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Appropriate Acid Suppression for the Management of Gastro-Oesophageal Reflux Disease

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Abstract
Gastro-oesophageal reflux disease (GORD) results from an abnormally prolonged dwell time of acidic gastric contents in the oesophagus. Although GORD is primarily a motor disorder, the injurious effects of gastric acid are central to the pathogenic process of oesophagitis, and the severity of disease correlates with the degree and duration of oesophageal acid exposure. In the majority of patients with mild disease, oesophageal acid exposure occurs predominantly during post-prandial periods. Conventional doses of H_2-receptor antagonists cannot overcome the integrated stimulus to acid secretion resulting from a meal, and are thus relatively ineffective in preventing daytime, post-prandial oesophageal acid exposure. In patients with more severe grades of oesophagitis, there are abnormally high levels of nocturnal acid exposure, with the intra-oesophageal pH being less than 4.0 for 36% of the time, compared with 5% of the time in patients with mild GORD. Control of nocturnal acid secretion thus becomes increasingly important. This may be made worse by relative gastric acid hypersecretion in some patients with severe GORD. The long duration of action and effective inhibition of meal-stimulated acid secretion probably explains the superiority of omeprazole in treating GORD. Preliminary meta-analysis shows that the healing rate of erosive oesophagitis at 8 weeks by antisecretory agents is directly related to the duration of suppression of gastric acid secretion achieved over a 24-hour period ($r=0.87$; $p<0.05$).

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In Western society, approximately 7% of the population suffer from gastro-oesophageal reflux disease (GORD) [1]. Reflux of gastric contents into the oesophagus produces the symptoms of heartburn and regurgitation, which largely account for the widespread use of over-the-counter antacid medications [2].

GORD is primarily a motor disorder, and dysfunction of the lower oesophageal sphincter (LOS) is probably the most significant abnormality [3]. Transient relaxations of the LOS lasting up to 35 seconds and independent of normal peristaltic activity, are seen in 60–83% of reflux episodes. Studies are needed to determine whether the postural control of transient LOS relaxations that is seen normally in healthy subjects is impaired in patients with reflux disease. Studies to date indicate that some suppression occurs, but that this is against a background of a higher overall occurrence, so that in the supine position patients with reflux disease have a significantly higher rate of transient LOS relaxations than controls. Complete cessation of LOS tone for periods of up to 10 minutes can account for 22% of reflux episodes, especially in patients with the more severe forms of disease [4]. Once reflux has occurred, impaired clearance of gastric contents from the oesophagus contributes to the prolonged dwell time of acid in the lower oesophagus.

The Injurious Action of Acid

Despite the spectrum of motor abnormalities described in reflux oesophagitis, gastric acid is central to the development of mucosal injury. The pH dependency of oesophageal mucosal injury has been demonstrated in various animal models [5, 6]. Goldberg et al. showed that perfusion of the feline oesophagus over a 1-hour period with hydrochloric acid produced oesophagitis only when solutions of pH equal to or less than 1.3 were utilized [5]. The addition of porcine pepsin to the perfusate increased the severity of oesophagitis and also caused inflammation to occur with solutions of between pH 1.3 and 2.3. Pepsin solutions above pH 2.3 did not cause mucosal injury in this study, reflecting the *in vitro* activation of porcine pepsin at a pH below 2.5. Similar results were reported by Zaninotto et al., who observed mucosal erosions in rabbit oesophagus perfused with pepsin solutions at pH 1.5 and 2.0, but not when solutions of pH 3.0 or 4.0 were used [6]. Bile salts may also increase the injurious effects of acid by increasing the permeability of the oesophageal mucosa to hydrogen ions [7]. This may play a role in a subgroup of patients with complicated Barrett's oesophagus [8].

The sensation of pain in the oesophagus is also pH-dependent [9]. Smith et al. measured the time taken to sense pain caused by infusing solutions of varying pH in patients with symptomatic GORD. They found a positive correlation ($r = 0.77$) between the time elapsed before pain sensation and the pH of the solution infused. The most significant difference was seen between pH 1.0 and 2.0. Between pH 2.0 and 4.0, the time progressively increased, before levelling off above pH 4.0.

