A single night time dose of ranitidine in the acute treatment of gastric ulcer: a European multicentre trial

F P RYAN, R JORDE, R S B EHSANULLAH, K SUMMERS, AND J R WOOD

From the Northern General Hospital, Sheffield, University Hospital of Tromsøe, Tromsøe, Norway; Clinical Research Division, Glaxo Pharmaceuticals Ltd., Greenford, Middlesex

SUMMARY Four hundred and twenty eight patients with endoscopically diagnosed gastric ulcers, randomly allocated to treatment with ranitidine 300 mg at night or ranitidine 150 mg twice daily, were evaluated in a double blind multicentre trial conducted in 10 European countries. After four weeks, complete ulcer healing was observed in 138 of 211 patients (65%) treated with ranitidine 300 mg nocte and in 155 of 217 patients (71%) receiving 150 mg bd. Cumulative healing rates at eight weeks were 90% and 93%, respectively. There was no statistically significant difference between the healing rates at either four or eight weeks. The treatment regimens were equally effective at rapidly reducing the incidence of ulcer related symptoms. Adverse events reported were minor and equally distributed between the two groups. The results of this trial show that 300 mg of ranitidine administered at night is an effective and safe alternative to the current twice daily regimen for the short term treatment of gastric ulcer.

Controlled clinical trials in a large number of patients with peptic ulcer disease have shown that ranitidine in a dose of 150 mg given twice daily is an effective and safe agent which promotes complete healing of the majority of peptic ulcers within four to eight weeks of treatment.¹ Ranitidine (Zantac®) was introduced into clinical practice in 1981 and its extensive usage since then has confirmed the safety and efficacy of the drug.

Recent studies have shown that the same total daily dose (300 mg) given at night is an effective and safe alternative to the standard twice daily regimen in the treatment of duodenal ulceration.^{2,3} In view of the established efficacy of ranitidine 150 mg twice daily in the treatment of gastric ulcer,⁴ the above findings raise the possibility that a single daily dose of ranitidine may also have a place in the treatment of gastric ulcer. To evaluate this, the present trial compared the use of ranitidine 300 mg at night with ranitidine 150 mg bd in the treatment of gastric ulceration.

Methods

PATIENTS

Five hundred and seventy one patients aged over 18 years with endoscopically diagnosed gastric ulcers were recruited into a double blind trial conducted in 96 centres in 10 European countries (Austria, Denmark, Holland, Ireland, Norway, Poland, Sweden, Switzerland, United Kingdom and West Germany), using a common protocol. Exclusion criteria comprised: ulcer perforation, upper gastrointestinal haemorrhage requiring transfusion during the previous week, pyloric stenosis, Zollinger-Ellison syndrome, concomitant use of potentially ulcerogenic drugs, peptic ulcer medication during the preceding 30 days (except for low dose antacids), pregnant and lactating women, liver disease, and other concurrent medical conditions. Patients with malignant changes found on histological examination of gastric biopsies were also excluded. Patients gave their informed consent to the study which was approved by ethics committees in individual countries. The trial was conducted in accordance with the Declaration of Helsinki, Tokyo Amendment, 1975.

Patients were randomly allocated to treatment

Address for correspondence: Dr F P Ryan, Northern General Hospital, Sheffield, S5 7AU.

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with either ranitidine 300 mg given as a single night time dose with a matching placebo in the morning or the conventional regimen of ranitidine 150 mg twice daily. All tablets were identical in size and appearance. No other peptic ulcer treatment was permitted during the trial except for antacid tablets (Rennie®), with an acid neutralising capacity of 15.1 mmol, which were supplied for symptomatic relief.

Treatment was provided initially for four weeks, after which endoscopy was repeated and ulcer related symptoms assessed. Patients whose ulcers had not healed continued treatment for a further four weeks and were re-endoscoped and reassessed at the end of this period. At each visit, a physical examination was carried out and venous blood samples were taken for routine biochemical and haematological analyses. Biopsies of the ulcers were taken to exclude malignancy. Ulcer healing was defined as no break in the continuity of the mucosa with no exudate present as observed on endoscopy. Statistical analyses were carried out using the χ^2 test (without continuity correction and following the Mantel-Haenszel method) and Student's *t* test. Tests were considered to be significant if the *p* value was less than the conventional 5% level.

Patients were included in the statistical analyses of ulcer healing rates if their second endoscopy was done within 28 ± 4 days of the beginning of the trial, and within 56 ± 4 days for those patients whose ulcers were unhealed at the time of the second endoscopy.

