoubtedly healed according to current endoscopic trial criteria, but most clinicians would regard them as evidence of ongoing disease warranting continued treatment. The concept of Mohnihan's disease, so brilliantly enunciated by Spioro, covers the spectrum of duodenal ulcer disease ranging from unequivocal ulceration to duodenitis and, perhaps, mucosal changes demonstrated by electron microscopy. The 'all-or-none' attitude towards endoscopic healing in ulcer trials warrants modification.

I wish to thank Dr E. Polakow, of Ayerst International (South Africa) for supplies of magaldrate and the butriptyline trial tablets, and also the South African Medical Research Council.

REFERENCES