A threshold of pH 4.0 was suggested by Johnson and DeMeester to discriminate between aggressive and non-aggressive reflux during oesophageal pH monitoring [10]. Schindlbeck et al. have evaluated this threshold formally by applying discriminant analysis to define optimal thresholds for evaluating pathological reflux [11]. They found that a maximum sensitivity (93.3%) and specificity (92.9%) could be achieved by considering the percentage of time above pH 4.0 and applying thresholds of 10.5% of the time in the upright position and 6.0% of the time in the supine position as levels of 'normal' oesophageal acid exposure. Furthermore, although other pH

thresholds could differentiate between normal and pathological reflux, pH 4.0 proved optimal [12].

Oesophageal pH monitoring has shown that the severity of oesophageal reflux disease is related to the degree of oesophageal acid exposure, there being a progressive increase in the percentage of time that oesophageal pH is less than 4.0 from mild to complicated disease and Barrett's oesophagus [13–15]. De Caestecker et al. showed correlation coefficients of 0.49–0.70 (all $p<0.001$) between oesophageal acid exposure in the supine, upright, total and post-prandial periods, and the grade of oesophagitis [16]. The same holds true for symptoms, with their severity increasing with oesophageal acid exposure, both in patients with erosive oesophagitis and in those with a macroscopically normal oesophagus [17].

The time taken for intra-oesophageal pH to return to 4.0 or above is also influenced by the pH of the refluxate; the lower the pH of the refluxate, the longer the clearance time. Diffusion of hydrogen ions into the unstirred, and presumably mucous, layer of the oesophagus is thought to be an important determinant of clearance [18]. The amount of hydrogen ions that diffuse is dependent firstly upon the dwell time of acidic gastric contents within the oesophageal lumen. In some patients with reflux disease, this dwell time is substantially prolonged by oesophageal body dysfunction. Secondly, the concentration of hydrogen ions in the refluxate influences the rate at which the unstirred layer is acidified. The lower the pH of the unstirred layer, the longer it will take for salivary bicarbonate to neutralize this acidity, and return intra-oesophageal pH to values that are non-injurious.

Patterns of Gastro-Oesophageal Reflux

It has been widely held that nocturnal reflux is the most important factor in the pathogenesis of reflux disease. Twenty-four-hour oesophageal pH studies have, however, shown that this is incorrect for the majority of patients with reflux disease who have mild erosive oesophagitis or no endoscopic abnormality. In these patients, most reflux occurs in the daytime post-prandial periods, and especially in the early evening, with relatively little reflux during the night [14, 16, 17, 19, 20]. With more severe oesophagitis, there is progressively greater acid exposure, which is predominantly due to an increase in nocturnal reflux. In this situation, the aggressiveness of the gastric contents and the effectiveness of nocturnal oesophageal clearance become very important. The longest period of unbuffered basal gastric output occurs at night, and there is impaired clearance of acid from the oesophagus and reduced neutralization by salivary bicarbonate due to the effects of sleep on salivation and oesophageal motility. The supine position is likely to contribute to impairment of oesophageal acid clearance, but, as yet, there are no data that address this factor in a controlled manner. The increased importance of nocturnal oesophageal acid exposure has been demonstrated by Robertson et al., who found that patients with complicated oesophagitis had a mean nocturnal oesophageal acid exposure time of 35.6%, compared with 5.2% in patients with reflux disease who had either patchy erosions or no endoscopic abnormality. The corresponding values for the daytime period were similar in the two groups: 17% and 13%, respectively [14].