Results

One hundred and forty three patients entered into the trial were excluded from the analysis of healing rate at four weeks for reasons listed in Table 1. The distribution of exclusions was similar in the two treatment groups.

Of the 428 patients who were available for analysis at four weeks, 211 received ranitidine 300 mg nocte and 217 received the twice daily

regimen. The two treatment groups were comparable with respect to patient sex, age, weight, smoking habits, alcohol consumption, duration of dyspeptic history and current episode, and evidence of haematemesis/melaena (Table 2).

ULCER HEALING

After four weeks, complete gastric ulcer healing was observed in 138 out of 211 patients (65%) in the 300 mg nocte group and in 155 of 217 patients (71%) in the 150 mg bd group. At eight weeks, the cumulative healing rates were 90% (176 of 196 patients) and 93% (189 of 204 patients), respectively. There were no statistically significant differences between the healing rates in the two groups at either four ($p=0.18$) or eight weeks ($p=0.31$).

There was no evidence that the healing rate at either four or eight weeks was influenced by patient sex, smoking habits or alcohol consumption (Table 3) or that it differed for single or multiple ulcers. Although healing rates varied from country to country, no statistically significant differences were observed at four or eight weeks between the two treatment groups in the individual countries.

ULCER RELATED SYMPTOMS

The degree of severity and incidence of ulcer related symptoms (epigastric pain, heartburn, nausea and vomiting) were found to be similar in the two

Table 2 Demographic background of population

	Ranitidine 300 mg nocte	Ranitidine 150 mg bd
Patients (No)	211	217
Sex (M:F)	116:95	119:98
Age (yr): mean $\pm$ SD	55 $\pm$ 14	56 $\pm$ 15
Weight (kg): mean $\pm$ SD	67 $\pm$ 14	66 $\pm$ 15
Smoking status:		
None	82	94
Light	96	85
Heavy	33	38
Alcohol intake:		
None	120	121
<2oz/day	82	87
$\geq$ 2oz/day	8	8
Unspecified	1	1
Duration of dyspeptic history (yr): Median	3	4
Interquartile range	1-8	1-10
Duration of current episode (mth): Median	2	2
Interquartile range	1-3	1-3
Evidence of haematemesis/ melaena:		
Yes	38	31
No	172	186
Unspecified	1	0

Table 1 Reasons for excluding patients from analysis

Reason	Patients (no)	
	Ranitidine 300 mg nocte	Ranitidine 150 mg bd
No follow up endoscopy	13	15
Early/late endoscopy	54	54
Duodenal ulcer only	1	2
Adverse event		
necessitating withdrawal	3	1
Total	71	72

Table 3 *Healing rates randomised for smoking and alcohol intake*

	<i>Ranitidine 300 mg nocte</i>	<i>Ranitidine 150 mg bd</i>
Four weeks		
Non-smokers	57/82 (70%)	68/94 (72%)
Smokers	81/129 (63%)	87/123 (71%)
Eight weeks		
Non-smokers	68/78 (87%)	80/89 (90%)
Smokers	108/118 (92%)	109/115 (95%)
Four weeks		
No alcohol	81/120 (67%)	86/121 (71%)
Alcohol consumers	57/90 (63%)	68/95 (72%)
Eight weeks		
No alcohol	101/111 (91%)	103/113 (91%)
Alcohol consumers	75/85 (88%)	85/90 (94%)

treatment groups at the pretrial, four, and eight week visits. Both treatment regimens were equally effective at rapidly reducing the incidence of these symptoms.

COMPLIANCE

Test tablet compliance and antacid consumption were assessed by returned tablet counts at the end of the four week treatment period. Treatment compliance and antacid consumption were similar in the two groups. The compliance was excellent in both treatment groups, and the average daily consumption of antacid tablets was 0.4 and 0.5 in the 300 mg nocte and 150 mg bd groups, respectively.

CARDIOVASCULAR PARAMETERS

There were no statistically significant differences between the two treatment groups at either four or eight weeks with respect to systolic or diastolic blood pressure or pulse rate.

