

Prevention of relapse in reflux esophagitis: A placebo controlled study of ranitidine 150 mg bid and 300 mg bid

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OBJECTIVE: To compare the efficacy and safety of long term use of ranitidine 150 mg bid, 300 mg bid and placebo in prevention of endoscopic and symptomatic relapse of reflux esophagitis in an international, double-blind, placebo controlled, parallel group study.

PATIENTS AND METHODS: A total of 279 patients at least 18 years old from hospital out-patient departments with healed esophagitis (grade 0) with no or mild symptoms entered the study. Patients were randomly allocated to receive ranitidine 150 mg, 300 mg or placebo twice daily for 48 weeks. Patients returned for symptom assessments at eight-week intervals and for re-endoscopy every 16 weeks.

RESULTS: Both ranitidine regimens were significantly more effective than placebo in preventing endoscopic and symptomatic relapse of reflux esophagitis ($P=0.003$ for ranitidine 150 mg bid; $P<0.001$ for ranitidine 300 mg bid). No statistically significant differences were observed in relapse rates between the two ranitidine regimens. The percentage of patients with endoscopic relapse (grade 2) after 48 weeks were 60%, 37% and 27% for placebo, ranitidine 150 mg bid and ranitidine 300 mg bid, respectively ($P=0.002$ for ranitidine 150 mg bid versus placebo; $P<0.001$ for ranitidine 300 mg bid versus placebo). Ranitidine was well tolerated.

CONCLUSIONS: Ranitidine 150 mg bid and 300 mg bid are safe and effective treatments in the prevention of reflux esophagitis relapse.

Key Words: *Clinical trial, Endoscopic relapse, Placebo, Ranitidine, Reflux esophagitis, Symptomatic relapse maintenance*

Prévention de la récurrence de l'œsophagite de reflux : étude contrôlée par placebo sur la ranitidine 150 mg b.i.d. et 300 mg b.i.d.

OBJECTIF : Comparer l'efficacité et l'innocuité de l'emploi prolongé de la ranitidine à 150 mg b.i.d. et à 300 mg b.i.d. et celles du placebo en prévention de la récurrence endoscopique et symptomatique de l'œsophagite de reflux dans le cadre d'une étude internationale à double insu contrôlée par placebo avec groupe parallèle.

PATIENTS ET MÉTHODES : En tout, 279 patients d'au moins 18 ans provenant de services externes hospitaliers et ayant une œsophagite cicatrisée (degré 0) avec symptômes nuls ou légers ont participé à l'étude. Les patients ont été assignés aléatoirement à la ranitidine 150 mg ou 300 mg ou à un placebo à prendre deux fois par jour pendant 48 semaines. Les patients ont fait évaluer leurs symptômes à des intervalles de huit semaines et ont subi une endoscopie toutes les 16 semaines.

RÉSULTATS : Les deux schémas de ranitidine ont été significativement plus efficaces que le placebo à prévenir les récurrences endoscopiques et symptomatiques de l'œsophagite de reflux ($P = 0,003$ pour la ranitidine 150 mg b.i.d., $P < 0,001$ pour la ranitidine 300 mg b.i.d.). Aucune différence statistiquement significative n'a été observée quant aux taux de récurrence entre les deux schémas de la ranitidine. Les pourcentages de patients présentant une récurrence endoscopique (grade II) après 48 semaines ont été de 60 %, 37 % et 27 % pour le placebo, la ranitidine 150 mg b.i.d et la ranitidine 300 mg b.i.d. respectivement ($P = 0,002$ pour la ranitidine 150 mg b.i.d vs le placebo; $P < 0,001$ pour la ranitidine 300 mg b.i.d. vs le placebo). La ranitidine a été bien tolérée.

CONCLUSIONS : La ranitidine à 150 mg b.i.d. et 300 mg b.i.d. est sûre et efficace en prévention de la récurrence de l'œsophagite de reflux.

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Ranitidine has been shown to be effective in the treatment of reflux esophagitis (1-6). Comparative studies have shown healing of esophagitis in approximately 60% of patients treated with ranitidine 150 mg bid for eight weeks, increasing to 77% of patients after 12 weeks (7-11). However, gastroesophageal reflux disease is known to be a chronic recurrent disease, with relapse occurring rapidly after cessation of medical therapy.

