Leading article

Histamine-2-receptor antagonists in gastro-oesophageal reflux

While the widespread use of histamine-2-receptor antagonists (H₂RA) in reflux oesophagitis can be justified by the results of clinical trials, they are not effective in all cases. Gastro-oesophageal reflux disease (GOR) results from prolonged contact time of refluxed noxious agents (especially acid) with the mucosal surface cells in the distal oesophagus. It may also result from impaired mucosal defences such as alteration in the mucus layer. Prolonged contact because of poor oesophageal clearance is also a factor in some cases, notably systemic sclerosis. The frequency and volume of refluxed fluid is important, being determined by gastric contents and the competence of the anti-reflux mechanism. Finally the composition of the refluxate is central, especially the concentration of gastric acid, possibly with pepsin and bile influencing its damaging effect. H₂RAs can only reduce the concentration of acid and possibly the volume of fluid that refluxes. This may be sufficient to induce symptomatic relief and promote healing, especially in the milder cases, but as only one of several factors responsible for GOR is affected by H₂RAs, it is not surprising that not all cases respond. This review examines the role of H₂RAs in reflux oesophagitis at a time when newer treatments enable the clinician to manipulate gastric acidity and upper gastrointestinal motility more effectively.

Gastro-oesophageal reflux disease is the most common endoscopic finding – 22% of new referrals in one district.¹ Even that figure is an underestimate of the frequency of GOR since many patients are treated by self medication or symptomatically by their general practitioners. Furthermore abnormal reflux may occur without focal oesophagitis.² Gastro-oesophageal reflux is puzzling in many ways. Severe oesophagitis and even ulcers may be present with virtually no symptoms, and conversely, no focal lesion in the presence of severe pain. One heading for such a wide spectrum of disease is probably appropriate because of the common underlying mechanisms, but when assessing therapy for GOR this wide range of severity must be considered. Clinical trials of treatment in GOR usually specify the severity of oesophagitis, but not always using an internationally agreed grading. The severity of oesophagitis must be classified as objectively as possible. The Table summarises a recommended adaptation of the grading of Savary and Miller³ for endoscopic appearances. Continuous pH monitoring may be required in the future to provide additional objective data.

Several drugs including antacids have been assessed in the treatment of

GOR (not always with convincing superiority over placebo) but none as fully as the H₂RAs.^{4,6} Response to these drugs has until recently been used

Table Grades of oesophagitis as observed at endoscopy.

Grade 1	Discrete erythematous lesions immediately proximal to the mucosal junction.
Grade 2	Isolated circular or linear erosions with non circumferential erythematous areas.
Grade 3	Circumferential, confluent erythematous areas and erosions.
Grade 4	Complicated oesophagitis – deep ulcer or stricture formation.

Adapted from Savary and Miller³

as the therapeutic 'gold standard'. The H₂RAs available for longest (cimetidine and ranitidine) have been the most extensively investigated. The level of acid suppression reported for later H₂RAs such as famotidine, nizatidine, etintidine, roxatidine are similar to those of cimetidine and ranitidine, so that similar efficacy in the treatment of GOR might be expected but as yet there are insufficient published studies to enable a full evaluation. Trials of treatment for GOR comparing H₂RAs against placebo (with antacid as needed) show a marked trend in favour of cimetidine or ranitidine and usually achieve statistical significance. For cimetidine nine of 13 randomised trials showed symptomatic improvement with the active drug, but with endoscopic improvement of the oesophagitis in only four of 12 studies.⁴ For ranitidine there was significant relief of reflux symptoms in 12 of 14 studies when compared with placebo and significant improvement in endoscopic appearance was achieved in nine of 13 studies. Between a half and three-quarters of the patients in the actively treated group benefited symptomatically from therapy,^{4,6} which is clinically useful but leaves a substantial number of unresponsive patients.

