

Maintenance treatment of duodenal ulceration: ranitidine 300 mg at night is better than 150 mg in cigarette smokers

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Abstract

Two hundred patients received either ranitidine 150 mg or 300 mg at night for 18 months to prevent duodenal ulcer relapse. Recurrence rates were lower in patients receiving the higher dose of ranitidine (3.1% *v* 9.7%, $p=0.78$; 6.5% *v* 16.7%, $p=0.037$; and 8.9% *v* 17.0%, $p=0.121$ at six, 12, and 18 months respectively). In patients receiving ranitidine 150 mg, recurrences were significantly more common in smokers than non-smokers after 12 and 18 months, while in patients receiving ranitidine 300 mg recurrence rates were similar in smokers and non-smokers. Ranitidine 300 mg at night abolishes the adverse effect of smoking observed during maintenance treatment with ranitidine 150 mg at night and may therefore be an appropriate maintenance dose for smokers who relapse during standard dose maintenance treatment.

Several drugs are effective in healing of duodenal ulcers but relapse occurs in up to 90% of patients during the following 12 months if treatment is stopped. Maintenance therapy is recommended in selected patients to reduce the likelihood of relapse and the associated morbidity and complications. Maintenance therapy with cimetidine 400 mg or ranitidine 150 mg provides one year ulcer-free intervals in 65-80% of patients. Nevertheless, patients who relapse on standard dose maintenance treatment pose a therapeutic problem. The present study was undertaken to determine whether maintenance treatment of duodenal ulcer with ranitidine 300 mg at night further reduces the incidence of recurrence compared with ranitidine 150 mg at night over an 18 month period.

Patients and methods

The study was a randomised double blind, single centre comparison of ranitidine 150 mg with ranitidine 300 mg at night administered for 18 months. Patients were entered into the study if they presented with dyspepsia or upper gastrointestinal bleeding, or both, and were shown to have one or more duodenal ulcers >5 mm in diameter which healed during four to eight weeks' treatment with an H₂ receptor antagonist. Patients with gastric ulceration, previous gastric surgery other than oversewing of a perforation, coincidental medical disease, or those who were receiving ulcerogenic drugs were excluded. The study was approved by the Ethics Committee of the Blackpool Fylde and Wyre Health Authority and all patients gave informed consent. Clinical

assessment was carried out at two-monthly intervals. Endoscopic examinations were performed at six, 12, and 18 months and in those patients who developed symptoms suggestive of ulcer recurrence. Blood was withdrawn for standard haematological and biochemical safety checks at endoscopy visits.

STATISTICAL METHODS

Numbers of recurrences on each dose of ranitidine, and in smokers and non-smokers were compared using Fisher's exact test. Cumulative recurrence rates were calculated using the product limit life table method. Patients who were withdrawn from the study for reasons other than ulcer relapses were included in analysis up to the time of the last valid endoscopic examination. Differences were deemed statistically significant if p was less than 0.05 for a two tailed test.

Results

Two hundred patients entered the study between April 1985 and April 1987. One hundred patients received ranitidine 150 mg at night and 100 received ranitidine 300 mg. Demographic features and ulcer history were similar in the two treatment groups (Table I). Twenty two patients (12 receiving ranitidine 150 mg) were withdrawn for reasons other than ulcer recurrence (Table II).

All other patients continued in the trial until either a recurrence had been detected or 18 months' treatment had been completed.

ULCER RECURRENCE

Recurrent duodenal ulcers were detected in 23 patients (15 receiving ranitidine 150 mg). In no patient was recurrent ulceration associated with haemorrhage or perforation. Five of the recurrences (three in patients receiving ranitidine 150

TABLE I Features of the two treatment groups at entry to the trial

	150 mg ranitidine (n=100)	300 mg ranitidine (n=100)
Mean (SD) age (years)	48.5 (13.6)	48.8 (13.6)
Sex M:F	68:32	65:35
Alcohol excess (>6 units daily)	14	10
Smokers: non-smokers	66:34	63:37
Gastrointestinal haemorrhage:		
Recent	11	11
Previous	4	3
Both	3	1
Total	18	15

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TABLE II Patient outcome

	0-6 months	7-12 months	13-18 months
Ranitidine 150 mg:			
Withdrawals:			
Poor compliance	2	2	2
Intercurrent illness	2	3	3
Possible side effects	1	1	1
Moved away	1	2	2
Dropouts	1	2	4
Total analysed	93	90	88
Ranitidine 300 mg:			
Withdrawals:			
Poor compliance	0	0	0
Intercurrent illness	0	0	2
Possible side effects	1	1	1
Moved away	2	4	5
Dropouts	1	2	2
Total analysed	96	93	90

TABLE III Cumulative relapse rates for patients receiving ranitidine 150 mg and 300 mg at night

Time (mths)	No	150 mg	No	300 mg	95% CI
6	93	9 (9.7%)	96	3 (3.1%)	-0.3-13.5
12	90	15 (16.7%)*	93	6 (6.5%)	1.1-19.4
18	88	15 (17.0%)	90	8 (8.9%)	-1.7-7.9

*Fisher's exact test $p=0.04$.

mg) were asymptomatic and detected at pre-arranged endoscopic follow up. Cumulative combined (symptomatic plus asymptomatic) recurrence rates are given in Table III. Cumulative symptomatic recurrence rates were 7.5%, 13.3%, and 13.6% in patients receiving ranitidine 150 mg and 2.1%, 4.0%, and 7.0% in patients receiving ranitidine 300 mg at six, 12, and 18 months respectively.

