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Ranitidine 150 mg at night in the prevention of gastric ulcer relapse

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SUMMARY After healing of a gastric ulcer, 53 patients were randomly allocated to either 12 months maintenance treatment with ranitidine 150 mg at night or an identical placebo. Fifty patients completed the trial. The patients were interviewed every third month. If symptoms indicated a relapse, endoscopy was done; and if an ulcer was found the maintenance trial was terminated. All remaining patients were endoscoped after one year. The accumulated relapse rate in the ranitidine group (36%) was significantly lower ($p<0.01$) than in the placebo group (76%), as also was the antacid consumption ($p<0.01$). Four of the six ulcers found at the final one year endoscopy were asymptomatic. In all but two of the 26 patients with relapse of symptoms an ulcer was found at endoscopy. The patients that suffered a recurrence had significantly ($p<0.05$) higher maximal acid output than those without ulcer recurrence. The time needed for healing of the relapse ulcers (four or eight weeks) corresponded to that needed for healing of the preinclusion ulcers. It is concluded that ranitidine 150 mg at night significantly reduces the gastric ulcer recurrence rate, and that relapsing ulcers are similar to the initial ones in healing response.

With the new and potent antiulcer drugs healing of a peptic ulcer is usually achieved within six to eight weeks in most patients.[1,2] Without treatment two thirds of the patients will experience a relapse within one year.[3,4] The optimal medical prevention of these relapses is yet to be defined, but it has been repeatedly shown that the H_2-receptor antagonists significantly reduces the relapse rate in duodenal ulcer patients,[5–8] and a few studies have confirmed this in gastric ulcer patients as well.[9–10] In spite of this, little is known about patients most likely to benefit from such maintenance treatment.

The present study was therefore undertaken to evaluate ranitidine 150 mg at night in the prevention of gastric ulcer relapse; to see whether possible prognostic factors like the gastric H^+ secretion might affect the recurrence rate; and finally to compare the relapsing ulcers with the original ones in respect of symptomatology and healing response.

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Methods

PATIENTS

After the healing of a gastric ulcer, with either ranitidine 150 mg twice daily or 300 mg at night for four to eight weeks, 53 patients were recruited in a double blind placebo controlled trial for the prevention of gastric ulcer relapse. The ulcers had a diameter of 5–50 mm and were located at least 2 cm proximal to the pylorus. Patients with ulcers associated with gastrointestinal haemorrhage, pyloric stenosis, Zollinger-Ellison syndrome, concomitant use of potentially ulcerogenic drugs, pregnant or lactating women, current medical illnesses or malignant ulcers, were excluded.

The patients were given either ranitidine 150 mg at night or an identical placebo. For symptomatic relief, both groups were supplied with antacid tablets (Rennies®, containing calcium carbonate 680 mg and magnesium carbonate 80 mg, with an acid neutralising capacity of 15 mmol). After three, six, and nine months the patients were interviewed with grading of the dyspeptic symptoms nausea, vomiting, epigastric

pain and heartburn. All unused treatment and antacid tablets were counted and the patients supplied with drugs for the next three months period. Endoscopy was only done if symptoms indicated a relapse. If an ulcer was found, the maintenance trial was terminated and the patient given open treatment with ranitidine 300 mg at night. Healing was controlled endoscopically after four weeks, and if necessary the treatment was extended for another four weeks before final endoscopic control. The remaining patients were all interviewed and endoscoped after 12 months, and relapses treated as above.

Before starting treatment of the ulcer leading to inclusion in the present study, a pentagastrin test (6 μg pentagastrin/kg sc) was performed in all the patients.

The statistical analyses were performed with Gehans test for censured data, classical congenital analysis, Wilcoxon's rank-sum-test, and Fisher-Erwin exact probability test; $p<0.05$ was considered statistically significant.

Results

Three of the 53 patients failed to meet at the scheduled three month control and neither did they respond to further call-in. They were therefore excluded from the following presentation. Thus, 25 patients received ranitidine 150 mg at night and the other 25 patients received the placebo. The two groups were similar in sex and age distribution, duration of dyspeptic history, length of current episode, duration or type of treatment given for ulcer healing before inclusion in the maintenance study, smoking habits, and basal (BAO) and maximal acid output (MAO) (Tables 1, 2).

