

Treatment of reflux oesophagitis with ranitidine

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SUMMARY The efficacy of ranitidine was evaluated using a two-staged trial in patients with endoscopically moderate or severe reflux oesophagitis. The results of a six week double blind placebo controlled trial (stage I) in 36 patients shows that ranitidine (150 mg bd) is superior to placebo in the acute treatment with significant symptomatic improvement concerning heartburn and regurgitation, and in healing or improvement of endoscopic lesions. Prolonged treatment with ranitidine for another six weeks (stage II) proved to be effective in more resistant cases. No clinical side effects or significant biochemical changes were noted during this trial.

Histamine H₂-receptor antagonists have potential use in the management of gastrooesophageal reflux disease, because they inhibit basal, nocturnal, and stimulated, gastric acid secretion and pepsin secretion.¹⁻⁴ Results of several trials with cimetidine show that treatment with this drug in the case of reflux oesophagitis usually results in a rapid symptomatic improvement, reduction in the amount of concomitant antacid consumption, and improvement of the reflux damaged mucosa as can be seen from endoscopic and histologic assessments.⁵⁻⁸ The new H₂-receptor antagonist ranitidine appears to be more potent¹ and probably longer acting.⁹ Furthermore, some workers report a positive influence on the lower oesophageal sphincter pressure¹⁰ although this has not been confirmed.¹¹ It therefore seemed appropriate to evaluate the efficacy of ranitidine in the acute treatment of reflux oesophagitis.

Methods

PATIENTS

Thirty eight adult outpatients were selected for this trial. The diagnosis was based upon a careful medical history, endoscopy, and biopsy. Informed consent was obtained from all patients.

MEDICAL HISTORY

All patients were asked to record the severity of heartburn, regurgitation, and retrosternal pain, previous treatment, and duration of the disease.

Each patient was provided with diary cards for a daily record of symptoms, scoring the number of episodes of reflux symptoms, the degree of severity (none, mild, moderate, or severe), and the number of antacids (Rennies) taken during the test period to relieve symptoms not controlled by the test medication.

ENDOSCOPY AND BIOPSY

Endoscopy was performed with standard forward-viewing instruments. Oesophagitis was defined as mild (erythema, friability; grade I), moderate (erosions; grade II), or severe (ulceration; grade III) using the criteria previously described.⁶ Endoscopy was performed by experienced endoscopists without knowledge of patient symptomatology or treatment. The endoscopic findings at the end of the study were scored as unchanged (same degree), worse, or improved (when there was a change of at least one degree) or healed when compared to the pretrial findings. The degree of oesophagitis in the five or more pre- and post-trial endoscopic biopsies were defined as mild (grade I), moderate (grade II), and severe (grade III) using the criteria previously described.⁶ The pre- and post-trial biopsies were compared for each patient, and interpreted by experienced pathologists as unchanged (same degree), improved or worse (change of at least one degree). Only patients with endoscopically moderate or severe oesophagitis were admitted. Patients with concomitant ulcer, pregnant and lactating women, patients with previous oesophageal or stomach surgery, patients with strictures, and patients with serious diseases such as heart, liver, and kidney failure were excluded.

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Table 1 Characteristics of 36 patients (stage I)

Treatment group	Age (yr)		Sex		Disease duration (mean)	Symptoms			Endoscopy		Histology	
	Mean	Range	M	F		Mild	Mod-erate	Severe	Mod-erate	Severe	Mod-erate	Severe
Ranitidine	53.8	31-75	14	5	54.2 m	2	10	7	14	5	9	10
Placebo	60.2	39-76	11	6	67.1 m	2	11	4	12	5	7	10

In the first part of the trial (stage I) the patients were randomly allocated to either ranitidine (150 mg bd) or placebo treatment of six week duration. Each patient was also given a known number of antacid tablets (Rennies) to be taken solely for relief of symptoms when not controlled by the test medication. All patients were evaluated after six weeks for physical examination, for laboratory analysis (haemoglobin, blood erythrocyte sedimentation rate, peripheral blood count, plasma urea, serum creatinine, bilirubin, alkaline phosphatase, transaminases, and urinalysis), and another endoscopy with biopsies. The diary cards were checked, the number of antacid tablets taken during the test period was recorded, and any trial medication not consumed was registered. For statistical analysis the χ^2 test was used. In the second part of the trial (stage II) patients whose oesophagitis were not healed during stage I received six week open treatment with ranitidine (150 mg bd), with the same evaluation procedure at the end of the trial period.