Ranitidine use in the long term management of reflux disease has not been extensively studied. A preliminary study with a single night-time dose showed little benefit (12). However, McCallum et al (3) reported that symptomatic relapse occurred in only 16% of patients treated with ranitidine 150 mg bid compared with 44% of patients treated with placebo over 12 months ($P < 0.05$). Two of 21 patients (9.5%) who received ranitidine 150 mg bid and five of 20 patients (25%) who received placebo showed a worsening of their esophagitis grade after 12 months. These results suggest that, as in the acute treatment of reflux esophagitis, frequency of dosing is important.

Results of other studies using H_2 receptor antagonists support the hypothesis that twice-daily dosing is required for long term treatment (13-16). The objective of this maintenance study was to compare the efficacy of 48 weeks treatment of ranitidine 150 mg bid and 300 mg bid with placebo in the prevention of endoscopic and symptomatic relapse of reflux esophagitis in patients whose reflux esophagitis had been healed with ranitidine in the acute phase of this study.

PATIENTS AND METHODS

Design: In this international, multicentre, double-blind, parallel group comparative study, patients with healed esophagitis (grade 0) and no or mild symptoms were randomized to receive one of three study medications according to a predefined randomized code: ranitidine 150 mg bid, ranitidine 300 mg bid or placebo. This study forms the maintenance phase of an acute healing and maintenance treatment study.

Ethics: The study was conducted in accordance with the Declaration of Helsinki (Hong Kong amendment 1989), and ethics committee approval or its equivalent was obtained from all participating centres. Informed consent was obtained from all patients recruited.

Patients: Patients were recruited from 37 investigating centres in seven countries: Belgium, Canada, Holland, Ireland, Norway, Poland and the United Kingdom. A total of 632 patients with moderate or severe reflux esophagitis (at least grade 2, modified Savary and Miller grading scale) were recruited into the acute healing phase of the study. Of these, 203 received ranitidine 300 mg qid, 221 received ranitidine 300 mg tid and 208 received ranitidine 150 mg bid. Endoscopy after four or eight weeks of treatment showed complete healing of esophagitis in 373 patients. There were 349 patients who met all entry criteria for the long term study: reported no symptoms or only mild symptoms at the end of acute treatment; were at least 75% compliant with acute phase study medication; and had no other medical condi-

tion that contraindicated participation in a long term study. Two hundred and seventy-nine patients agreed to participate.

Clinical procedures: Following baseline assessment patients were instructed to take their allocated medication twice a day for 48 weeks. Patients were asked to return for symptom assessments at eight-week intervals (56-8 days) and to return for re-endoscopy every 16 weeks (assessment at 16, 32 and 48 weeks). Patients were permitted to take antacid tablets for pain relief if required, and the number of antacids taken was recorded. The severity of heartburn, acid regurgitation and epigastric pain during the seven days preceding the visit was recorded as none, mild, moderate or severe. In addition, patients were asked whether they had experienced moderate or severe symptoms for at least seven consecutive days since the last visit. Patients were encouraged to return to the clinic if they experienced significant symptoms. Patients were withdrawn from the study if they had an endoscopic relapse or a symptomatic relapse regardless of the endoscopic appearance of the esophagus. Patients were free to withdraw from the study.

DATA ANALYSIS

Sample size: The predicted relapse rates after 48 weeks in the maintenance phase were 60% for placebo, 35% for ranitidine 150 mg bid and 25% for ranitidine 300 mg bid. In order to demonstrate these differences between each of the active treatments and placebo at the two-sided 5% level of significance with 80% power, it was estimated that 258 patients would be required to complete the acute phase of the study and enter the maintenance phase. To detect a difference between the predicted relapse rates for ranitidine 150 mg bid and 300 mg bid, a sample size of 660 patients would be required. A study of this size was not considered feasible.

Study populations: The total population comprised all patients who were randomized to treatment. This population formed the basis of the safety analysis. The modified intent-to-treat population included all patients who were randomized to treatment and who returned for at least one follow-up visit/endoscopy. The per protocol population was the modified intent-to-treat population with the exclusion of patients who had significantly violated or deviated from the protocol. Data up to the point of deviation were included.

Compliance: Patient compliance with the study medication as well as antacid consumption were assessed by recording returned tablet counts.

Endoscopic relapse: Patients were considered to have endoscopically relapsed if they had endoscopically proven reflux esophagitis of grade 2 or greater. Grade 2 was the minimum grade for eligibility to the acute phase of the study. The primary efficacy analysis was based on time to endoscopic relapse. Differences were examined by use of the log rank test (17). Cutler-Ederer life-test estimates of the probability of relapse over 16-week intervals were used to aid comparison between the three treatment groups at scheduled assessment visits (18).