The relapse rate in the ranitidine group was significantly ($p<0.01$) lower than in the placebo group from the first control at three months till the end of the study (Fig. 1). The accumulated one year relapse rates were 36% and 76% in the ranitidine and placebo group, respectively. Also when considering the smokers alone, those that were given ranitidine had significantly ($p<0.01$) lower recurrence rate than those given placebo, 25% (4/16) and 71% (15/21), respectively. The antacid consumption in tablets per week treatment was significantly ($p<0.01$) lower in the ranitidine group throughout the study. Furthermore, the patients receiving placebo had significantly ($p<0.05$) more epigastric pain and heartburn than the ranitidine group, whereas the two groups did not differ significantly regarding nausea and vomiting. The patients needing eight weeks treatment for healing of their ulcer before inclusion in the maintenance trial had a higher relapse rate than those with ulcers healed after four weeks (Fig. 2). This difference, however, was significant ($p<0.05$) during the first six months only. There was a tendency for smokers as a group to have less relapses than non-smokers, but the difference did not reach statistical significance ($p=0.08$) (Fig. 3). In both the ranitidine and placebo treated groups, the patients that suffered a recurrence had higher BAO and MAO than those without a recurrence (Table 2). When all the patients

Table 1 *Sex and age distribution, duration of dyspeptic history (yr) and length of current episode (months) in the patients with and without a relapse in the ranitidine and placebo groups. Except for the sex distribution the figures represent the median and range*

	Sex M	Sex F	Age	Dyspeptic history (duration)	Current episode (length)
Ranitidine group	16	9	56 (40–71)	10 (0·2–25)	2 (1–6)
With relapse	5	4	54 (44–71)	10 (1–20)	3 (1–6)
No relapse	11	5	56 (40–70)	6·5 (1–25)	2 (1–6)
Placebo group	19	6	55 (34–71)	6·5 (0–30)	2 (1–12)
With relapse	14	5	56 (34–71)	5 (1–30)	2 (1–12)
No relapse	5	1	50 (35–57)	9 (0–11)	2 (1–5)

Table 2 *Basal (BAO) and maximal acid output (MAO) (normal range 0–5 and 15–30 mmol/h, respectively) in the patients with and without a relapse in ranitidine and placebo groups. The values represent median and range*

	Gastric H^+ secretion BAO	MAO
Ranitidine group	1·9 (0–9·7)	18·6 (2·8–44·1)
With relapse	2·7 (0–9·7)	21·5 (2·8–44·1)
No relapse	1·4 (0–6·4)	16·1 (6·1–42·2)
Placebo group	2·4 (0–11·7)	20·9 (3·8–46·9)
With relapse	3·0 (0–11·7)	24·1 (3·8–46·9)
No relapse	1·7 (0–7·1)	14·5 (9·6–16·9)

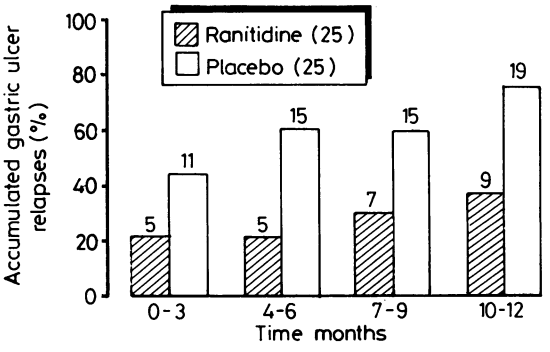

Fig. 1. *Accumulated gastric ulcer relapses in the ranitidine and placebo groups. In this and the subsequent figures the numbers on the top of the columns represent the number of patients with a relapse in that group.*

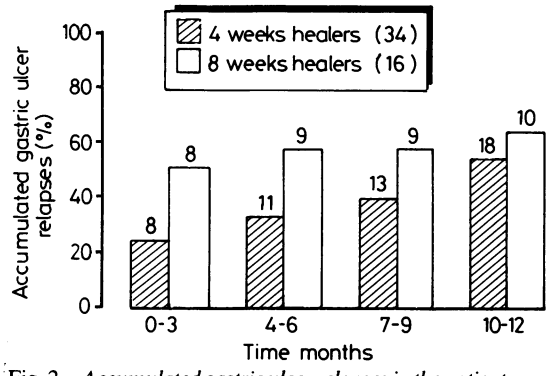

Fig. 2 *Accumulated gastric ulcer relapses in the patients needing four or eight weeks treatment for ulcer healing before inclusion in the maintenance trial.*

were considered together, as well as when the placebo group was considered alone, the differences in MAO between relapsers and non-relapsers were statistically significant ($p<0.05$). The recurrence rate was not related to sex, age, duration of dyspeptic history or present episode (Table 1).

At the 12 months control six ulcers were found (Fig. 1), four in the placebo group and two in the ranitidine group. Only one ulcer in each group caused dyspeptic symptoms. All ulcer recurrences, with and without symptoms, occurred at the site of the original ulcer. In 24 of the 26 patients with dyspepsia, indicating a relapse, an ulcer was found at endoscopy.

