Clinical trial

Duodenal ulcer healing after presentation with haemorrhage

W R MURRAY, G LAFERLA, G COOPER, AND M ARCHIBALD

From the University Department of Surgery, Western Infirmary, Glasgow

SUMMARY Forty patients who were managed conservatively after haemorrhage from an endoscopically verified duodenal ulcer were randomised at discharge from hospital to enter a blind study of ranitidine therapy (150 mg bd) *versus* a placebo tablet. The patients were re-endoscoped after four weeks, ulcer status defined and the trial code broken revealing that five of 20 placebo patients had healed their duodenal ulcer compared with 16 of 20 ranitidine patients ($p=0.001$). Lifestyle parameters of both groups improved during the study period but no directly related benefit in duodenal ulcer healing could be shown. We conclude that effective anti-ulcer therapy, such as ranitidine, is required to heal a duodenal ulcer which presents with haemorrhage.

During the years 1983 and 1984 the Haematemesis Management Team at the Western Infirmary, Glasgow, treated 279 patients who had bled from a duodenal ulcer with an overall mortality of 2.2%. Twenty eight patients (10%) underwent surgery to control haemorrhage while 245 patients (88% of the total number) were discharged with an active duodenal ulcer which had stopped bleeding after conservative management during a mean hospital stay of five days. Forty nine of these patients (20%) had no dyspepsia on admission and by the time of discharge from hospital 208 (85%) of the patients managed conservatively without the use of H₂ antagonists denied the presence of upper gastrointestinal symptoms.

Haematemesis Management Team members have observed a ready willingness on the part of the patients under their care to change, in the short term at least, personal habits such as smoking and drinking alcohol which may have a detrimental effect on duodenal ulcer healing.¹⁻³ If patients who leave hospital without dyspepsia after conservative management of a duodenal ulcer which has bled do in fact alter their lifestyle in a potentially beneficial way, then a satisfactory short term ulcer healing rate might be achieved without the use of an H₂ receptor antagonist drug. We have tested this hypothesis using a prospective randomised blind clinical study

of patients who had bled from an endoscopically verified duodenal ulcer.

Patients

METHODS

The patients included in this study were admitted to the Western Infirmary, Glasgow, during 1984 with a diagnosis of acute upper gastrointestinal haemorrhage. All patients with this clinical diagnosis were endoscoped within 24 hours of admission and potential study patients defined as those having blood in the upper gastrointestinal tract with a duodenal ulcer as the only lesion present. Patients receiving H₂ receptor antagonist therapy at the time of admission were excluded from the study. Final selection for this study was made at the time of discharge from hospital when patients who had stopped bleeding from their duodenal ulcer on conservative management without specific anti-ulcer therapy and had no upper abdominal pain were offered entry into the clinical trial. Study patients were discharged with trial tablets containing either ranitidine (150 mg) to be taken twice a day or a placebo preparation to be taken at the same frequency. All patients were given a supply of antacid tablets (Rennie's, Glaxo Pharmaceuticals) to be taken as required and were counselled by the members of the Haematemesis Management Team responsible for their care.

Before discharge from hospital 32 data items were recorded for each study patient giving pre-admission

Address for correspondence: Mr W R Murray, MD, FRCS, Department of Surgery, Western Infirmary, Glasgow G11 6NT.

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and inpatient details. These data included social factors, dyspeptic history, drug history, gastrointestinal symptoms in hospital, haematology, endoscopic findings and an evaluation of lifestyle parameters. This evaluation included dietary history, smoking habits, alcohol consumption and the frequency with which patients went out in the evenings for what were termed 'pleasurable pursuits'.

During the study patients were given open access to the study team *via* our research staff nurse (MA) and were encouraged to inform the team of any problems encountered. The patients were recalled four weeks after discharge to undergo an outpatient endoscopy at which time the presence or absence of duodenal ulceration was recorded. Lifestyle parameters were reassessed and data collected concerning postdischarge upper gastrointestinal symptoms, tablet compliance and haematology. The study code was then broken.

Results

Forty patients entered the study and were equally randomised between the ranitidine and placebo groups. Analysis of the data collected revealed that the two groups of patients were well matched, the only statistically significant difference being that smokers in the ranitidine group smoked more cigarettes per day than smokers in the placebo group (Table 1).

At the four week postdischarge endoscopy it was found that five of the 20 patients receiving placebo tablets had healed their duodenal ulcer while 16 of the 20 patients receiving ranitidine had healed their duodenal ulcer. This difference is statistically highly significant ($p=0.001$; Fisher's exact test) and led to the study being terminated after only 40 patients had entered. A secondary analysis was carried out to compare the 21 patients who had a healed duodenal ulcer four weeks postdischarge with the 19 patients

whose duodenal ulcer was still present. The only statistical significant difference between these two groups was found to be the use of ranitidine by patients with a healed duodenal ulcer ($p<0.001$).

