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Clinical trial

Acute treatment of duodenal ulcer: a multicentre study to compare ranitidine 150 mg twice daily with ranitidine 300 mg once at night

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SUMMARY A randomised double blind clinical trial was undertaken in the UK and Ireland to compare ranitidine 300 mg given as a single bed time tablet with raniditine 150 mg twice daily in the acute treatment of duodenal ulcers. Of the 594 patients with endoscopically diagnosed duodenal ulcer entered into the trial, 424 patients had complete endoscopic findings on which healing rates at four weeks were determined. By this time 156 of 201 (78%) patients healed with ranitidine 300 mg nocte compared with 186 of 223 (83%) receiving ranitidine 150 mg twice daily ($p=0{\cdot}28$). After eight weeks of treatment 97% of the patients in each group were healed. The healing rates for smokers and non-smokers did not differ significantly at either four or eight weeks. Each regimen was equally effective in reducing day and night-time pain. Adverse events were reported in 23 patients overall; 12 were withdrawn from the trial. Minor abnormalities in liver function tests were noted in three patients. The trial confirmed that a single dose of ranitidine 300 mg given at night is a safe, effective alternative treatment to ranitidine 150 mg bd for the acute treatment of duodenal ulcer.

The importance of increased nocturnal gastric acid secretion in the pathophysiology of duodenal ulceration has been considered for many years and provided the basis for Dragstedt's proposal that such hypersecretion could be controlled by vagotomy.[1 2] The effect of vagotomy is not, however, confined to an effect on nocturnal gastric acid secretion as it reduces gastric acidity to all forms of stimulation[3 4] over the entire 24 hour period.[5 6] Dosage regimens for the histamine-H_2-receptor antagonists have sought to mimic this reduction in both day and night time secretion to achieve ulcer healing.

In a carefully controlled study of 24 hour intragastric acidity in patients with recently healed duodenal ulcers, ranitidine 150 mg morning and evening was found to reduce day and night time acidity by approximately 55%. This reduction was similar to that achieved by cimetidine 200 mg tds plus 400 mg nocte.[7] Clinical trials in duodenal ulcer have confirmed that the healing rates were also similar for the two drugs.[8]

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Further studies of 24 hour intragastric acidity with these agents have shown that the same overall reduction could be achieved using a single night time dose of either ranitidine 300 mg or cimetidine 800 mg, but that acid inhibition was greatest in the overnight period.[9] Clinical trials of these simplified dosage regimens have shown comparable healing rates with those achieved with the twice daily regimen of both ranitidine[10] and cimetidine[11] although the number of patients in each trial (102 and 48 respectively) was not large enough to exclude a type II statistical error. The purpose of the present clinical trial was to evaluate a large number of patients to compare the effectiveness and safety of ranitidine given as a single night time tablet (300 mg nocte) with the standard twice daily dose (150 mg bd).

Methods

PATIENTS

Five hundred and ninety four patients with endoscopically confirmed duodenal ulcers (>5 mm in diameter) were recruited in 58 centres in the United

Kingdom and Ireland. The study was a randomised double-blind comparison of ranitidine 150 mg twice daily and ranitidine 300 mg nocte. All patients were treated according to a common protocol which was approved by the Ethics Committee of each centre. Written informed consent was obtained from each patient.

Patients were excluded if they met any of the following criteria: aged under 18 years, treatment with ulcerogenic drugs, recent peptic ulcer perforation, upper gastrointestinal haemorrhage requiring transfusion within the previous week, concomitant gastric ulcer or pyloric stenosis, pregnancy or lactation, peptic ulcer medication (except antacids, taken for symptomatic relief) during the preceding four weeks, and any other serious medical condition or inability to cooperate with the trial requirements. Patients were randomised to receive either ranitidine 150 mg twice daily or 300 mg at night. Those taking 300 mg at night also took a placebo tablet in the morning. All tablets were identical in size and appearance and were foil wrapped. One day's supply was packed in a plastic sachet. The tablet to be taken in the morning was marked '1' and the evening dose '2'. Supplies were dispensed in coded boxes containing 35 days' supply. Treatment was for an initial period of four weeks. If the ulcer was unhealed, treatment was continued for a further four weeks and endoscopy carried out again at eight weeks. At each visit a physical examination was carried out and blood samples were taken for routine haematological and biochemical determinations. Any adverse events were also recorded.