Patients were withdrawn from the study if repeat endo-

TABLE 1
Demographic characteristics of patients recruited into the study by treatment group

	Placebo	Ranitidine 150 mg bid	Ranitidine 300 mg bid	Total
Total population	92	92	95	279
Mean age (years) ± SD	53.8 (14.4)	52.2 (14.3)	49.4 (14.2)	
Sex (male:female)	60:31	50:40	61:32	279
Smokers:nonsmokers*	20:55	17:72	22:66	252
Alcohol:no alcohol*	28:47	36:53	31:58	253
Reflux esophagitis grade at entry to the acute phase (%)				
0	0	1 (1.1)	0	
2	73 (79.4)	75 (81.5)	77 (81.1)	
3	16 (17.4)	15 (16.3)	17 (17.9)	
4	3 (3.3)	1 (1.1)	1 (1.1)	

*Missing data for some patients

TABLE 2
Cutler-Ederer life-table estimates for the percentage of patients with endoscopic relapse (grade 2)

Time interval	Placebo	Treatment		Treatment comparison*		
		Ranitidine 150 mg bid	Ranitidine 300 mg bid	Placebo versus ranitidine 150 mg bid	Placebo versus ranitidine 300 mg bid	Ranitidine 150 mg bid versus ranitidine 300 mg bid
0-16 weeks	40 (5.4)	17 (4.1)	12 (3.4)	P<0.001	P<0.001	P=0.30
0-32 weeks	5.1 (5.7)	32 (5.5)	24 (4.8)	P=0.007	P<0.001	P=0.19
0-48 weeks	60 (5.8)	37 (5.8)	27 (5.1)	P=0.002	P<0.001	P=0.15

Values in parentheses are the standard error. *Compared using a life-table extension of the Mantel and Haenszel test

scopic examination showed reflux esophagitis grade 2, ie, confluent erosive and exudative lesions. Because isolated erosions are often taken to indicate relapse, a second analysis was performed that censored data if endoscopic examination reported the presence of grade 1 esophagitis (patients were not withdrawn from the study at this time). Cutler-Ederer life-table estimates for the interval 0 to 16 weeks, 0 to 32 weeks and 0 to 48 weeks were compared by a life-table extension of the Mantel and Haenszel test (19).

Symptomatic relapse: Patients were considered to have had a symptomatic relapse if they experienced moderate (ie, troublesome but not debilitating) symptoms or severe (ie, completely debilitating) symptoms for seven or more consecutive days, or if symptoms were severe enough to prompt patient withdrawal from the study regardless of the endoscopic appearance of the esophagus. Actuarial life-table estimates for the probability of relapse were calculated and compared by means of the log rank test.

Prognostic variables: Logistic regression models were used to examine the influence of potential prognostic variables on endoscopic and symptomatic relapse. The variables investigated were age, sex, smoking habit, alcohol consumption, country of residence, grade of reflux esophagitis on entry into the acute phase, treatment received during the acute phase and time to healing in the acute phase.

RESULTS

All 279 patients recruited into the study were included in the intent-to-treat population. The demographic characteristics of patients recruited into the study by treatment group are shown in Table 1. The three treatment groups were simi-

TABLE 3
Life-table for assessment of endoscopic relapse (grade 2): Symptomatic relapse and symptomatic plus endoscopic relapse

Time interval*	# patients at start [†]	Number of patients relapsed		
		Endoscopic	Symptomatic	Both
Placebo				
16 weeks	90	32	31	22
32 weeks	44	7	4	2
48 weeks	34	4	5	4
Ranitidine 150 mg bid				
16 weeks	90	14	18	7
32 weeks	62	8	6	5
48 weeks	48	3	2	5
Ranitidine 300 mg bid				
16 weeks	93	9	9	7
32 weeks	72	10	8	7
48 weeks	54	2	2	1

*Plus eight days; [†]Number with at least one symptom assessment during interval

lar with respect to age, sex, smoking habit and alcohol consumption. However, overall a higher proportion of males entered the study. About 80% of patients entered the acute phase of the study with grade 2 esophagitis. The distribution of grades was similar among the treatment groups.

