Two year maintenance treatment of duodenal ulcer disease with ranitidine 150 mg: a prospective multicentre randomised study

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Abstract

Maintenance treatment of duodenal ulcer (DU) with ranitidine 150 mg/day was compared with placebo in a two year prospective multicentre randomised study. Three hundred and ninety nine patients were included (mean age: 44.7 years, M/F ratio=2.47/1; 37.6% of smokers) in placebo (n=202) and ranitidine (n=197) groups. Efficacy was assessed by the length of time to the first ulcer pain attack (with or without endoscopic confirmation) or DU complication. One hundred and fourteen patients of 399 (28.6%) had incomplete follow up. Actuarial survival curves of patients without ulcer pain (26 and 53% at two years in placebo and ranitidine groups, respectively) were significantly different ($p<0.0001$). Endoscopies were performed depending on physicians' decision (mainly where there was severe pain or complication). Patients without relapses from endoscopy were more frequent in the ranitidine group (83%) than in the placebo group (47%, $p<0.0001$). A greater incidence of complications, mainly bleeding, was also seen in the placebo group (13 complications *v* two in the ranitidine group, $p<0.002$). No factor predicting DU relapse was identified. No important side effect was encountered. Ranitidine 150 mg/day is effective and well tolerated in preventing ulcer pain attacks and DU complications for up to two years.

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The efficacy of longterm ('maintenance') treatment of duodenal ulcer (DU) disease with H_2 blockers is well established, at least for one year of treatment¹⁻⁷; review in ref 6. Less information is available about longer periods and fewer controlled trials of at least two year duration have been published.⁸⁻¹⁵ Two major problems are encountered, however, when one analyses such trials. Firstly, the number of patients lost to follow up is comparatively high, ranging from 20¹⁴ to 70-90%, namely in the placebo groups.⁹⁻¹⁵ Secondly, the number of patients included in these trials rarely exceeds 150. This is of critical importance because the criteria for assessing the efficacy of longterm treatment are currently becoming more accurate. If it is expected that longterm treatment should decrease morbidity and mortality related to DU disease, not only should ulcer pain be alleviated for the patient but the incidence of potentially serious complications (mainly bleeding) should also be diminished. As calculated in this study (see methods), such an aim needs 200 patients to be studied per group.

Finally, clinical studies should be conducted pragmatically, in conditions resembling as closely as possible current practice. This should limit selection bias and systematic procedures (visits, endoscopies) that would not have been performed otherwise. The aim of this study was to compare the efficacy of ranitidine 150 mg/day and placebo for up to two years in preventing occurrence of ulcer pain and DU complications.

Patients and methods

PATIENTS

Three hundred and ninety nine DU patients without ulcers were included within 15 days of endoscopy in this prospective study. They were randomly allocated to receive either ranitidine 150 mg once daily (n=197) or placebo (n=202) after dinner for 24 months. Table I shows the patients' main characteristics and they were similar in the two groups except for the proportion of alcohol users. Mean daily alcohol intake, however, was similar in the two groups. Patients with gastric ulcer, Zollinger-Ellison syndrome, gastric surgery, or major organ failure were excluded, as were pregnant women and lactating mothers.

METHODS

The study was undertaken in a prospective randomised double blind, placebo controlled way and was multicentric, with 59 French gastroenterologists participating who were in private or in hospital practice.

Follow up visits were scheduled every three months for 24 months, and whenever symptoms recurred. Treatment failure was defined by recurrence of epigastric pain, identical to pre-

TABLE I Main characteristics of the 399 patients with healed duodenal ulcers (DU) before treatment with ranitidine 150 mg or placebo

	Placebo (n=202)	Ranitidine (n=197)
Sex ratio (M/F)	2.4 (143/59)	2.5 (141/56)
Mean age (years (SEM))	45.8 (0.83)	43.7 (0.88)
Patients with previous ulcer attacks	69.2%	71.3%
Mean duration of DU disease (year (SEM))	7.9 (0.70)	7.4 (0.53)
Mean incidence of relapse (per year (SEM))	1.34 (0.13)	1.34 (0.10)
Patients with erosive duodenitis at inclusion	10.5%	10.7%
Smokers	38.1%	37.1%
Mean quantity (g/day (SEM))	14.9 (1.10)	14.7 (1.03)
Alcohol users	34%	24%*
Mean quantity (g/day (SEM))	45.9 (4.08)	43.4 (5.42)

* $p<0.05$ *v* placebo.

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TABLE II Patients' follow up during the two years of study

	Placebo (n=202)	Ranitidine (n=197)
Lost to follow up	15	21
Withdrew consent during the study	22	33
Side effects	7	3
Pregnancy	0	6
Severe concomitant disease	4	3
Complete follow up	154	131

Fisher's exact test (two tail) $p=0.021$.

