

H₂ antagonists in the treatment of reflux oesophagitis: can physiological studies predict the response?

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SUMMARY Ambulatory oesophageal pH, oesophageal manometry and fasting serum gastrin concentrations were carried out on 28 patients with reflux oesophagitis, before and during treatment with ranitidine 300 mg bd. Fourteen patients healed endoscopically at six weeks (group A) and 14 had residual oesophagitis (group B). Group A were characterised by a lower serum gastrin concentration before treatment (4.52 pmol/l; 2.4-10: mean and range) than group B (11.1 pmol/l; 3.5-21: $p < 0.05$) and showed a marked reduction in acid reflux on treatment to near normal values. Mean per cent time below pH4 fell from 14.9 to 4.2 in group A ($p < 0.05$) but was not affected in group B (14.2-15.6, not significant). Abnormal oesophageal motility was found in 13 patients from each group. This did not inhibit the response to ranitidine, and was not improved by healing of oesophagitis.

H₂ antagonists are widely used in the treatment of gastroesophageal acid reflux, but as many as 50% of patients fail to respond to conventional or high dose regimes such as cimetidine 800 g bd,¹ either symptomatically or with endoscopic healing of oesophagitis. The reason for this high failure rate is unknown. H₂ antagonists reduce acid secretion, and therefore the potency and volume of refluxed material, but other properties of these drugs may also be important. H₂ antagonists cause an increase in gastrin concentrations which may increase the tone in the lower oesophageal sphincter in oesophagitis² and affect oesophageal motility. Abnormal motility with poor lower oesophageal sphincter function is common in oesophagitis, and persistence of these abnormalities may decrease the value of reduced gastric acid secretion in oesophagitis. We have measured ambulatory oesophageal pH, oesophageal motility, and fasting gastrin concentrations before and during endoscopically controlled treatment of oesophagitis with ranitidine 300 mg bd in an attempt to identify factors which may predict response to this agent. A

high dose regime was used as this is often required for effective control of symptoms in reflux oesophagitis, and produces a greater reduction of gastric acid secretion.

Methods

PATIENTS

Twenty eight patients identified at gastroscopy with oesophagitis were studied. Details are shown in Table 1. Frequency of reflux and severity of symptoms on a subjective 0-5 scale were recorded before treatment. All drugs were stopped four days before the investigation, which included oesophageal manometry, ambulatory oesophageal pH recording and fasting gastrin (19 subjects). These were repeated three weeks after starting treatment with ranitidine 300 mg bd. Gaviscon was allowed as required and general advice about reflux given. This included firm advice to stop smoking and reduce weight where necessary. During the six week study period, none of the smokers successfully stopped smoking. Manometry was done using a Hewlett Packard physiological recording system with 125 cm triple lumen tube perfused with distilled water through an Arndorfer capillary perfusion system. Lower oesophageal sphincter pressure was measured

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Table 1 Patient characteristics on entry to the study. Group A were healed endoscopically after six weeks' treatment, group B were not. There are no significant differences in any criterion between the groups

	Group A	Group B
Mean age (range)	51 (32-65)	52 (19-70)
Male/female	5/9	9/5
Mean duration of symptoms (months)	47	75
Obesity	5	3
Smoking	2	6
Severity of oesophagitis ¹		
Grade 1	7	5
2	4	4
3	3	3
4	0	2
Drugs taken in month before entry to study		
H ₂ antagonists	7	2
Antacids	11	9
Mean symptom score		
Severity (0-5)	3.2	3.2
Frequency day	5.6	6.0
night	1.9	1.7

using both pull through and station techniques. Oesophageal contractions were assessed with 10×3 ml swallows with the lower opening of the triple lumen tube just above the lower oesophageal sphincter, and then with the highest opening just below cricopharyngeus. The number of abnormal waves (simultaneous, repetitive, variable amplitude, incompletely propagated or spontaneous waves) was recorded. The antimony pH probe (Synectics) was positioned 5 cm above the manometrically defined lower oesophageal sphincter and connected to a portable digital recorder (Digitrapper Mark II 6100). There were no dietary restrictions. pH recordings were made for a three hour postprandial period, 12 noon to 3:00 pm in 12 subjects, and for 24 hours in 16 subjects. The criteria for abnormal acid reflux were greater than 4% time below pH 4, or two or more reflux episodes greater than five minutes duration.⁴ Data were recorded and analysed on an IBM PC computer. Statistical methods used were Wilcoxon's Rank-sum-test for paired and unpaired data, and Spearman-Rank correlation. Endoscopic and symptomatic assessment and measurement of fasting gastrin levels was repeated at six weeks. Blood for gastrin estimation was collected with minimal venous occlusion, and the plasma frozen at -20°C in Trasylol (5000 IU/ml) until measurement by radioimmunoassay.