Patient compliance with the study medication was good in all treatment groups, with medians ranging from 93% to 99%. Antacid consumption was low in all groups, but gener-

TABLE 4
Cutler-Ederer life-table estimates for the percentage of patients with endoscopic relapse (grade 1)

Time interval	Placebo	Treatment		Treatment comparison*		
		Ranitidine 150 mg bid	Ranitidine 300 mg bid	Placebo versus ranitidine 150 mg bid	Placebo versus ranitidine 300 mg bid	Ranitidine 150 mg bid versus ranitidine 300 mg bid
0-16 weeks	66.3 (5.2)	43.2 (5.3)	23.0 (4.5)	P<0.001	P<0.001	P=0.005
0-32 weeks	78.7 (5.0)	56.0 (5.6)	37.1 (5.3)	P<0.001	P<0.001	P=0.007
0-48 weeks	82.4 (4.7)	63.1 (5.5)	44.1 (5.6)	P<0.001	P<0.001	P=0.006

Values in parentheses are the standard error. *Compared using a life-table extension of the Mantel and Haenszel test

TABLE 5
Actuarial life-table for the percentage of patients with symptomatic relapse

Time interval	Placebo	Ranitidine 150 mg bid	Ranitidine 300 mg bid
0-16 weeks	36.1	21.6	9.9
0-32 weeks	42.0	29.6	21.1
0-48 weeks	54.1	32.6	24.5

ally higher in patients who had received placebo than those who received ranitidine 150 mg bid or ranitidine 300 mg bid, with medians ranging over the study from 20 to 48, 10.5 to 40 and 3.5 to 9 tablets per eight-week period, respectively.

There were no notable differences among treatment groups regarding incidence of concurrent disease.

Endoscopic relapse: Both ranitidine 150 mg bid and 300 mg bid significantly increased the time to endoscopic relapse in the modified intent-to-treat population compared with placebo ($P=0.003$ and $P<0.001$, respectively). Cutler-Ederer life-table estimates for the percentage of patients with endoscopic relapse (grade 2) at the scheduled visits are given in Table 2, and details of the number of patients available at the start and who relapsed during each interval are listed in Table 3.

From the 16-week assessment onwards, the endoscopic relapse rate during treatment with both doses of ranitidine was approximately half that observed in those who received placebo. A trend was seen where patients who received ranitidine 300 mg bid had slightly lower relapse rates than those who received ranitidine 150 mg bid. However, the difference in time to endoscopic relapse was not statistically significant ($P=0.25$).

Cutler-Ederer life-table estimates of recurrence, defined as the observation of grade 1 esophagitis, are presented in Table 4. There was an increase in the observed relapse rate in all treatment groups but the therapeutic advantage of both doses of ranitidine was retained. Treatment with ranitidine was associated with a statistically significant reduction in recurrence throughout the study, and there was a statistically significant benefit associated with the higher dose of ranitidine.

Results for the per protocol population were consistent with the intent-to-treat population.

Symptomatic relapse: Highly statistically significant differences were observed in the symptomatic relapse rates between ranitidine 150 mg bid and placebo ($P=0.0167$) and

between ranitidine 300 mg bid and placebo ($P<0.001$) in the modified intent-to-treat population. A summary of the actuarial life-table estimate for the percentage of patients with symptomatic relapse at the scheduled visits is given in Table 5.

The endoscopic relapse rate for each of the two ranitidine treatment groups was approximately half that of the placebo group; this effect was maintained from 16 weeks (Figure 1). Again a trend suggesting a lower rate of relapse for patients who received ranitidine 300 mg bid versus those who received ranitidine 150 mg bid was observed but did not reach statistical significance. The odds of relapsing were three times greater for patients who received placebo compared with those who received ranitidine 300 mg bid, and twice as great for patients receiving placebo versus ranitidine 150 mg bid.

The results for the per protocol population were consistent with the intent-to-treat population.

Effect of prognostic variables on endoscopic relapse: There was no statistically significant effect of age, sex, smoking habit, alcohol consumption and treatment regimen in the acute phase on the endoscopic relapse rate. Similarly, none of these factor by treatment interactions was significant at the 5% significance level.

The grade of reflux esophagitis at entry into the acute phase, however, had an effect on outcome in the maintenance phase; the more severe the grade of reflux esophagitis at entry into the acute phase, the more likely the patient was to have an endoscopic relapse in the maintenance phase ($P=0.002$). Similarly, the time to heal in the acute phase was inversely related to the time of endoscopic relapse ($P=0.047$). A significant country of residence effect was also observed ($P=0.0004$) in which Norwegian patients (18.2% of the study population) had a higher number of endoscopic relapses.

