

## Effect of the H<sub>2</sub>-receptor antagonist ranitidine on depression and anxiety in duodenal ulcer patients

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### Summary

Depression and anxiety were measured during the course of a double-blind, placebo-controlled trial of the histamine H<sub>2</sub>-receptor antagonist, ranitidine (150 mg twice daily), in patients suffering from duodenal ulcer but free of systemic disease. There were 25 patients in the ranitidine group (mean age: 33.2 years) and 28 in the placebo group (mean age: 37.2 years). In both groups there was a highly significant and progressive decrease in depression and anxiety scores over the 4 weeks of treatment. There were no instances of mental confusion. In our group of otherwise physically healthy patients, ranitidine appeared to be free of neuropsychiatric complications.

KEY WORDS: ranitidine, histamine H<sub>2</sub>-receptors, depression, anxiety, duodenal ulceration.

### Introduction

Ranitidine is a histamine H<sub>2</sub>-receptor antagonist which differs from cimetidine in that the central imidazole ring of histamine has been replaced by a furan ring and the cyanoguanidine side-chain has been slightly modified. Ranitidine is 4-10 times as potent as cimetidine on a molar basis in inhibiting gastric acid secretion (Domschke and Domschke, 1980) and both compounds have proved of equivalent efficacy against duodenal ulceration (Langman *et al.*, 1980).

Cimetidine is a known cause of mental confusion, especially in the elderly and in those with renal and/or hepatic impairment (Russell and Lopez, 1980). Furthermore, cimetidine has been associated with depression (Johnson and Bailey, 1979; Crowder and Pate, 1980; Billings, Tang and Rakoff, 1981), even in physically healthy younger patients.

The aim of the present study was to evaluate whether ranitidine treatment for duodenal ulcer resulted in mental state changes, with particular reference to depression and anxiety.

### Patients and methods

Consecutive outpatients to the Gastrointestinal Clinic, Groote Schuur Hospital, Cape Town, South Africa who had endoscopically proven duodenal ulceration and were free of systemic disease were allocated according to a randomized double-blind code to either ranitidine hydrochloride, one tablet (150 mg) twice a day, or to one matching placebo tablet twice a day. This regimen continued for 4 weeks. Antacid tablets were allowed when necessary for pain relief. All other medicines were discontinued. Patients were excluded if they had received cimetidine or antidepressant medication in the preceding month. Patients underwent endoscopy at the beginning of the trial. They made a second visit after 2 weeks of treatment and a third after 4 weeks when endoscopy was again performed to assess the extent of healing. The clinical aspects of the trial have been reported elsewhere (Marks *et al.*, 1982). Informed consent was obtained and the trial was approved by the Ethical Review Committee of the University of Cape Town Medical Faculty.

The following mood rating scales were administered at the first visit (baseline), after 2 weeks and after 4 weeks of treatment: (1) Hamilton Rating Scale for depression (HRS) (Hamilton, 1960); (2) Montgomery-Asberg Rating Scale for depression (MARS) (Montgomery and Asberg, 1979); (3) Hamilton Anxiety Scale (HAS) (Hamilton, 1959).

Symptom relief (gastrointestinal) was rated at 2

TABLE 1. Effect of ranitidine and placebo on mood rating scales after 2 weeks and 4 weeks

	HRS†			MARS†			HAS†		
	Ranitidine	Placebo	P*	Ranitidine	Placebo	P	Ranitidine	Placebo	P
Baseline	24 (19-32)	26.5 (17-34)	NS	9 (4.5-12.5)	11 (4.5-16.5)	NS	11(6-14)	10 (6-13)	NS
2 weeks	8 (3-16.5)	16 (6-22.5)	<0.05	1.5 (0-4)	4 (1.5-7)	<0.05	3 (1.5-7.5)	5.5 (2.5-10)	NS
4 weeks	8 (1-12)	9.5 (4.5-17.5)	NS	2 (0-5)	1.5 (0-6)	NS	2.5 (0-6)	3 (1.5-7)	NS
P‡	<0.001	<0.001		<0.001	<0.001		<0.001	<0.001	

†Scores expressed as median (interquartile range); \*ranitidine v. placebo (Wilcoxon sum of ranks test); ‡Friedman's two-way analysis of variance; NS=not significant.

weeks and at 4 weeks in terms of three categories: resolved, improved and unchanged/worse.

Compliance was checked at 2 weeks and at 4 weeks both by tablet count and by plasma ranitidine determinations. Plasma ranitidine was assayed on all patients by the high performance liquid chromatography method of Carey and Martin (1979). Non-compliant patients were excluded. Non-parametric statistics were applied in the form of Friedman's two-way analysis of variance, the Wilcoxon sum of ranks test and the chi-square test.

