Clinical trial

Comparison of twice-daily ranitidine with standard cimetidine treatment of duodenal ulcer

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SUMMARY One hundred and three outpatients with endoscopically diagnosed duodenal ulcer were randomly allocated to treatment with either cimetidine 200 mg tds and 400 mg *nocte,* or ranitidine 150 mg bd for four weeks. The endoscopists were not aware of the treatment and took no part in the clinical management. On completion of treatment ulcers had healed in 43 of 51 (84%) patients given cimetidine and in 40 of 52 (77%) patients given ranitidine. There were no serious unwanted effects in either treatment group. The results show no significant difference between healing rates after four weeks of standard cimetidine therapy or ranitidine 150 mg bd.

Cimetidine, the first histamine H_2-receptor antagonist to be widely available, is accepted as effective therapy for duodenal ulcer.[1] Ranitidine (Fig. 1) is a new H_2-receptor antagonist with a different chemical structure and greater potency than cimetidine.[2-8] We have previously shown that in duodenal ulcer patients ranitidine 150 mg twice daily is at least four times as potent as cimetidine in the standard dosage of 200 mg three times daily and 400 mg at night in inhibiting intragastric acidity and nocturnal acid output.[8] We now compare the effect of these two dose regimes on the healing of duodenal ulcer in a therapeutic trial.

Fig. 1   *Chemical structure of cimetidine and ranitidine.*

Methods

PATIENTS

Adult patients with endoscopically diagnosed duodenal ulcers entered the trial; excluded were patients with previous oesophageal or gastric surgery, pyloric stenosis, gastric, pre-pyloric, pyloric canal, or post-bulbar ulcers, recent perforation, or patients on steroids and anti-inflammatory drugs. Patients with severe concurrent disease, pregnant or lactating women, and those treated with a H_2-receptor antagonist within four weeks were also excluded.

PROCEDURE

Patients were seen three to seven days after the first endoscopy and those fulfilling the criteria for entry were randomly allocated in stratified groups of 10 to treatment with either ranitidine 150 mg bd or cimetidine 200 mg tds after meals and 400 mg at night. They attended the clinic two and four weeks after entry. Antacids (Rennie tablets) were taken as needed for the relief of symptoms throughout the study. Tablet counts at each visit were used for assessment of antacid consumption. Symptoms were assessed with the aid of diary cards completed daily by each patient recording individual episodes of pain during the day and night. A second endoscopy was done within three days of completion of the four
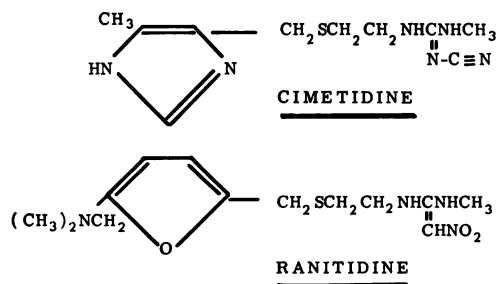
Table 1   *Clinical details of ranitidine and cimetidine groups*

	Number	Sex		Age (yr)		Smoking (%)	Length of history (yr)		Previous H₂ antagonist (%)
		M	F	Mean	Range		Mean	Range	
Cimetidine	51	39	12	41·5	18–70	75	8·4	0·25–36	39
Ranitidine	52	40	12	42·4	16–70	65	8·6	0·25–33	31

Table 2   *Ulcer healing rates in ranitidine and cimetidine groups*

	Healers				Non-healers			
	Age (yr) Mean±SEM	Sex (% female)	Smoking (%)	Previous H₂ antagonist	Age (yr) Mean±SEM	Sex (%) female	Smoking (%)	Previous H₂ antagonist
Cimetidine	40·5±2·4	23	72	15	44·8±5·2	25	100	5
Ranitidine	41·3±2·4	25	63	11	46·1±3·5	21	75	5

week treatment schedule. The same endoscopist performed both examinations in the majority of the patients and no endoscopist took part in the clinical management, thus remaining unaware of the patient's treatment. Duodenal ulcer was defined as a break in the mucosa with slough at the base and the absence of both denoted healing. The presence or absence of macroscopic oesophagitis and duodenitis was recorded at each endoscopy, but did not affect the assessment of healing. Routine haematological and biochemical profiles were taken before and after therapy. All patients gave informed consent to the trial, which was approved by the relevant hospital ethical committees.

Statistical analysis of the results was by Fisher's exact test of significance and the χ^2 test for ulcer healing. The Mann-Whitney U test was used for comparisons of the incidence of pain and antacid consumption in the treatment groups.

Results

One hundred and seven patients (81 male, 26 female) entered the trial. Four patients who failed to adhere to the protocol were excluded from analysis. In three cases the second endoscopy was delayed for independent medical reasons (two on ranitidine, one on cimetidine). The fourth patient stopped medication at two weeks as he was asymptomatic (ranitidine). Of the remaining 103 patients, 51 received cimetidine and 52 ranitidine. The two groups were comparable with respect to age, sex, length of history, smoking, and previous H₂-receptor antagonist therapy (Table 1).

