

Ranitidine in the prevention of gastric and duodenal ulcer relapse

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SUMMARY Prophylactic maintenance therapy for one year using ranitidine 150 mg at night or a placebo was assessed in 68 patients whose gastric or duodenal ulcers had previously healed after therapy with ranitidine 150 mg twice daily or placebo. Gastroscopy was carried out on symptomatic relapse and at the end of the year. Of the duodenal ulcer group, seven out of 20 relapsed on ranitidine compared with 15 out of 17 on placebo ($p < 0.001$). Of the gastric ulcer group one of 15 patients relapsed on ranitidine compared with 11 of 16 patients on placebo ($p < 0.005$). There were no adverse effects from ranitidine during the trial period. Ranitidine in low dose maintenance therapy is therefore reasonably effective in the prevention of relapse of duodenal ulcers and appears to be particularly effective in preventing relapse of gastric ulcers at least for one year. As gastric ulcers occur more frequently in the older patients in whom there are often medical contraindications to surgery, maintenance treatment may be appropriate for many such patients.

After healing of duodenal ulcers by the H_2 receptor antagonist, cimetidine, a lower maintenance dose has been shown to be reasonably effective in preventing symptomatic recurrence,¹ although it may be less useful in preventing endoscopic relapse.² Comparable maintenance therapy for healed gastric ulcer has not been well documented. Ranitidine, a new H_2 receptor antagonist, differs from cimetidine both in its chemical structure and its greater potency, on a molar basis, of acid inhibition.³⁻⁵ It has been shown to be effective in the initial healing of both duodenal ulcer⁶⁻⁸ and gastric ulcer.⁹ We have assessed for the first time the efficacy of once daily ranitidine in the prevention of relapse of both duodenal and gastric ulceration.

Methods

PATIENTS

Eighty one patients entered the trial. All patients had previously completed Stages 1 and 2 (acute

phase ulcer healing) when their ulcers had been shown to heal, either as a result of ranitidine therapy (150 mg bd) or placebo.⁹ Of these patients, 45 had duodenal ulcers and 36 had gastric ulcers.

Informed consent was obtained from all patients. The period of follow-up was one year, during which they were allocated either ranitidine (150 mg at night) or a similar looking placebo tablet on a random and double blind basis. They were assessed routinely at four monthly intervals with a medical examination, urinalysis, and laboratory testing (which included full blood count, renal function, and liver function tests). A patient could ask to be seen without delay if either symptoms warranted it or there was a suspicion of adverse reaction. Endoscopy was performed whenever symptoms suggested a relapse and routinely in all patients at the end of the trial. All patients were supplied with a standard quantity of antacid (Rennies tablets) and the consumption of these was carefully assessed throughout.

In the event of ulcer relapse, patients were treated, as for stages 1 and 2, with open ranitidine 150 mg bd.

A single relapse was taken as a failure of prophylaxis.

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Results

Of the original 81 patients who entered the trial, 10 defaulted (two with gastric and eight with duodenal ulcers). Three patients with gastric ulcers were withdrawn for medical reasons. One of these had acute pancreatitis after excessive intake of alcohol. A second patient developed serious cardiac disorder unrelated to the trial and was withdrawn because of this. One patient, taking placebo, was found on routine biopsy to have dysplasia at the edge of his gastric ulcer, amounting to carcinoma *in situ* and was subjected to partial gastrectomy, after which, a small early carcinoma (IIb, IIc) was found in the edge of the ulcer. This patient had had several previous gastroscopies with biopsies which had missed the neoplasm, presumably because of its small size and early nature. Sixty-eight patients therefore completed the study, 37 with duodenal ulcers and 31 with gastric ulcers.

The mean duration of symptoms in the gastric ulcer group was nine years compared with seven years in the duodenal ulcer group. The mean age of the gastric ulcer group was older, 56 years, compared with the duodenal ulcer group, 44 years. Patients on active and placebo treatment were well matched for sex, and drinking and smoking habits. Patients in the duodenal group on active ranitidine had a mean age of 48 years as compared with 41 years for those on placebo, but this was thought unlikely to have materially affected the results. In the gastric ulcer group, the mean age of those on active treatment and those on placebo was identical at 56 years.

Of the 37 patients with duodenal ulcers who completed the trial, 20 were allocated to ranitidine and 17 to placebo. The relapse rate for those receiving ranitidine was seven out of 20 (35%) and for those receiving placebo was 15 out of 17 (87%), a difference which is statistically significant (Chi-squared test using Yates correction, $p < 0.001$). Two relapses were asymptomatic, only being diagnosed at routine endoscopy.