Results

Fourteen patients had healed with no evidence of oesophagitis after six weeks treatment with ranitidine 300 mg bd (group A). Fourteen still had oesophagitis

(group B) which had improved in five, deteriorated in four or was unchanged in five patients. There was no correlation between healing and age, sex, obesity, or smoking. In contrast with the healing rate, there was an overall symptomatic benefit in 26 of the 28 patients, with reduction in mean severity of pain score from 3.2 to 2.0 ($p < 0.001$), frequency of daytime pain from 5.8 to 2.8 episodes per day ($p < 0.001$) and nocturnal pain from 1.8 to 1.2 ($p < 0.001$).

Abnormal oesophageal motility was common, affecting 26 of the 28 patients with an average frequency of abnormal peristaltic waves 6.5/20 swallows before treatment, 6.3/20 swallows after treatment. This was more marked in group B (7.2/20 swallows) than group A (5.9/20 swallows), but not significantly so. Lower oesophageal sphincter pressure was not affected by treatment (mean 27.0 mmHg pretreatment, 27.7 mmHg post-treatment) and was similar in both groups (group A 27.8 mmHg, group B 26.8 mmHg).

Fasting gastrin concentrations increased significantly during treatment ($p < 0.01$) (Fig. 1). In addition, group A had a significantly lower pretreatment gastrin level than group B (4.52 pmol/l against 11.1 pmol/l, $p < 0.05$). There was evidence of abnormal acid reflux in 24 of the 28 patients.⁴ Acid reflux characteristics are shown in Table 2 and Figure 2 before and after treatment. In group A there was a significant reduction in both the frequency and duration of acid reflux which did not occur in group B. There was relatively little nocturnal reflux, mean time below pH4 was 3.4% (0.0-15.0) between the hours of 12 midnight and 8:00 am. There was a close correlation between reflux data in the 16 patients undergoing 24 hour pH studies for the three hour postprandial period compared with the 24 hours.⁵ The frequency/duration index⁶ for three hours correlated with frequency duration index for 24 hours ($r = 0.89$, $p < 0.001$).

Table 2 Reflux response to ranitidine 300 mg bd. Mean values with ranges of % time below pH4 and the frequency and duration of reflux

	Group A		p	Group B		
	Treatment			Treatment		
	(Pre)	(Post)		(Pre)	(Post)	
% time below pH4	14.9 (0-67)	4.2 (0-23)	$p < 0.05$	14.2 (0-68)	15.6 (0-60)	NS
Episodes/h (n)	2.0 (0.0-5.6)	0.9 (0-4.3)	$p < 0.001$	2.0 (0-6.3)	1.5 (0-3.6)	NS
Mean duration of each episode (min)	6.3 (0.5-16.3)	1.7 (0-13.8)	$p < 0.01$	7.9 (0-38)	12.2 (0-35)	NS

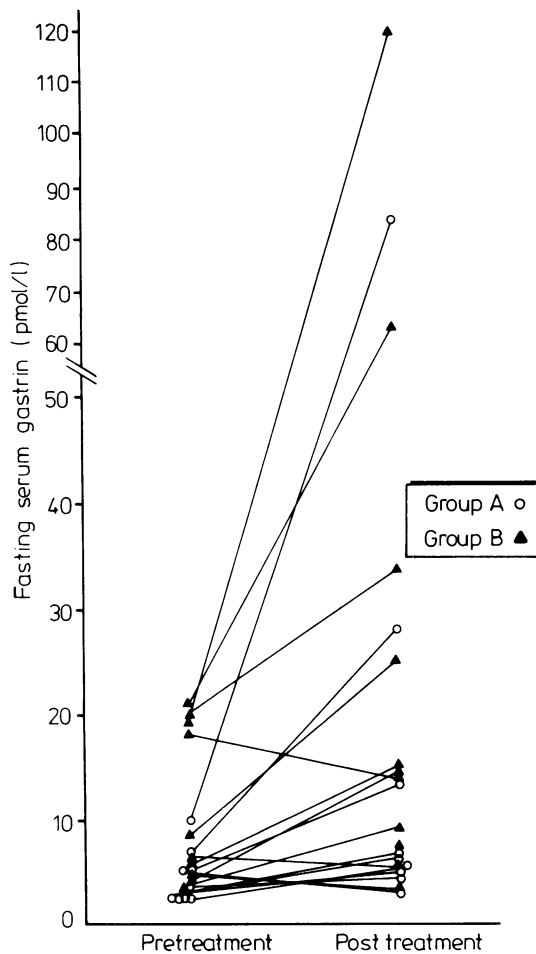


Fig. 1 Fasting gastrin concentrations in patients before and during treatment with ranitidine 300 mg bd. There is a significant increase in gastrin concentrations with treatment ($p < 0.01$), and group A have significantly lower concentrations before treatment than group B ($p < 0.05$).