STATISTICAL ANALYSIS

The Mantel-Haenszel χ^2 test was used to assess healing rates across different centres. Other data were analysed by means of Student's t test or Fisher's exact test. In order to be included in the analysis of four and eight week healing rates, endoscopy had to be undertaken within four days of the prescribed date (that is 24–32 days and 52–60 days respectively after the start of treatment). The power of the study gave a 95% probability of detecting a 15% difference in healing rates when $\alpha=0{\cdot}05$.

Results

Details of patients who were evaluated are shown in Table 1. The two treatment groups were well matched for age, sex distribution, duration of disease, duration of current episode, history of previous haematemesis or melaena and smoking and alcohol consumption. Four hundred and twenty four of the 594 patients were evaluable for determination of healing rates at four weeks and 400 for cumulative analysis of eight week healing rates. One hundred and ninety five patients were excluded from this analysis: 131 for early or late endoscopy outside the above limits, 12 for adverse events, 30 were lost to follow up and 12 were excluded for other reasons. The distribution of non-evaluable patients across the

Table 1 *Demographic data for trial patients available for analysis*

	300 mg nocte	*150 mg bd*	*Test for difference*
Total entered	290	304	
Number analysed (at 4 weeks;	201*	223	
Number excluded (at 4 weeks)	89	81	
Sex M:F	141:61	152:71	p=0·75
Age (yr±SD)	46·1±1·05	45·9±1·06	p=0·89
Weight (kg±SE)	68·1±0·79	67·0±0·87	p=0·35
Non-smokers	69 (34%)	83 (37%)	p=0·64
Smokers	132 (66%)	140 (63%)	p=0·64
Not specified	1 —	0 —	
Alcohol consumption			
None	49 (24%)	68 (31%)	p=0·34
Drinkers	151 (76%)	154 (69%)	p=0·34
Not specified	2	1	
Duration of ulcer disease (yr±SE)	7·3±0·49	7·0±0·52	p=0·39
Length of current episode (month±SD)	3·6±1·24	3·5±0·63	p=0·28
Number of patients with previous haematemesis/malaena	41	41	

*One patient was evaluable at 8 weeks but not at 4 weeks (failed endoscopy).

two treatment groups was similar at both four and eight weeks (Table 2).

HEALING RATES

The effect of ranitidine 300 mg nocte on ulcer healing at four weeks was similar to ranitidine 150 mg bd (78% and 83% respectively; p=0·28). By eight weeks the cumulative healing rate in both groups had reached 97% (Table 3). The differences in healing rates between smokers and non-smokers did not reach statistical significance (Table 4). There were no differences in pain relief between the two treatment regimens: by four weeks, 88% of patients receiving 300 mg nocte and 91% receiving 150 mg bd were free of day time ulcer related pain (p>0·05). The proportion free of night time pain was also similar in both groups (89% *vs* 95%; p>0·05).

Table 2 *Criteria for exclusion of duodenal ulcer patients from analysis of 4 and 8 week healing rates*

	4 weeks		*8 weeks*	
Reason	*300 mg nocte*	*150 mg bd*	*300 mg nocte*	*150 mg bd*
Lost to follow up	11	9	7	3
Adverse event	6	2	2	2
Early/late endoscopy	61	59	7	4
Anti-ulcer drug within 30 days of entry	4	6	0	0
*Other	7	5	0	0
Total	89	81	16	9

*Other includes refusal of endoscopy (2), surgery (2), GI bleed (3), failure to carry out endoscopy (2), compliance failure (1), chest infection (1) and incomplete endoscopy (1).