TABLE III Actuarial rates of patients free of ulcer pain at two years according to possible predictive factors of duodenal ulcer (DU) relapse

	Placebo (n=202)	Ranitidine (n=197)
Age (<40 years v ≥ 40 years)	25 v 26	55 v 53
Sex (male v female)	28 v 22	54 v 51
Smoking (yes/no)	26 v 27	42 v 59
Alcohol (<40 g/day v 40 g/day)	26 v 30	29 v 56
Duration of DU disease (<5 years v ≥ 5 years)	30 v 21	50 v 60
Erosive duodenitis at DU healing (yes/no)	31 v 26	43 v 55
Incidence of recurrences (<2 v ≥ 2)	32 v 18	51 v 61

None of the comparisons was statistically significant. All values shown are percentages.

vious episodes or persisting for at least three days, or by the occurrence of a DU complication. The protocol originally mentioned that in the event of treatment failure patients should receive ranitidine 300 mg/day for four weeks and resume the trial if the DU was healed.^{4,16} The high rate of protocol violations – that is, patients' refusal to take a possibly inactive drug in the case of DU relapse, led us to discontinue the study at the time of the first symptomatic recurrence. Endoscopy was performed on the physician's decision, which was mainly where there were severe symptoms or DU complication. The study was approved by the Ethics Committee of Bichat-Claude Bernard Hospital, Paris and informed consent was obtained from all patients.

Results are presented as lifetable analysis – (that is, the length of time to the first clinical episode). Statistical significance was set at the 0.05 value. The number of patients included was determined on the assumption that ranitidine treatment would reduce the rate of DU complications from 5 to 0.5% at one year and was calculated at 200 patients per group (bilateral

Figure 1: Actuarial curves of patients without ulcer pain in the ranitidine (—●—) and placebo (—○—) groups during 24 months. The difference is statistically significant (log rank test, $p<0.0001$). Each value is represented as mean $\pm$ 95% confidence intervals.

Figure 2: Curves of patients without ulcer relapse at endoscopy according to Kaplan-Meier's method in the ranitidine and placebo groups during 24 months. The difference is statistically significant (log rank test, $p<0.0001$).

test). Qualitative data about patients' characteristics at baseline were compared with χ^2 or bilateral Fisher's exact tests when appropriate. Length of time to the first symptomatic recurrence and search for predictive factors of relapse were calculated according to the actuarial method. Length of time to the first endoscopic recurrence or complication was calculated according to the Kaplan-Meier's method. Curves were compared by the log rank test. SAS version 6 software (SAS Institute Inc, Cary NC, USA) was used.

Results

Thirty six patients (9%) were lost to follow up. Fifty five more patients (13.8%), however, withdrew their consent to participate during the study, most of them at the end of the first year of treatment. In these patients the duration of follow up was thus shorter than the two years initially planned. Table II shows the causes of incomplete follow up in 114/399 patients (28.6%).

The length of time to the first episode of pain is shown in Figure 1 and was significantly longer in the ranitidine group than in the placebo group ($p<0.0001$). Twenty six per cent and 53% of the patients were free of ulcer pain at two years in the placebo and ranitidine groups, respectively.

Patients free of endoscopic relapse (Fig 2) – 47 and 83% of the patients were free of endoscopic

Figure 3: Curves of patients without duodenal ulcer (DU) complications according to Kaplan-Meier's method in the ranitidine (—●—) and placebo (—○—) groups during 24 months. The difference is statistically significant (log rank test, $p<0.002$).

relapse at two years, in the placebo and ranitidine groups, respectively ($p < 0.0001$).

DU complications – 15 patients had a DU complication throughout the study, 13 in the placebo group and two in the ranitidine group (Fig 3, $p < 0.002$). In the placebo group, 10 patients presented with DU bleeding. Haemorrhage was mild in five cases; five patients required a stay in hospital (mean duration, 12 days); one of them had surgery for persistent bleeding. Three patients had endoscopic stenosis of the duodenal cap, but none had surgery during the study period. In the ranitidine group, one patient experienced haematemesis because of a bleeding DU, while receiving anticoagulant treatment for thrombophlebitis. DU healed with reinforcement of medical treatment (300 mg/day); the patient stayed in hospital for nine days and required blood transfusion. Another patient presented with an incomplete stenosis of the duodenal cap at endoscopy and was not operated on.

Predictive factors of DU relapse (Table III) – none of the following factors was predictive for DU relapse, either in the placebo or in the ranitidine group: age, sex, smoking, alcohol consumption, duration of DU disease and incidence of recurrences, presence of erosive duodenitis at time of DU healing.

Compliance and adverse events – compliance to medical treatment was assessed by the number of tablets returned at each control visit. Compliance was very satisfactory in both groups (89 and 93% of the tablets were effectively taken in the placebo and ranitidine groups, respectively). Adverse events leading to withdrawal occurred in 10 patients (Table II), but none was thought by the investigator to be related to the study drug. Minor side effects were seen in 13 (6.4%) and 9 (4.5%) patients in the placebo and ranitidine groups, respectively.