The healing rate of the relapsing ulcers were identical in the ranitidine and placebo groups, being, respectively, 75% and 73·6% after four weeks, and 100% and 94·7% after eight weeks. On the other hand, the four week healing rate of the relapsing ulcers was significantly lower ($p<0.01$) in the patients initially needing eight weeks for ulcer healing before inclusion in the maintenance study (33·3% (3/9)), compared with the healing rate of the patients initially healed after four weeks (94·4% (17/18)).

One patient in the ranitidine group complained of headache and modest dyspepsia at the three month control. This patient had an ulcer recurrence and was referred to surgery. He was therefore included in the relapse analyses, but not in the data on healing of the recurrences. Except for the headache, which might have been caused by ranitidine as it disappeared after stopping the drug, no serious side effects or ulcer complications like perforation or bleeding were seen.

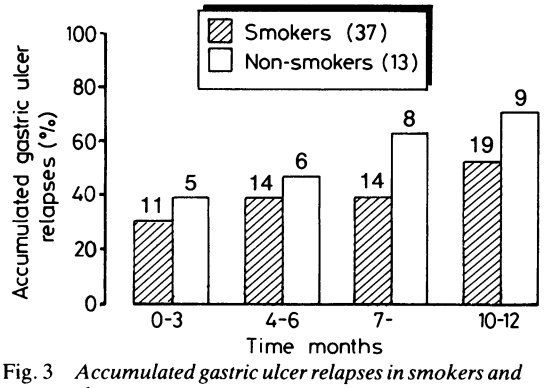

Fig. 3 *Accumulated gastric ulcer relapses in smokers and non-smokers.*

Discussion

In the present one year study we have shown that ranitidine 150 mg at night significantly reduces the relapse rate in gastric ulcer patients. Thus, in the placebo group the relapse rate was 76% or more than twice that in the ranitidine group. These relapse rates are comparable with those reported by others,[9-11] and underlines the chronicity of the gastric ulcer disease. Furthermore, the patients in the placebo group had significantly more epigastric pain and heartburn together with a significantly higher antacid consumption. Accordingly, the ranitidine treatment not only reduced the recurrence rate but also the dyspeptic symptoms.

The relapse rate of 36% in the treatment group cannot, on the other hand, be considered as satisfactory, particularly as the recurrence rate after surgical treatment seems to be lower.[12] The patients in our study, however, were all given the same standard maintenance treatment, 150 mg ranitidine at night, and like all other long term medications, the dosage of antiulcer drugs should also be individualised. Such individualisation is likely to reduce the failure rate considerably, and might be achieved within reasonable time as most of the relapses, indicating a higher maintenance dose, occur during the first three months.

Of the possible prognostic factors considered in the present study, only the length of the treatment needed for initial ulcer healing and the gastric H^+ secretion differed between the patients with and without ulcer recurrence. Thus, the patients needing eight weeks for initial ulcer healing had significantly more relapses during the first six months than the four weeks healers, but the difference tapered off and almost disappeared after one year. On the other hand, the association between a high MAO and ulcer recurrence was more pronounced, particularly in the placebo group. Accordingly, the high secretors are the ones benefiting the most from successful treatment. Because these patients were those with the highest relapse rate in the ranitidine group as well,

they probably also need a higher than the standard maintenance dose.

Although we could not verify the prognostic value of the other factors tested, this negative observation should be interpreted cautiously. In particular, the number of non-smokers in our study was only 13, and the somewhat unexpected tendency towards more recurrences in this group, that could not be explained by more smokers receiving ranitidine, should only be taken to indicate that the effect of smoking on peptic ulcer is far from clarified.

Four of the 28 ulcer recurrences were asymptomatic. If these ulcers heal spontaneously, this is probably an underestimate of their true incidence as endoscopy without symptoms was only done at the end of the trial. The significance of these ulcers is not known and awaits further studies.[13]

To our knowledge, there is no study on the likelihood of an ulcer relapse if typical symptoms recur in a patient with previous gastric ulcer disease. In our study only two of 26 patients with recurrence of symptoms did not have an ulcer at subsequent endoscopy. Accordingly, if malignant disease has previously been ruled out, endoscopy cannot be considered necessary at each relapse in a gastric ulcer patient, and treatment can often be started after history taking alone.

In addition to the symptomatology, the relapsing ulcers also behaved similarly to the original ulcers in healing response, an observation we believe has not been reported before. Thus, in only one third of the original eight weeks healers healing of a recurrent ulcer was seen after four weeks, whereas nearly all the original four weeks healers also healed after four weeks when having a recurrence. Gastric ulcer patients should therefore, on recurrence, be given treatment according to their initial healing response.

In conclusion, we have found that ranitidine 150 mg at night significantly reduces the recurrence rate in gastric ulcer patients; that the gastric H^+ secretion may give an indication of the likelihood of a relapse; and that the initial healing response may be a guideline for the length of treatment needed if a relapse occurs.

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