The effects of prolonged oesophageal acid exposure may be compounded by gastric acid hypersecretion in some patients. Johansson et al. found pathologically high pentagastrin-stimulated peak acid outputs in 66% of a group of 100 patients referred to a surgical clinic for evaluation of reflux oesophagitis [21]. In another study from the same centre, the age- and body-weight-corrected maximum acid out-

put was found to be above the normal range in 76% of 41 patients with confirmed oesophagitis [22]. An earlier study, however, showed no correlation between maximally stimulated acid output and oesophageal acid exposure, as measured by oesophageal pH monitoring [23]. It is interesting that this latter study failed to show a correlation between the pH of basal acid secretion and oesophageal acid exposure, but did find that the volume of basal acid secretion correlated with the percentage of time that oesophageal pH was less than 4.0.

A study from Finland showed that basal acid output did not vary with the severity of symptoms of oesophagitis, but that men with ulcerative oesophagitis had significantly higher basal and maximum acid outputs than those with reflux disease without endoscopic abnormalities [24]. A similar trend was also seen in female patients, but failed to reach statistical significance owing to the small number of patients studied.

Although the data on maximally stimulated acid secretion by pentagastrin are confusing, it is possible that patients with oesophagitis may have an exaggerated meal-stimulated acid response, which would be more relevant to the pathophysiology of GORD. Such studies on meal-stimulated gastric acid secretion in patients with GORD have not yet been performed. Collen et al. prospectively evaluated gastric acid output in a group of 23 patients with chronic heartburn [25]. Twelve of these patients remained symptomatic, despite 3 months of standard antisecretory therapy with ranitidine. These patients had significantly higher basal acid outputs than those who responded to ranitidine. When compared with patients whose symptoms responded, the refractory patients had a significantly greater upright, but not supine, acid exposure time. Nine of the 12 patients with refractory GORD (39% of the total) had gastric acid hypersecretion, defined as a basal acid output of greater than 10 mmol/hour. Ten of these 12 non-responders had Barrett's oesophagus, compared with only 1 of the 11 initial responders. These data need to be interpreted with caution, as they may be substantially influenced by rebound hypersecretion secondary to H_2-receptor antagonist withdrawal. This is because the measurements were made after a minimum 72 hours' withdrawal of antisecretory therapy, a time at which rebound hypersecretion is at a maximum [26–28]. Thus, rebound hypersecretion could have caused misclassification of some of these patients as hypersecretors.

Patients with Zollinger–Ellison syndrome (ZES) also have a high incidence of reflux oesophagitis, which appears to be related to the high basal gastric acid output in such patients [29]. Sixty-one per cent of a group of 122 patients with ZES were found to have symptomatic or endoscopic evidence of oesophagitis, and 23% had moderate to severe disease [30].

Medical Treatment of Reflux Oesophagitis

The aims of medical therapy of GORD are to relieve the symptoms, to heal established oesophageal mucosal damage and to prevent the development of complications. In order to do this, treatment needs to either prevent the reflux of acidic gastric contents into the oesophagus, or to eliminate or reduce the injurious action of acid to a level that will allow healing of the oesophageal epithelium. At present, there are no agents that are fully effective in correcting motor defects that cause pathological oesophageal acid exposure.

The prokinetic agents bethanecol, metoclopramide, domperidone and cisapride have all been used for reflux oesophagitis, with varying success. Of these, only cisapride is free from

troubling side-effects [31]. It increases the LOS pressure and enhances oesophageal acid clearance by stimulating peristalsis via selective stimulation of postganglionic neurones of the myenteric plexus. Cisapride is significantly better than placebo and, in divided doses of 40 mg daily over a 6–12-week period, is as effective as ranitidine, 150 mg twice daily, or cimetidine, 400 mg twice or four times daily [32]. The effect on oesophageal acid exposure, however, is insufficient to produce a consistently high response rate in severe grades of GORD.

Sucralfate binds to damaged epithelium and may act as a barrier to acid and pepsin. There is some evidence that it binds epidermal and fibroblast growth factors, and may thus promote healing. When administered as a suspension, sucralfate, 1 g four times daily, results in symptomatic relief and endoscopic improvement similar to that achieved with H_2-receptor antagonists [32].