Discussion

This study shows the efficacy of ranitidine 150 mg taken as a single daily dose after dinner in the two year maintenance treatment of DU disease. Ranitidine significantly increased the length of time to the first clinically relevant episode – that is, ulcer pain or DU complication, and thus the number of symptom free patients after a two year survey. A total of 28% patients failed to complete the two year follow up. This comparatively high proportion has been noted in other longterm trials in DU disease.⁸⁻¹⁵ A possible explanation is that patients who are symptom free do not wish to continue with maintenance treatment for a condition that is perceived as being benign.¹⁷ This was seen in this study, as 33 patients in the ranitidine group (17%) withdrew consent because they did not wish to continue taking treatment in the absence of symptoms. When this is taken into account the reason for the significant discrepancy in follow up rates between the ranitidine and the placebo treated groups (66 and 76% respectively, Table II) is explained.

Treatment success was defined by the absence of any ulcer pain (identical to previous episodes or lasting for at least three days) during the two

years of study. Endoscopy was not required to confirm the diagnosis of relapse, as is often the case in current clinical practice. Moreover, typical pain episodes without visible ulcer at endoscopy have been recorded in DU patients with a percentage as high as 62% of the patients.¹³ On the contrary, the absence of regularly scheduled endoscopies in this study means that the prevalence of asymptomatic ulcers was not assessed. The clinical importance of these ulcers occurring in patients under maintenance treatment is highly questionable,¹⁸ and some studies have shown that their course is to heal or remain asymptomatic, rarely to become symptomatic and even less frequently to become complicated.¹⁹

With the stringent above mentioned criteria, more than one patient of two was relapse free at two years in the ranitidine group (as compared with one of four in the placebo group). Some randomised double blind studies of DU maintenance treatment with H_2 blockers for at least two years have been published, either with cimetidine,^{8,9,13,15} ranitidine,^{8-12,14} or nizatidine.¹⁰ In most of them, the number of patients included was small or the number of drop outs high. Van Deventer *et al* found in 140 DU patients (who re-entered the maintenance phase after healing of recurrent ulcers), that prophylactic treatment with ranitidine reduced the relapse rate from 63 to 37% after two years of treatment.¹⁴ These data included, however, asymptomatic ulcers found at routine endoscopy at 12 and 24 months (almost two thirds of the ulcers in the ranitidine group and one third in the placebo group, were asymptomatic). On the other hand, pain episodes without endoscopically confirmed DU relapse were not taken into account in this study.

A pragmatic protocol, close to the present one, was used by Pym *et al* with cimetidine (400 mg/day).¹³ Patients were contacted monthly by phone and ulcer symptoms then recorded. Endoscopy was performed only if the gastroenterologist considered it necessary and if the patient agreed. The proportion of patients with major ulcer like symptoms ranged from 65 to 72% during each of the three years of treatment without any difference between the cimetidine and placebo groups. In addition, cimetidine has been shown to be less effective than ranitidine in maintenance treatment of duodenal ulcer.^{20,21} This is related to a less potent inhibition of nocturnal acid secretion by 400 mg cimetidine compared with 150 mg ranitidine.^{22,23}

Although controlled studies of maintenance treatment with ranitidine for more than two years are not available, interesting results have been recently provided by Penston and Wormsley in 464 patients treated with 150 or 300 mg ranitidine for up to nine years in an open manner.²⁴ Cumulative remission rates in the patients receiving maintenance treatment throughout the entire study period were significantly better to those seen in the patients remaining at least one period without such treatment. The results of this open study may explain why the difference in efficacy between the ranitidine and placebo treated groups in our controlled study is not greater. In effect, continuous placebo treatment seems to be associated with a

higher degree of efficacy than intermittent treatment, so that the results presented here are not comparable with those from studies with intermittent treatment.

The results of this study showed a significant reduction in the rate of DU complications, mainly bleeding. This is at variance with several studies in which the complication rate was surprisingly low, even in the placebo group.¹⁴ Jensen *et al* showed, however, that ranitidine 150 mg/day for up to three years decreased rebleeding in patients with recent severe DU haemorrhage.¹¹ In addition, Penston and Wormsley found a cumulative risk of bleeding of 1.3% after three years in 265 DU patients on continuous maintenance treatment with ranitidine, compared with 15.2% after three years in 123 patients without anti-ulcer treatment.⁵

Surprisingly, we could not find evidence of any predictive factors of DU relapse, in particular smoking, as in some^{14,25} but not all²⁶ studies. The predictive value of such factors, however, is usually limited to patients receiving placebo.¹⁴ Moreover, this has been established with conventional criteria – that is, endoscopic relapses, but data taking into account symptomatic relapses are not available.

Finally and as suggested by some authors, the decrease in the use of medical resources with maintenance treatment parallels a decrease in the cost of patients' management.^{13,27,28} The efficacy of maintenance treatment on DU relapses and complications could thus have important economic implications.

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