ULCER HEALING
Ulcers healed in 43 patients on cimetidine (84%) and

in 40 patients on ranitidine (77%). This difference is not significant. Combined ulcer healing rates were similar in all three centres: 75%, 83%, and 82% respectively. No difference in healing rates in males or females was apparent with either treatment. There
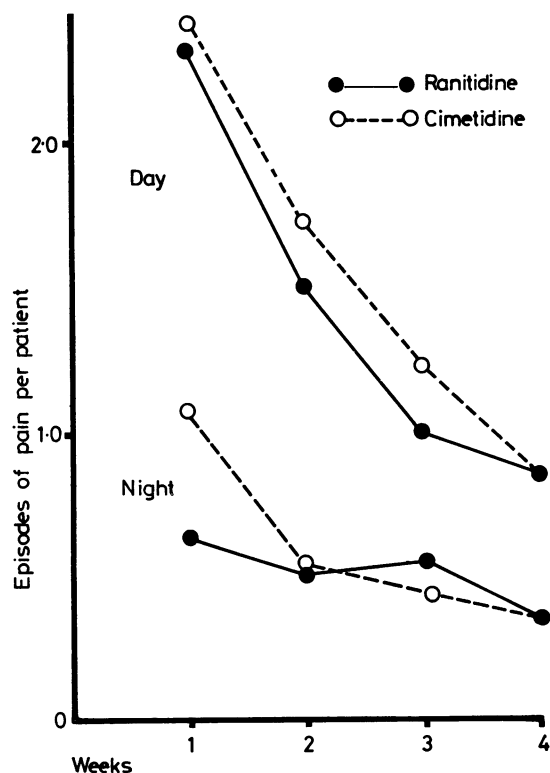

Fig. 2   *Mean number of episodes of pain recorded during both day and night.*
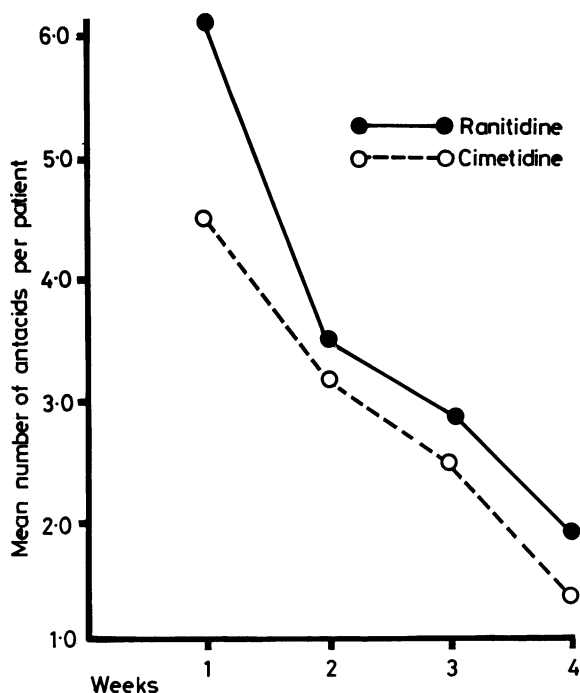
Fig. 3 *Mean number of antacid tablets taken by patients in both treatment groups.*

was no significant difference between the mean age of healers compared with non-healers (Table 2).

PAIN RELIEF AND ANTACID CONSUMPTION
The number of episodes of pain was significantly decreased by both drugs during the first two weeks of treatment ($p < 0.001$) (Fig. 2), and significantly fewer antacid tablets were consumed by patients as treatment continued (Fig. 3) ($p < 0.01$). The reduction was similar in both groups.

UNWANTED EFFECTS
Twelve patients complained of mild side-effects (eight on ranitidine and four on cimetidine), ranging from headaches and dizziness to urinary and upper respiratory tract infections. No patients were withdrawn from the trial because of unwanted effects. Biochemical and haematological profiles showed minimal rises in creatinine (three on cimetidine, one on ranitidine) γ-glutamyl transpeptidase (one in each group) and LDH (four in each group). No other changes were detected.

Discussion

This study shows that ranitidine 150 mg twice daily

is as effective in the short-term healing of chronic duodenal ulcers as cimetidine 1 g daily in divided dosage. In terms of patient compliance and convenience a twice-daily regime may be preferable. The healing rate of duodenal ulcers in this trial is similar to healing rates previously reported with cimetidine[9-16] and with ranitidine 100 mg twice daily[17,18] and 150 mg twice daily.[19] Variations in healing rates between centres were not significant.

Pain was diminished by both treatments and similar decreases in antacid consumption were observed. Observations in this study illustrate two points bearing on the relationship of pain, duodenitis, and healing, which are important clinically. Antacid consumption correlated reasonably well with symptoms, but neither antacid consumption nor persistence of pain could be used as predictors of lack of healing. Only five (31%) of 16 patients experiencing three or more episodes of pain during the final week had unhealed ulcers. By contrast, of 77 patients asymptomatic during the last week, 11 (14%) had unhealed ulcers. Equal proportions (65% and 64%) of patients with or without symptoms in the final week of the trial had persistent duodenitis Investigation of the effect of more prolonged treatment on duodenitis would be interesting.

Results of this study suggest that ranitidine, like cimetidine, is effective clinically in the short-term management of duodenal ulcer.

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