Results

PATIENT CHARACTERISTICS

Two patients were excluded from final analysis; a 56 year old female patient, receiving placebo, stopped

the trial medication within 10 days because of persistent complaints and refused further cooperation; a 34 year old male patient receiving placebo, ended the trial after three weeks because he was admitted to the hospital because of severe pain due to a herniated intervertebral disc. The characteristics of the 36 patients who completed stage I of the trial are summarised in Table 1, 19 patients having received ranitidine and 17 placebo. Both groups were comparable for age, sex, duration of disease, severity of symptoms, and the degree of reflux oesophagitis scored endoscopically and histologically.

EXPERIMENTAL RESULTS

The experimental results are summarised in Table 2. *Stage I* There was a significant improvement in symptoms such as heartburn and regurgitation in the ranitidine treated patients. Less retrosternal pain was observed in this ranitidine group, although not significantly so. The daily antacid consumption was slightly lower in the second three week period in the ranitidine group. The difference was not significant. Using endoscopic criteria, 15 of the 19 ranitidine treated patients healed or were definitely improved, whereas four remained unchanged. In the placebo treated group, four patients healed or improved, 10 remained unchanged, and in three the oesophagitis

Table 2 Experimental results (stage I)

Symptomatology	Treatment group								
	Ranitidine				Placebo				
	Symptom free	Improved	Unchanged	Worse	Symptom free	Improved	Unchanged	Worse	
Heartburn	6	2	11	0	2	8	7	0	p<0.05
Retrosternal pain	2	6	11	0	0	3	13	1	NS
Regurgitation	8	4	5	2	1	5	11	0	p<0.05
Antacid consumed/ 3 weeks (w)*	First 3 w 31 (\pm 28)		Second 3 w 19 (\pm 25)		First 3 w 30 (\pm 25)		Second 3 w 25 (\pm 22)		NS
Endoscopy + histology evaluation	Healed	Improved	Unchanged	Worse	Healed	Improved	Unchanged	Worse	
Endoscopy	7	8	4	0	2	2	10	3	p<0.01
Histology	1	10	8	0	1	3	11	2	p<0.05

* SD is given in parentheses.

Table 3 Treatment group (stage II)

Patient characteristics	Ex-ranitidine				Ex-placebo			
	Mild	Moderate	Severe		Mild	Moderate	Severe	
Symptomatology	3	5	0		5	3	2	
Endoscopy	3	4	1		0	4	6	
Histology	1	4	3		0	4	6	
Experimental results	Treated with 12 w ranitidine				Treated with 6 w ranitidine			
	Cured/ healed	Improved	Unchanged	Worse	Cured/ healed	Improved	Unchanged	Worse
Symptomatology	3	1	4	0	6	0	3	1
Endoscopy	4	1	3	0	3	6	1	0
Histology	0	3	5	0	0	5	5	0

became worse. The statistical difference between the incidence of healing or improvement vs lack of improvement between ranitidine and placebo treated patients was highly significant ($p < 0.01$). The overall histological gradings showed improvement or healing in 11 patients during ranitidine treatment, and in four patients during placebo treatment; also a significant difference ($p < 0.05$).

Stage II The characteristics of the 18 patients who received a six week open treatment with ranitidine because they had not healed endoscopically in the stage I period, are summarised in Table 3. As seen, eight patients were treated with ranitidine and 10 with placebo during stage I of the trial. The ex-placebo group had had more serious disease at the start of this stage II of the study regarding endoscopical and histological findings. Another six week treatment with ranitidine in the ex-ranitidine group resulted in improved symptomatology, endoscopical, and histological findings in approximately half of the patients, while this improvement was more pronounced in the ex-placebo group, now receiving ranitidine for six weeks, as can be also seen in Table 3.

Discussion

The double blind prospective study (stage I) showed that ranitidine is superior to placebo in the acute treatment of patients with endoscopically moderate or severe reflux oesophagitis. The results of this six week study compare well with the results of double blind trials with cimetidine in patients with endoscopically and histologically established reflux oesophagitis, reporting endoscopic improvement in 67% of the patients treated for eight to 12 weeks with cimetidine 1.6 g/day.^{5 6 12} To achieve better results, the acute treatment may have to be continued for 12 weeks as shown in the stage II period of the trial. Until now, the problem of preventing the recurrence of gastrooesophageal

reflux disease has been unresolved. Possibly a lower dose, such as an evening dose, or intermittent drug therapy together with antireflux measurements will prove to be sufficient. Further long-term maintenance therapy studies in a substantial number of patients are needed to know how to reduce the relapse rate in this complex disease. Like cimetidine, ranitidine proved to be a safe and clinically well tolerated drug and appears to be another useful drug in the treatment of reflux oesophagitis.

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