Table 3 *Healing rates at 4 and 8 weeks*

Ranitidine	*4 weeks (%)*	*8 weeks cumulative*
300 mg nocte		
Healed	156 (78%)	180 (97%)
Not healed	45	6
Total	201	186
150 mg bd		
Healed	186 (83%)	207 (97%)
Not healed	37	7
Total	223	214
χ^2	1·17	0·152
p	0·2792	0·6967

ADVERSE EVENTS

Twenty nine adverse events were reported by 23 patients, 12 of whom were withdrawn from the study. These are summarised in Table 5. One 68 year old man sustained a cardiac arrest and died at three days into the trial. He had a past history of myocardial infarction and his pretreatment examination revealed cardiomegaly and a pansystolic murmur. A 27 year old male patient receiving ranitidine 300 mg nocte was found at review (five weeks) to have a benign breast nodule histologically

Table 5 *Summary of adverse events*

	300 mg nocte		*150 mg bd*	
	Number	*Withdrawn*	*Number*	*Withdrawn*
Diarrhoea	4	2	1	0
Nausea/ vomiting	1	1	1	0
Depression	2	1	0	0
Dizziness/ malaise	4	2	3	2
Rash	3	2	2	1
Breast pain	0	0	1	1
Breast lump (benign)	1	0	0	0
Blurred vision	0	0	1	1
Headache	2	1	1	1
Abdominal swelling	1	1	0	0
Death	1	1	0	0
Reports (n)	19	11	10	6
Patients (n)	15	8	8	4

Table 4 *Effect of smoking on healing rates*

	Ranitidine Number healed (%)			
	150 mg bd		*300 mg nocte*	
	4 weeks	*8 weeks*	*4 weeks*	*8 weeks*
Smokers	116 (83%)	131 (96%)	98 (74%) 1, 2	113 (96%)
Non-smokers	70 (84%)	76 (99%)	58 (84%)	67 (99%)

1 *versus* smokers 150 mg bd p=0·16 N.S.
2 *versus* non-smokers 300 mg nocte p=0·15 N.S.

similar to one resected from the same breast three years previously.

LABORATORY DATA

Two patients treated with ranitidine 300 mg nocte and one patient taking 150 mg bd developed minor changes in liver function tests without symptoms or clinical signs of liver disease: In a 60 year old man taking ranitidine 300 mg nocte for eight weeks carbamazepine concomitantly, there was an increase in alkaline phosphatase from 151 U/l to 287 U/l at four weeks which fell to 207 U/l at eight weeks (normal range 60–280 U/l); gamma glutamyl transferase increased from 26 U/l to 61 U/l at four weeks and fell to 34 U/l at eight weeks (normal range 0–50 U/l). The second patient treated with ranitidine 300 mg nocte was a 34 year old man whose ALT increased from 28 U/l to 57 U/l at four weeks (range 10–35 U/l). His bilirubin also increased from 18 μmol to 23 μmol at four weeks (range 0·17 μmol). An 82 year old man receiving ranitidine 150 mg bd, prochlorperazine and mianserin developed an increased AST (38 to 220; normal 0·40 U/l) and bilirubin (14–50; normal 0·21 μmol/l) and had abnormal alkaline phosphatase and gamma glutamyl transferase at baseline and at four weeks.

Discussion

Several clinical trials have recently reported that single night time doses of ranitidine[10 12] or cimetidine[11 13] are effective in healing duodenal ulcers. The present trial confirmed the effectiveness of ranitidine 300 mg nocte in a large number of patients.