Of the 31 patients with gastric ulcers who completed the trial, 15 received ranitidine and 16 placebo. The relapse rate for those on ranitidine was one out of 15 (7%) compared with 11 out of 16 (70%) for those on placebo, a difference which was again statistically significant ($p < 0.005$). Again, one relapse was only diagnosed at routine endoscopy, the patient being asymptomatic.

The mean antacid consumption was considerably more for patients taking placebo (70 tablets monthly) compared with those on ranitidine (22 tablets monthly), so that any beneficial effect of antacids on relapse rate would have been weighted

towards the placebo group.

Discussion

It is now possible to heal most duodenal and gastric ulcers using one of the increasing selection of drugs available.⁶⁻¹¹ A more intractable problem in ordinary clinical practice has been the maintenance of the induced remission after acute healing. It is generally agreed that in duodenal ulcer patients there is little to be gained by prolonging the treatment by an H₂ receptor antagonist in full dosage, as many studies (recently confirmed and reviewed by Bardhan)¹² have shown that the relapse rate after discontinuing treatment continues to be just as high. The high relapse rate of patients allocated placebo in our study is in keeping with this. Unless the patient is referred for surgery, the choice lies between prolonged maintenance therapy using either a full or reduced dose of drug and prompt treatment of symptomatic relapse with no attempt at therapy between relapses.

In the case of duodenal ulcer there have been several studies of prevention of relapse using cimetidine, with which our study must inevitably be compared. The relapse rate of our patients on placebo was similar to that reported in other series.¹³⁻¹⁵ Ranitidine 150 mg at night reduced this considerably but by no means to zero, the incidence of relapse (three per cent per month) being very similar to that reported for a very large series treated similarly with cimetidine in a dose of 400 mg nocte.¹ Symptomatic relapse, requiring surgery or full dose treatment, has still occurred in all trials and a strong case for the alternative course of waiting for symptomatic relapse and then treating with a short full dose has been argued for cimetidine¹⁶ and could equally be made for ranitidine.

Relapse of gastric ulcer after healing is perhaps an even greater problem, partly because treatment of each relapse has to be monitored by endoscopy and biopsy in case the ulcer should be malignant, yet maintenance treatment has been reported in very few trials and these involving only small numbers of patients. The high (70%) relapse rate of gastric ulcer in our series within one year on placebo therapy is similar to that of other recent studies in the United Kingdom, for instance, Machell *et al* (85%)¹⁷ and Hollanders *et al* (59%),¹⁸ while only one of our 15 patients on ranitidine 150 mg at night relapsed during the year. In similar studies using cimetidine, Machell *et al*,¹⁷ using cimetidine 1 g daily over an 11 month period, reported nine out of 11 (80%) ulcer free on active treatment, compared with two out of 14 (14%) on placebo, and Birger Jensen *et al*,¹⁹ using cimetidine 400 mg twice daily, reported no

relapses in 10 patients on active treatment, compared with 55% (five out of nine) relapses on placebo. In a recent study more comparable to ours in that cimetidine 400 mg at night was assessed as maintenance therapy, Morgan *et al*²⁰ reported four relapses in 28 patients (14%) over one year.

Gastric ulcer patients are often elderly, our series being typical with the mean age of 56 years, and often have associated medical conditions which are a relative contraindication to surgery. Maintenance therapy with ranitidine 150 mg daily merits serious consideration in such patients, providing that malignancy is meticulously excluded, both by biopsy and by endoscopic confirmation of complete healing.

Ranitidine 150 mg at night proved in this study an effective agent for the prophylaxis of recurrent gastric and duodenal ulcer over a one year period. Choice between the alternative managements of surgery or intermittent medical treatment will be governed by considerations such as comparative cost to the community or individual of relapsing ulcer disease, and freedom from unwanted side-effects. In our series, ranitidine has been free of detectable short term side-effects, which so far reflects general experience. It has the advantage over cimetidine of not affecting the enzyme cytochrome P40 and therapy affecting the metabolism of certain other drugs.²¹ Unlike cimetidine, it appears to have no effect on plasma testosterone levels or those of luteinising hormone²² and does not in our experience produce gynaecomastia in patients who have developed this while taking cimetidine. Safety in administration of ranitidine over several years, however, remains to be established.

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