EFFECT OF SMOKING ON ULCER RECURRENCE

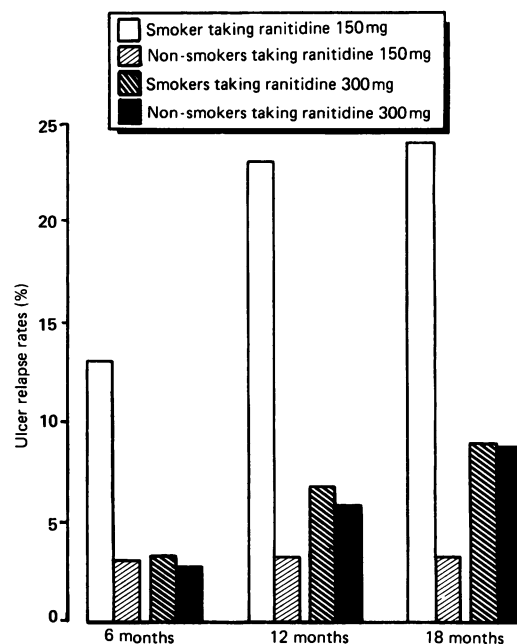
In patients receiving ranitidine 150 mg at night, ulcer recurrence was statistically significantly more common in smokers than in non-smokers after 12 and 18 months (Table IV and Figure). In patients receiving ranitidine 300 mg at night, however, recurrence rates were similar in smokers and non-smokers throughout the period of the study (Table IV and Figure). Thus, increasing the maintenance dose of ranitidine to 300 mg at night abolished the adverse effect of cigarette smoking that was observed during maintenance with ranitidine 150 mg.

ADVERSE EVENTS

One patient in each treatment group experienced diarrhoea, that was possibly attributable to ranitidine and which resolved on stopping treatment. Each patient subsequently received ranitidine for ulcer healing without recurrence of diarrhoea. No changes in individual patients' laboratory values occurred which were thought

TABLE IV Cumulative recurrence rates in smokers and non-smokers at each dose of ranitidine

Time (mths)	Ranitidine 150 mg		Ranitidine 300 mg		95% CI†
	Smokers	Non-smokers	Smokers	Non-smokers	
6	13%	3.2%	3.3%	2.8%	0.1-19.1
12	23%*	3.3%	6.8%	5.9%	4.0-29.0
18	24%**	3.3%	8.9%	8.8%	1.9-28.5

*Fisher's exact test, $p=0.025$; ** $p=0.02$; †Smokers 150 mg v 300 mg.

Cumulative recurrence rates in smokers and non-smokers at each dose of ranitidine.

to be caused by treatment. There were no significant changes in population mean values for any of the haematological or biochemical indices during treatment with either dose or ranitidine.

Discussion

Most duodenal ulcers recur within one year of healing if treatment is stopped. Only one agent, colloidal bismuth subcitrate, has been shown to be followed by reduced relapse rates,¹ but this effect is relatively short term.² Maintenance treatment is generally recommended for particular groups of patients with duodenal ulceration, for example those who have suffered previous ulcer haemorrhage or recent perforation with surgery limited to oversewing; elderly patients or patients unfit for surgery; and patients receiving anticoagulants, corticosteroids, or non-steroidal anti-inflammatory drugs. Low dose maintenance therapy with H₂ receptor antagonists reduces the annual cumulative recurrence rate to 20-30%.^{3,4} A recent meta-analysis of duodenal ulcer maintenance therapy with ranitidine 150 mg or cimetidine 400 mg at night concluded that cumulative combined (symptomatic plus asymptomatic) one year recurrence rates were 19% and 27% respectively.⁵ The cumulative one year recurrence rate observed during maintenance treatment with ranitidine 150 mg at night in the present study (17%) was thus similar to rates reported in the medical reports.

A proportion of patients still relapse, however, on standard maintenance treatment and full dose maintenance therapy has been recommended for these.⁶ In the present study recurrence rates during treatment with ranitidine 300 mg at night were approximately half those during treatment with ranitidine 150 mg. Two previously reported studies failed to show a therapeutic benefit from increasing the standard maintenance dose of cimetidine or famotidine in duodenal ulcer disease. A multicentre com-

parison of cimetidine 400 mg with 800 mg showed that symptomatic recurrence rates during treatment with either dose of cimetidine were similar (17% and 15% respectively at one year) but that asymptomatic recurrences were more frequent in patients receiving the higher dose of cimetidine (10% and 16% respectively).⁷ Similarly, in a study comparing famotidine 20 mg with famotidine 40 mg, recurrence rates were 23% and 25% respectively after one year.⁸ A study comparing ranitidine 150 mg at night with ranitidine 150 mg twice daily in the maintenance of duodenal ulcer healing showed, however, that recurrence rates were reduced from 27% to 17% at one year by the higher dose of ranitidine.⁹

It has previously been reported that recurrence during maintenance treatment is more common in smokers than in non-smokers.^{4,10} This may relate to an adverse effect on plasma concentration of orally administered ranitidine in cigarette smokers.¹¹ In the present study 83% of all recurrences were in smokers. The relative risk for ulcer recurrence was statistically significantly greater in smokers than in non-smokers receiving ranitidine 150 mg at night. In patients receiving ranitidine 300 mg at night, however, the recurrence rates were similar in smokers and non-smokers. This suggests that the reduction in recurrence rates during maintenance treatment with ranitidine 300 mg was attributable to a specific therapeutic benefit of the higher dose in cigarette smokers, although the possibility of a type I error cannot be entirely excluded. The

results of the present study indicate that in patients who relapse during standard dose maintenance therapy and who are smokers (the majority), maintenance treatment with ranitidine 300 mg at night is an effective and safe therapeutic option to reduce the risk of further recurrence.

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