Discussion

The response to treatment with ranitidine 300 mg bd is consistent with most previous studies, with improvement in the symptoms of oesophagitis but endoscopic healing occurring in only half of cases after six weeks' treatment, despite the high dose.^{7,8} In this study, the patients who responded endoscopically appeared to have acid reflux of similar severity to non-responders initially, but after three weeks' treatment there was a marked reduction in both the frequency and duration of acid reflux to levels just above the normal range, which was not observed in those who failed to heal. Reflux was mainly postprandial in these patients with uncomplicated oeso-

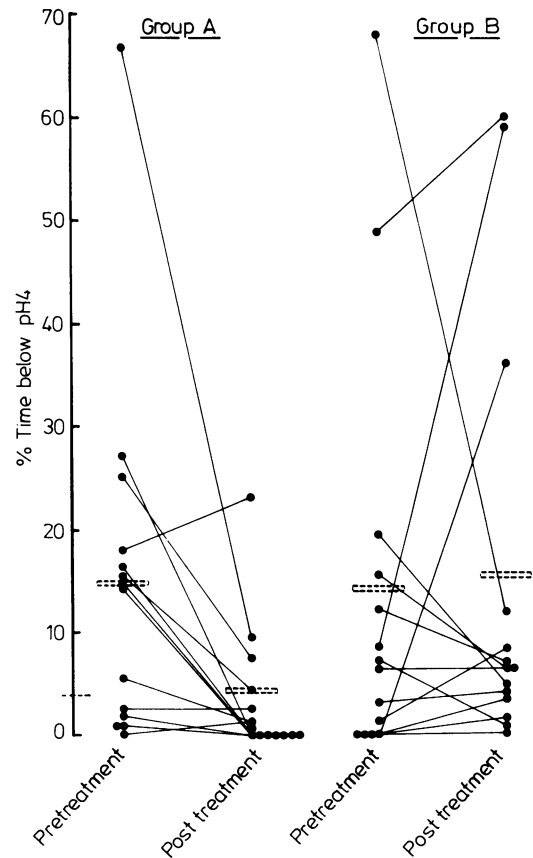


Fig. 2 Percentage time below pH4 before and during treatment. In group A there is a significant reduction with treatment ($p < 0.05$), but not in group B.

phagitis, and was often not severe; 10 patients (five in each group) recorded values of less than 4% of time below pH4, but six of these had two or more episodes of reflux longer than five minutes.

Ranitidine reliably reduces gastric acid secretion,⁹ and in duodenal ulcer this is associated with healing in approximately 90% of cases within six weeks. The 50% of patients who failed to heal in this study had acid reflux of similar severity before and during treatment, suggesting that their postprandial acid secretion is not adequately suppressed by ranitidine, or that other factors are more important in this group. We were unable to identify any significant clinical associations with healing. The patients who healed were more likely to be women, to be slightly younger, less likely to smoke, and have slightly less severe oesophagitis, with a shorter duration of symptoms, than those who failed to heal. These associations were weak and did not approach statistical significance. Frequency and severity of symptoms were similar in both groups. There was no

evidence that oesophageal dysmotility was more common or severe in non-healers.

Abnormal motility in the body of the oesophagus is common in oesophagitis,¹⁰ and occurred in most of our patients, with an average of 30% abnormal peristaltic waves. It is still not clear whether this is the cause or an effect of acid reflux, although recent studies¹¹ have shown that abnormal oesophageal motility improves after fundoplication, suggesting that dysmotility is secondary to reflux. In this study, the presence of abnormal peristalsis did not inhibit the response to ranitidine, but healing was not associated with an improvement in motility. This suggests that disturbed oesophageal motility is not of primary importance in healing of oesophagitis, although it may be an important feature in the development of oesophagitis. Furthermore, motility has been measured in the supine, fasting patient, often when symptoms have not been severe, and other methods of assessing motility may yet demonstrate important primary abnormalities. The lower oesophageal sphincter pressure was within the normal range for our laboratory and was not altered by treatment with ranitidine, although there was a marked increase in gastrin concentrations said to be associated with an increase in tone of the lower oesophageal sphincter.¹² In group A, the fasting pretreatment gastrin concentrations were significantly lower than in group B. It may be that lower gastrin concentrations in responders reflect a high basal acid output, and so identifies those patients who are most likely to respond to inhibitors of gastric acid secretion. The gastrin level was the only factor in the pretreatment assessment that was associated with a satisfactory response to ranitidine, but it is not suggested that this is a useful diagnostic test to identify potential responders, though low levels may reflect the underlying pathophysiology. Ambulatory pH recording did not identify patients likely to respond and cannot be recommended as a tool for patient selection for this form of therapy.

Although group B still had residual oesophagitis after six weeks treatment, 12 had improved symptomatically and no additional treatment was required. Two patients underwent antireflux surgery (follow up nine months).

It appears that the beneficial effects of ranitidine in oesophagitis can be entirely attributed to reduction in

acid secretion in those who respond, in whom there is a reduction in the frequency and severity of acid reflux. Patients who fail to respond do not have a reduction in severity or frequency of reflux, for reasons that are not clear.

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