## Results

There were 25 patients (20 males, five females) who were finally included in the ranitidine group and 28 patients (21 males, seven females) in the placebo group with mean ages ( $\pm$ s.d.) of 33.2 (9.1) years and 37.2 (12.2) years respectively. One patient had to be excluded from the ranitidine group because her plasma ranitidine levels were zero at both 2 and 4 weeks: one patient was omitted from the placebo group because at the 2-week visit his plasma contained 399 ng/ml of ranitidine (this might have reflected an error in the code).

The mean plasma ranitidine concentration was 217 ng/ml and 68 ng/ml at 2 and 4 weeks respectively in the ranitidine group and 0 ng/ml at both 2 and 4 weeks in the placebo group. The lower plasma ranitidine concentration at 4 weeks was because patients fasted overnight prior to the endoscopy and many omitted their usual morning dose of ranitidine—the mean time after the last dose was 9.1 hr at 2 weeks and 15.7 hr at 4 weeks. (The half-life of ranitidine is 2-3 hr).

Ranitidine and placebo treatments were associated with a highly significant overall decrease ( $P<0.001$ ) in all three of the mood rating scales over the 4 weeks of the trial (Table 1). Comparison of the ranitidine and placebo groups (Table 1) showed that at 2 weeks the ranitidine-treated patients had significantly lower scores ( $P<0.05$ ) on the HRS and MARS than did placebo patients: these differences were not present at 4 weeks.

Table 2 indicates that at both 2 weeks and 4 weeks

patients in the ranitidine group had a significantly greater degree of symptom relief ( $P<0.01$ ) than those in the placebo group.

TABLE 2. Effect of ranitidine and placebo on gastrointestinal symptoms after 2 weeks and 4 weeks

Symptom change	Ranitidine	Placebo
Two weeks		
Resolved	15 (60%)	4 (14.3%)
Improved	10 (40%)	20 (71.4%)
Unchanged/Worse	0 (0%)	4 (14.3%)
	$\chi^2=13.57; P<0.01$	
Four weeks		
Resolved	22 (88%)	13 (46.4%)
Improved	3 (12%)	13 (46.4%)
Unchanged/Worse	0 (0%)	2 (7.2%)
	$\chi^2=10.43; P<0.01$	

## Discussion

In this study the histamine H<sub>2</sub>-receptor antagonist ranitidine was administered for 4 weeks to a group of otherwise healthy duodenal ulcer patients (mean age 33.2 years) at a daily dose of 300 mg. Anxiety and depression ratings at 2 weeks and 4 weeks after the commencement of ranitidine showed a significant and progressive decline compared to pre-treatment values. The same pattern of change also emerged in the placebo group except that, at the 2-week assessment, the ranitidine-treated patients showed a greater improvement in depression than did the placebo group. This difference did not hold at 4 weeks and it is therefore unlikely that ranitidine can be regarded as having clear-cut antidepressant properties. However, the suggestion of an early antidepressant action with ranitidine is possibly worthy of further exploration, particularly on the theoretical basis that clinical antidepressant activity may be mediated by antagonism of brain histamine H<sub>2</sub>-receptors (Kanof and Greengard, 1978). On the other hand, it is important to note that only small amounts of ranitidine penetrate the blood-brain barrier in normal subjects (Walt *et al.*, 1981). None of our patients showed any signs of mental confusion during the testing periods.

Assessment of symptom change revealed that, at both 2 weeks and 4 weeks, patients in the ranitidine group reported a significantly greater degree of relief than the placebo subjects. It is thus probable that the more marked mood improvement with ranitidine at 2 weeks was secondary to the higher rate of symptom resolution in these patients. However, symptom disappearance *per se* is apparently not the total explanation. At the 4-week assessment, for example, the ranitidine-treated patients maintained their superiority over the placebo group in terms of symptom relief but not in terms of mood elevation.

The relatively raised baseline depression scores in our group of duodenal ulcer patients confirm previous studies which have highlighted a high prevalence of depression in medical outpatients, much of which is undetected by primary physicians (Nielsen and Williams, 1980). Our investigation has found that ranitidine proved safe for use and was free of neuropsychiatric complications in a group of young and otherwise healthy patients. It must be emphasized that the experience with cimetidine revealed that, where mental confusion occurred, the patients were generally elderly and had coexistent renal and/or hepatic impairment. The cases of depression, however, which have been linked to cimetidine tended to occur in younger and healthier patients (Johnson and Bailey, 1979; Crowder and Pate, 1980; Billings *et al.*, 1981).

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