No patient in the study was admitted to hospital during the study period and we are unaware of any significant complication arising from duodenal ulceration or its therapy in this group of patients in the four weeks after haemorrhage. No patients receiving placebo tablets required H₂ receptor antagonist therapy during the study. Despite the significant difference in duodenal ulcer healing rates, dyspepsia was reported as frequently from patients receiving ranitidine as from those receiving the placebo (11 in each group). Antacid consumption was found to be similar for the placebo and ranitidine groups and for patients with healed or unhealed duodenal ulcers at four weeks. Six of the 15 patients in the placebo group with an unhealed duodenal ulcer at four weeks denied dyspepsia during the study period.

No significant difference was noted in lifestyle parameters or their changes during the four weeks after discharge between ranitidine ($n=20$) and placebo ($n=20$) patients, healed ($n=21$), and unhealed ($n=19$) duodenal ulcer patients and healed ($n=5$) and unhealed ($n=15$) duodenal ulcer patients receiving the placebo preparation. Although lifestyle parameter changes did not correlate with duodenal ulcer healing, potentially beneficial changes were recorded amongst the 40 patients studied during the four week period after discharge from hospital (Table 2).

Discussion

Ulcer healing is generally accepted as a criteria of successful short term conservative management of a duodenal ulcer which has bled but has not led to urgent surgery. This study has shown that in this situation the use of an H₂ receptor antagonist such as ranitidine will achieve a significantly greater duodenal ulcer healing rate than placebo therapy. Our four week duodenal ulcer healing rates, as defined by endoscopy, were strikingly different for the two groups of patients studied. We are unaware

Table 1 Data analysed according to study group randomisation

	Placebo	Ranitidine	<i>p</i>
Men	16	19	NS
Age (yr)	56.6±4.5	52±3.6	NS
Cigarette smokers	9	14	NS
Cigarettes per day	11.2±1.6	22±3.2	<0.01
Alcohol drinkers	12	14	NS
Units alcohol per week	15±3.4	15±4.3	NS
Duodenal ulcer history	15	15	NS
Admission Hb (g/dl)	10.9±0.5	11.3±0.7	NS
Four week Hb (g/dl)	13.7±0.3	14±0.3	NS

(Student's non-paired *t* test: mean±standard error).
NS=not significant.

Table 2 Short term (4 weeks) lifestyle parameter changes after successful conservative management of haemorrhage from a duodenal ulcer in 40 patients

Took more rest – 60%
Alcohol drinkers reduced their intake significantly – 55%
Socialised less frequently – 48%
Slept longer – 45%
Improved their diet – 38%
Smokers smoked significantly less – 31%

of a comparable study of patients who have recently bled from a duodenal ulcer but the observed four week ranitidine healing rate of 80% can be regarded as satisfactory and in keeping with the literature on ranitidine treatment of a symptomatic duodenal ulcer without haemorrhage.⁴⁻⁸ The four week placebo healing rate of 25% is in the lower range reported for placebo treatment from any country and gives no indication of satisfactory spontaneous duodenal ulcer healing after presentation with haemorrhage.⁷⁻¹⁰ Paoluzi *et al* have recently shown that complete healing of a duodenal ulcer using full dose cimetidine therapy is associated with a significantly lower recurrent ulcer rate than if full dose therapy is reduced or stopped before complete duodenal ulcer healing.¹¹

The relationship between complete duodenal ulcer healing and the success of further medical management of the ulcer diathesis may well be important. The results of this study support the general view that the absence of dyspepsia does not correlate well with duodenal ulcer healing. Patients who leave hospital with an active duodenal ulcer which has bled should therefore undergo a further endoscopy to ensure that H₂ receptor antagonist therapy has completely healed the duodenal ulcer before the dose is reduced to maintenance level or therapy stopped.

The hypothesis that potentially beneficial changes in lifestyle parameters will encourage spontaneous duodenal ulcer healing after presentation with haemorrhage cannot be supported by this study. Our observations suggest that the majority of the study patients did alter at least one aspect of their lifestyle in an apparently beneficial way during the four weeks after discharge from hospital. Despite these observations we were unable to correlate short term postdischarge lifestyle changes with duodenal ulcer healing and conclude that beneficial lifestyle changes, even if they do occur, cannot be relied upon to induce satisfactory spontaneous duodenal ulcer healing in patients who have presented with haemorrhage.

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