The most established and effective treatment for reflux oesophagitis is to reduce the acidity and volume of gastric contents available for reflux by pharmacological gastric acid suppression. Cimetidine has been prescribed for GORD for 15 years, and it produces more rapid symptomatic relief than placebo, but has a lesser effect on the improvement of endoscopic grading [33]. Ranitidine is effective in the symptomatic relief of reflux disease and produces improvement in endoscopic appearances in 48–88% of cases within 6–8 weeks, depending upon the endoscopic grading and severity of GORD. Complete resolution of oesophageal erosions or ulceration is, however, seen less frequently, occurring in only 27–45% of patients. Similar results have been obtained with the newer H_2-receptor antagonists famotidine and nizatidine. The proton pump inhibitor omeprazole is significantly superior to the H_2-receptor antagonists, with complete healing of erosive oesophagitis in 67–92% of patients at 4 weeks, and similarly high rates of symptom relief. This is especially true for the more severe grades of oesophagitis [33]. Omeprazole seems to work solely by suppressing gastric acid secretion, as it has been shown to have no major effect on oesophageal motility or on the number of post-prandial reflux episodes [34].

Tailoring Acid Suppression to the Disease

As already described, gastro-oesophageal reflux is increased in the majority of patients, mainly in the post-prandial and early evening periods. H_2-receptor antagonists, however, cannot easily overcome the integrated stimulus to acid secretion produced by a meal [35, 36]. This may explain the relative ineffectiveness of conventional doses of these agents in reflux disease. Divided doses of H_2-receptor antagonists carry no advantage over single night-time dosing [37, 38]. Schaub et al. found that neither ranitidine, 150 mg twice daily, nor an increased dose of 300 mg twice daily, altered the 22-hour intra-oesophageal pH profile when compared with pretreatment recordings [39]. Attempts to improve the effect of ranitidine on reducing evening reflux, by dosing immediately after the evening meal rather than at bedtime, have also been unsuccessful [40]. H_2-receptor antagonists are more effective at reducing intragastric acidity when acid secretion is not otherwise stimulated, and this is probably the basis for their moderate efficacy in GORD. There is a modest therapeutic gain when the effects of cisapride on oesophageal acid clearance are added to the effects of ranitidine on the pH of the refluxate, but it is questionable whether the gains are sufficient to justify combination therapy [41–43].

Inhibitors of the parietal cell H^+, K^+-ATPase, the acid pump, such as omeprazole, effectively suppress gastric acid secretion

throughout the day, and can overcome meal-stimulated acid production. Targeting acid suppression for GORD during the day remains important, even for the higher grades of oesophagitis, as daytime acid exposure remains an important factor. In addition, though, nocturnal reflux is substantially more important in this patient group. Thus, the most effective therapy is likely to be one that suppresses both daytime and night-time acid secretion. In a direct comparison with cimetidine, omeprazole, 40 mg once daily, healed erosive and ulcerative oesophagitis in 71% of patients in 8 weeks, 60% of whom had grades III–IV oesophagitis, compared with 23% healing on cimetidine, 400 mg four times daily [44]. Twenty-four-hour oesophageal pH-monitoring showed that omeprazole abolished both nocturnal and daytime oesophageal acid exposure in those patients with healed oesophagitis, whereas three of the five patients healing on cimetidine still had more than 5% daytime reflux. Those patients failing to heal on omeprazole had no change in their mean nocturnal acid exposure.

Those patients with gastric acid hypersecretion may require higher doses of antisecretory drugs. Collen et al. found that symptomatic relief could be obtained in their group of acid hypersecretors resistant to conventional doses of ranitidine by increasing the dose to as much as 1800 mg daily [25]. Basal acid output had to be suppressed to below 1 mmol/hour for heartburn to be relieved. Combined intra-oesophageal and intragastric 24-hour pH-monitoring studies support the view that an incomplete response to omeprazole is primarily due to inadequate suppression of acid secretion in a small proportion of patients treated with up to 60 mg daily [45]. It would appear that in these patients division of dosage will lead to better control of the pH of refluxate throughout the 24 hours.