Effect of prognostic variables on symptomatic relapse: There was no evidence that age, smoking habit, alcohol consumption or acute phase treatment regimen influenced the symptomatic relapse rate. However, time to heal in the acute phase was inversely related to time to symptomatic relapse ($P=0.008$), and it was noted that Norwegian patients had a significantly higher rate of symptomatic relapse irrespective of the treatment received ($P=0.004$).

A significant sex by treatment interaction was observed. Males reported fewer symptomatic relapses during ranitidine treatment ($P=0.003$), whereas relapse rates for male and female patients were similar in those receiving placebo.

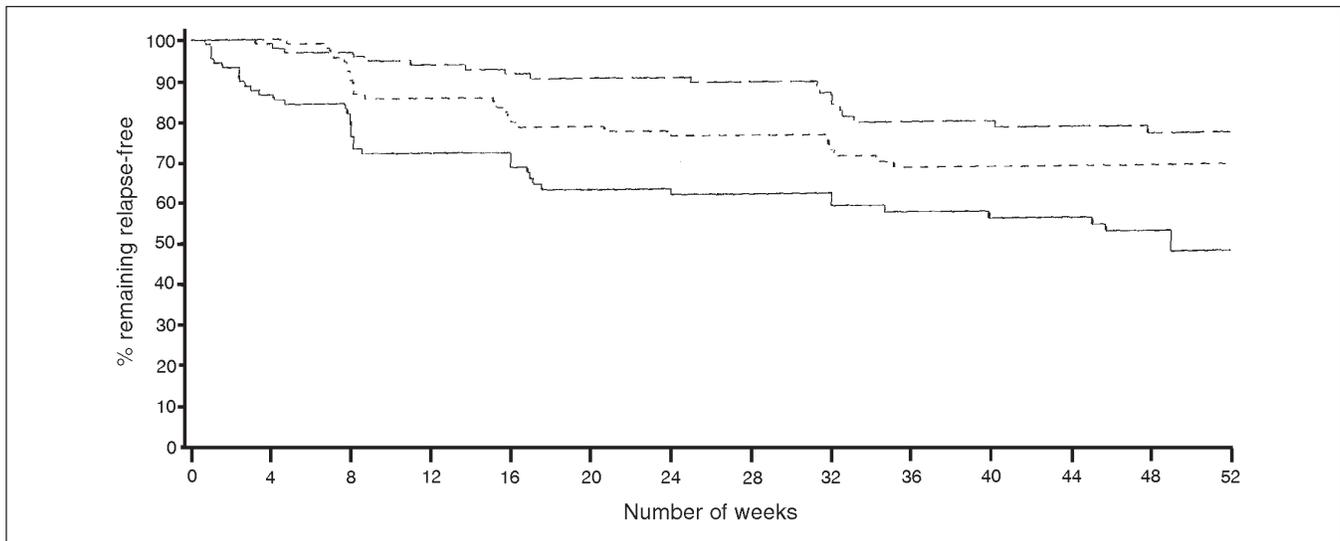


Figure 1) Time to symptomatic relapse. — Placebo; --- Ranitidine 150 mg bid; ··· Ranitidine 300 mg bid. Ranitidine 150 mg bid versus placebo: $P=0.017$ log rank test; ranitidine 300 mg bid versus placebo: $P<0.001$ log rank test; ranitidine 300 mg bid versus ranitidine 150 mg bid: $P=0.12$ log rank test

Safety: Sixty-six patients (24%) reported events during the 48-week study. The majority of adverse events were classified as nonserious and considered to be unrelated to study medication. Thirteen serious adverse events (ie, considered life-threatening, resulted in death or required hospitalization) were reported, one from the placebo group, six from the ranitidine 150 mg bid group and six from the ranitidine 300 mg bid group (differences in incidence were not statistically significant).

Of the 13 serious adverse events, one patient died following a traffic accident; three were diagnosed with carcinoma; four were hospitalized or received surgery; and five experienced cardiovascular events. In this last group of five, three suffered cerebrovascular accidents, two, myocardial infarctions and one, a transient ischemic attack. Four of these five patients were 60 years or older and had a history of cardiovascular disease. None of the serious adverse events were considered to be related to study medication. These results are consistent with those expected when studying this age group of patients over 48 weeks.

Twenty-six patients were withdrawn from the study due to adverse events (five from the placebo group, eight from the lower dose ranitidine group and 13 from the higher dose ranitidine group); differences between groups were not statistically significant.

No clinically significant changes in biochemistry or hematology measurements were observed during the study.