BIOCHEMICAL AND HAEMATOLOGICAL ANALYSES

All 571 patients who entered the trial were screened for abnormalities in the laboratory parameters determined. Modest and transient increases in some laboratory values which were considered to be possibly drug related were observed in three out of 211 patients receiving ranitidine 300 mg nocte and in four out of 217 patients receiving ranitidine 150 mg bd. One 86 year old woman showed raised urea (4 to 14.4 mmol/l, normal range 2.5–7.5 mmol/l) and creatinine (60 to 180 µmol/l, normal range 53–115 µmol/l) and one 74 year old woman was found to have a raised GGT (12 to 94 IU/l, normal range 7–33 IU/l) after four weeks treatment with ranitidine 150 mg bd. The remaining five patients exhibited small rises in SGPT or SGOT to just outside the normal ranges at four weeks of therapy.

ADVERSE EVENTS

A total of 18 adverse events were reported by 15 patients; eight patients (3%) receiving ranitidine 300 mg nocte and seven patients (2%) receiving 150 mg bd. The distribution of adverse events (Table 4) was comparable for the two treatment groups. No deaths were reported during the trial. Five patients, three in the nocte group and two in the bd group (one during the second treatment period), withdrew from the study because of adverse events. None of the events reported was serious or unexpected, and in none of the cases was a causal relationship with ranitidine considered to be likely.

Discussion

The results of this trial show that a single nocturnal dose of ranitidine 300 mg is as effective as the conventional 150 mg twice daily regimen in the acute healing of gastric ulcer. Ulcer healing rates assessed after four or eight weeks of treatment were not statistically significantly different in a patient population sufficiently large to enable the detection of a 15% difference with a 90% confidence. The majority of patients (90% or more) showed complete ulcer healing after eight weeks' therapy. The healing rates for the twice daily regimen are similar to those reported previously in trials comparing it with either placebo⁵ or other active drugs.^{6,7} Gastric ulcer healing in both treatment groups was found to be independent of patient sex, smoking habits and alcohol consumption. The latter results confirm previous findings of Kellow and others⁸ that smoking and alcohol intake did not influence the effect of ranitidine on gastric ulcer healing.

The incidence and severity of epigastric pain and other dyspeptic symptoms were rapidly reduced by

Table 4 *Adverse events*

	<i>Reports (no) (No withdrawn)</i>	
	<i>Ranitidine 300 mg nocte (n=282)</i>	<i>Ranitidine 150 mg bd. (n=289)</i>
Diarrhoea/constipation	0	3 (0)
Epigastric pain	0	1 (1)
Headache	2 (1)	0
Fatigue	2 (1)	2 (0)
Dizziness	1 (0)	0
Skin rash	2 (1)	2 (1)
Gynaecomastia	1 (0)	0
Chest pain	1 (1)	1 (1)
Total	9 (4)	9 (3)
Patients (No)	8 (3)	7 (2)
Total population (%)	3 (1)	2 (0.7)

both treatment regimens and antacid consumption was similar in the two groups. Compliance was good for both treatment regimens.

Clinical trials evaluating the effect of once daily ranitidine (300 mg at night) in the treatment of duodenal ulcer have shown that this regimen is equivalent to the standard 150 mg bd regimen in terms of ulcer healing. These findings have been taken as support for the hypothesis that nocturnal secretion of acid is of particular importance in the pathogenesis of duodenal ulcer. Nocturnal acid secretion in gastric ulcer disease is known to be normal or reduced.^{9 10} In view of this, the present findings suggest that the equivalence of once and twice a day ranitidine therapy for acute healing of peptic ulcer may result from comparable reductions in 24 hour gastric acidity by the two regimens rather than an effect due to nocturnal administration *per se*. Whilst studies have compared the effects of 150 mg bd and 300 mg nocte on 24 hour gastric acid secretion in duodenal ulcer and shown them to reduce gastric acidity to a comparable extent, similar studies have yet to be reported for gastric ulcer.

A recent study comparing gastric ulcer healing with ranitidine and omeprazole, an extremely potent inhibitor of gastric acid secretion,¹¹ reported healing rates of 45, 80 and 90% for ranitidine and 43, 81 and 95% for omeprazole after two, four and eight weeks, respectively, with no statistically significant difference between the two drugs at any time interval.¹² These results indicate that, in contrast with findings in patients with duodenal ulcer,¹³ suppression of gastric acidity to a greater extent than that achieved by the present two ranitidine regimens is unlikely to result in more rapid ulcer healing.

The absence of serious or unexpected adverse events in both treatment groups, and the lack of clinically significant biochemical or haematological changes during a treatment for up to eight weeks confirm that ranitidine, whether given in the conventional twice daily regimen or as a single night time dose, is a well tolerated and safe drug for the treatment of acute gastric ulceration. The single night-time dose may improve treatment compliance for certain patients.

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PARTICIPATING INVESTIGATORS

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