The healing rate of 78% in the group taking 300 mg at night was comparable with those at four weeks in previous trials which evaluated the use of ranitidine 150 mg bd for the treatment of duodenal ulcer. In a review of published data Meyrick-Thomas and Misiewicz[8] found that in double blind placebo controlled trials 78% (375/482) healed at four weeks with ranitidine 150 mg twice daily compared with 37% (169/461) on placebo. In single blind trials comparing ranitidine and cimetidine the mean healing rates for ranitidine 150 mg bd and cimetidine 1 g/day were 74% (407/549) and 68% (364/535 patients) respectively. In addition the present results confirm the finding of Ireland *et al*[10] and Brackmann *et al*[12] that the two treatment regimens evaluated are equivalent in terms of ulcer healing.

Recent studies of the effect of ranitidine on 24 hour intragastric acidity indicate that both the degree and the duration of inhibition of gastric acid secretion may play a role in ulcer healing and the prevention of ulcer recurrence. Dammann and colleagues[14] found that ranitidine 300 mg at night reduced 24 hour gastric acidity by 75% in volunteers. This dosage also reduced acidity by 62% in patients with duodenal ulceration[9] but in both studies the overall effect was greatest in the overnight period (85%–95% inhibition) while daytime acid suppression was relatively modest and did not last beyond midday. Twice daily administration of 150 mg reduces acidity through the whole 24 hour period.[7 9] Another study[15] found that 150 mg ranitidine given at bedtime decreased mean 24 hour intragastric acidity by 42% compared with placebo treatment in duodenal ulcer patients. There was a significant decrease in intragastric acidity which lasted from 2400 until 0900, with no significant subsequent change (1000 to 2300 hours). Ranitidine 300 mg at night thus inhibits intragastric acidity for some three to four hours longer and to a greater extent than 150 mg ranitidine but during the rest of the day normal concentrations of acid are present in the stomach. The recent study by Ireland *et al*[10] in 102 patients found that the larger nocturnal dose was more effective in smokers (96% healed four weeks) than the twice daily regimen (75% healed four week, $p<0·01$). The present study showed a small trend in the opposite direction although this did not reach statistical significance in the larger number of patients studied. In neither study, however, was the question of an adverse effect of smoking directly addressed by stratification for smokers and non-smokers during randomisation. Ippoliti *et al*[16] carried out an analysis of data from clinical trials where the effect of smoking was reported and noted a median 20% difference in ulcer healing between non-smokers and smokers irrespective of treatment regimen. Another clinical trial[17] stratified 123 patients for sex and smoking before randomisation to ranitidine, cimetidine, or oxmetidine. They also assessed smoking habits during the acute treatment and follow up over 12 months. Analysis of the data revealed that smoking adversely affected healing and that subsequent relapse rates were significantly higher in smokers. Boyd, Saunders, and Wormsley[18] suggested that this finding was because of decreased inhibition of nocturnal acid secretion in smokers. Studies of acid suppression by H_2-antagonists in smokers with duodenal ulcer disease have recently shown a reduced effect compared with non smokers but nocturnal doses of H_2-antagonists were more effective in smokers than the twice daily dose.[19] Therefore, the finding in the present study of equivalent healing rates in smokers and non-smokers taking ranitidine 150 mg twice daily may be regarded as an unexpected chance finding. The difference in healing rates between 300 mg at night

and 150 mg twice daily in the present study is, however, small in both smokers and non-smokers. Short term healing can thus be achieved using either a single dose of ranitidine 300 mg given at bedtime or ranitidine 150 mg twice daily.

The frequency of adverse reactions observed in the group of patients given the once daily regimen was similar to the frequency in patients given the twice daily treatment. This finding is in keeping with the known safety profile of ranitidine and the lack of dose dependent adverse effects observed in Zollinger Ellison patients treated with ranitidine up to 6 g/day.[20]

The present findings are consistent with the hypothesis that adequate suppression of nocturnal acid secretion is sufficient to heal most duodenal ulcers in four to eight weeks. Treatment with 300 mg of ranitidine at night is a safe, effective alternative to the twice daily regimen over which it may have a benefit in terms of patient compliance.

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APPENDIX

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