DISCUSSION

Both ranitidine 150 mg bid and ranitidine 300 mg bid were superior to placebo in reducing the rate of endoscopic and symptomatic relapse in patients with recently healed moderate to severe reflux esophagitis. Results for symptomatic relapse were very similar to those for endoscopic relapse. Just over half of the patients were classified as having an endo-

scopic and symptomatic relapse (60 of the 115 who relapsed during the treatment period). Twenty-six patients were reported to have a symptomatic relapse with no evidence of erosive esophagitis. For 29 patients, endoscopic relapse was not associated with symptoms of sufficient severity or duration to meet the definition of a symptomatic relapse. There was no suggestion of any difference in the distribution of endoscopic or symptomatic relapses among the treatment groups (Table 3).

At all assessment points there was a consistently lower relapse rate associated with ranitidine 300 mg bid treatment compared with ranitidine 150 mg bid treatment for both endoscopic and symptomatic relapse (not statistically significant).

The prognostic variables found to have a significant impact on endoscopic and symptomatic relapse were time to heal in the acute phase and country of residence. It is perhaps not surprising that patients who took a long time to heal before entering the study had a higher risk of relapse. The contribution of the number of patients from each country was similar, and hence the variation in relapse rate by country is difficult to explain.

A higher risk of endoscopic relapse was observed in patients with the more severe grades of esophagitis before healing. This finding is in agreement with other reports (20), but was not evident as a factor affecting the symptomatic relapse rate in our study. The rate of endoscopic relapse was similar for males and females in all treatment groups. However, there was a significant treatment by sex interaction with respect to symptomatic relapse. It is difficult to assess the clinical relevance of this observation. The lack of an effect of smoking is counter-intuitive but is found in other reports. Smoking has been found to have no effect on relapse of esophagitis following successful treatment with omeprazole (21) or to be associated with a longer period of remission in

patients receiving maintenance therapy with cisapride or placebo (20).

Primary analyses were based on a protocol definition of grade 2 endoscopic relapse. Evaluation of the literature with respect to acute treatment and long term management of reflux esophagitis is confounded by many grading systems and definitions of end-points. In order to allow some further comparison with the results of other studies, a post-hoc analysis was conducted applying an alternative definition of relapse (grade 1) and censoring data at that time. Not surprisingly the relapse rates were higher but the efficacy of ranitidine remained apparent. The life-table estimates suggest that ranitidine 300 mg bid may offer some advantage over ranitidine 150 mg bid, but this study was not designed to test that hypothesis. Because patients who developed grade 1 esophagitis were not withdrawn, this study allows some insight into the progression of isolated erosions. Many were clearly trivial lesions; more than half of the patients in the placebo treatment group had no significant symptoms, and no change in or healing of the lesion was noted at subsequent endoscopy.

Our results are supported by the findings of another recent large study (n=170) (22). Using an end-point of linear erosions limited to the distal 5 cm of the esophagus and involving less than 10% of the mucosal surface, cumulative 48-week relapse rates of 70% and 40% were reported during treatment with placebo or ranitidine 10 mg bid, respectively (P<0.001).

Symptom relief was generally better in the two ranitidine

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treatment groups versus in the placebo group. Furthermore, patients from the placebo group generally consumed more antacids than patients from the two ranitidine groups. There was nothing to suggest from the incidence of adverse events or laboratory data that there was any difference between the two ranitidine dosage regimens.

CONCLUSIONS

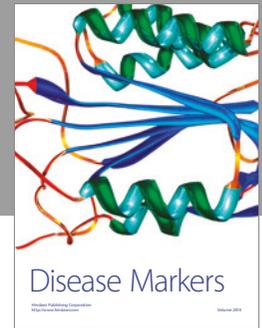
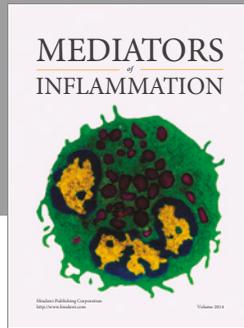
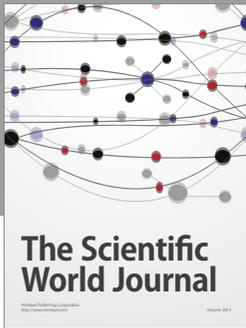
Both ranitidine 150 mg bid and 300 mg bid were shown to be more effective than placebo in reducing the risk of endoscopic and symptomatic relapse of reflux esophagitis. However, no significant differences in efficacy were seen between the two ranitidine regimens.

Ranitidine was well tolerated at both doses. The majority of adverse events reported were not serious and were considered to be unrelated to the study medication.

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