Dose is obviously important, and a number of treatment schedules have been tried. With cimetidine, higher dose levels have been used than is conventional for the treatment of peptic ulcer disease (between 1.0 and 1.6 g in divided doses either two or four times daily). No major differences have emerged between these schedules.⁴ With ranitidine the doses schedules have ranged between 150 mg bd, 300 at bedtime, and most recently 300 mg four times daily.^{7,8} In this last trial there was a clear advantage for the high treatment dose in patients with grades 2 and 3 oesophagitis. The conventional 150 mg bd regimen was followed by complete endoscopic healing of oesophagitis in 54% after eight weeks treatment, compared with 75% in the high dose group. The results for symptomatic relief were significantly different – 64% and 84% respectively. This trial is helpful because it indicates that better results are achieved by (presumed) greater suppression of acid secretion. This regimen is expensive, however, and 25% of patients do not respond. Prolonging treatment only increases the healing and symptom relief to a limited extent⁶; from 67% symptom relief at four weeks to 84% at eight weeks with the high dose schedule.⁸ The severity of oesophagitis is also important: the more severe grades being more resistant to therapy.^{9,10} This is also true for peptic strictures.¹¹ Other adverse factors include smoking^{10,12} and possibly alcohol.¹² Small trials comparing cimetidine and ranitidine have shown no striking advantage for either compound⁵ (three trials showing no difference, and one an advantage for cimetidine). While night time reflux may be important in many cases of GOR, a large trial

comparing ranitidine 150 mg twice daily with 300 mg at night showed no difference in healing rates.⁷

In order to improve results H₂RAs have been combined with additional treatment regimens, but small numbers in the studies make evaluation difficult. Elevation of the head of the bed provides an appreciable advantage for placebo and active treatment.¹² In theory a prokinetic drug is appropriate to improve the tone of the cardiac sphincter, oesophageal clearance and gastric emptying. Results of such studies have been inconsistent; although in one study a combination of cimetidine and metoclopramide was significantly better than placebo, but there was no improvement in lower oesophageal sphincter pressure.¹³ Cisapride in a multicentre study was comparable with ranitidine in the healing of mild oesophagitis,¹⁴ and improved healing in combination with cimetidine;¹⁵ more work is needed to define the place of prokinetic drugs in GOR and in combination therapy with H₂RAs.

Predicting which patients might respond to H₂RA treatment would be helpful. The grade of oesophagitis is probably the single most important factor for its use in clinical practice. In addition, patients with GOR responding to ranitidine had a lower mean serum gastrin concentration before treatment than those who did not respond.¹⁶ They also showed a much greater reduction in acid reflux on treatment (to near normal levels) than those who failed to improve. These findings have been confirmed where patients in a cimetidine group who responded, showed a satisfactory reduction in reflux of acid while those who failed to respond had no diminution in frequency or duration of reflux.¹⁷ In the omeprazole treated group of this study those few patients who did not completely heal also continued to reflux acid.

Recurrence of symptoms after healing is very common – about one third over the next six months¹⁰ – particularly if the sphincteric pressure is low.¹⁸ More severe oesophagitis relapses even more frequently.¹⁹ Prevention of relapse by low dose H₂RAs is probably ineffective.¹⁰ One group²⁰ claim successful healing of erosive oesophagitis with improved cardiac sphincteric tone but this was not associated with a fall in relapse rate.

Comparative trials of omeprazole and the H₂RAs have shown a clear advantage for omeprazole in all dose ranges studied (20 to 60 mg) when compared with ranitidine¹⁹⁻²³ and cimetidine.¹⁷ Omeprazole is presumably superior to other therapy for GOR because of its greater effect in inhibiting acid secretion. Because for most patients this is a relapsing condition requiring longterm therapy, however, the longterm use of any new drug requires careful monitoring for safety. Do the H₂RAs still have a place in the treatment of GOR?

Gastro-oesophageal reflux shows a great range of severity, and this must influence management. In deciding which therapy is best for individual patients more objective assessment of severity at endoscopy and, in selected cases, with 24 hour pH monitoring is important. Thus, in reflux type dyspepsia where there is no focal oesophagitis and antacids have failed²⁴ there is a place for H₂RAs, and for grade 1 and 2 reflux oesophagitis the H₂RAs are well documented and effective treatment resulting in good levels of symptomatic relief and healing. Experience with cimetidine and ranitidine is extensive and the safety record good (essential in any condition where therapy is likely to be prolonged). For patients with documented GOR not responding to an H₂RA, however, and in the less common

more severe reflux disease, omeprazole has superseded even high dose H₂RA therapy.

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