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 reflexes. 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. 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. 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 Miller 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.¹⁴ Response to these drugs has until recently been used 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.¹ 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,¹⁴ 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.¹ With ranitidine the doses schedules have ranged between 150 mg bd, 300 at bedtime, and most recently 300 mg four times daily.⁷ 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. The severity of oesophagitis is also important: the more severe grades being more resistant to therapy.⁹¹⁰ This is also true for peptic strictures.¹¹ Other adverse factors include smoking¹⁰¹² and possibly alcohol.¹² Small trials comparing cimetidine and ranitidine have shown no striking advantage for either compound’ (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

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**Table Grades of oesophagitis as observed at endoscopy.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Discrete erythematous lesions immediately proximal to the mucosal junction.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Isolated circular or linear erosions with non circumferential erythematous areas.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Circumferential, confluent erythematous areas and erosions.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Complicated oesophagitis – deep ulcer or stricture formation.</td>
</tr>
</tbody>
</table>

Adapted from Savary and Miller¹
comparing ranitidine 150 mg twice daily with 300 mg at night showed no
difference in healing rates.  

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 months18 – particularly if the sphincteric pressure is low.19
More severe oesophagitis relapses even more frequently.16 Prevention of
relapse by low dose H2RAs is probably ineffective.16 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 ranitidine19-22 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 failed16
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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References

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