Thus, optimal treatment for reflux oesophagitis can be achieved by abolishing oesophageal acid exposure throughout both the daytime and night-time periods. The less effective the LOS is in preventing reflux of gastric contents into the oesophagus, the more necessary it is to raise the pH of the stomach contents to above 4.0 throughout the 24 hours.

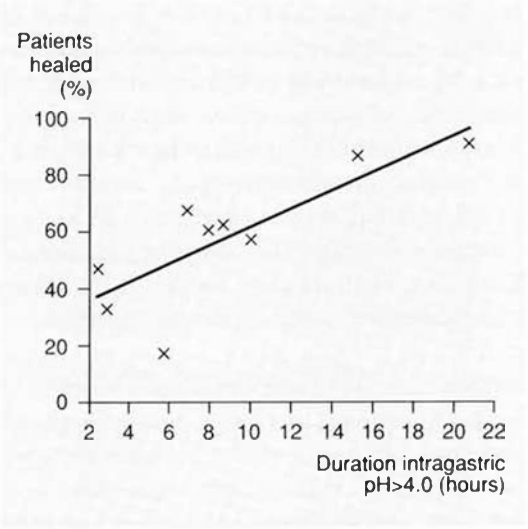

Fig. 1. Relationship between the healing of erosive oesophagitis at 8 weeks and the duration, in hours, out of the 24-hour period, that the intragastric acidity is raised above pH 4.0.

We have performed a meta-analysis of treatment trials of reflux oesophagitis, in which healing was assessed endoscopically. These results have been correlated with 24-hour gastric acid suppression data for each drug and dosage regimen, obtained from a previous meta-analysis using patients with duodenal ulcer [46]. We contend that using acid suppression data from patients with duodenal ulcer is more appropriate than data from normal volunteers, as they also have a higher incidence of gastric acid hypersecretors than the normal population, and there are limited gastric acid suppression data available from patients with GORD.

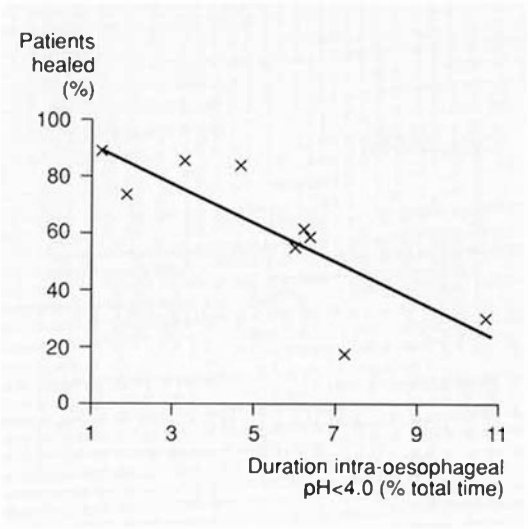

Fig. 2. Relationship between the healing of erosive oesophagitis at 8 weeks and oesophageal acid exposure.

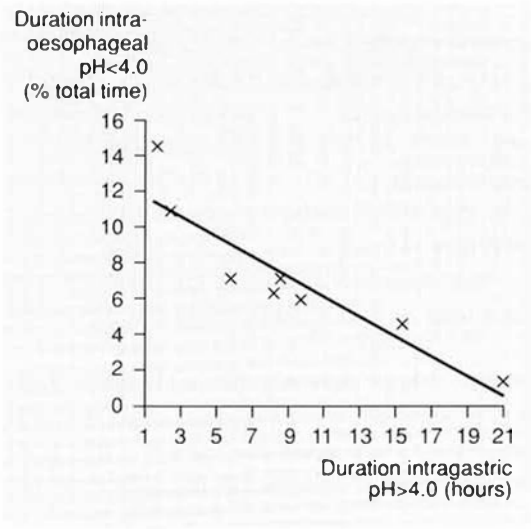

Fig. 3. Relationship between the duration of suppression of intragastric acidity in hours and oesophageal acid exposure.

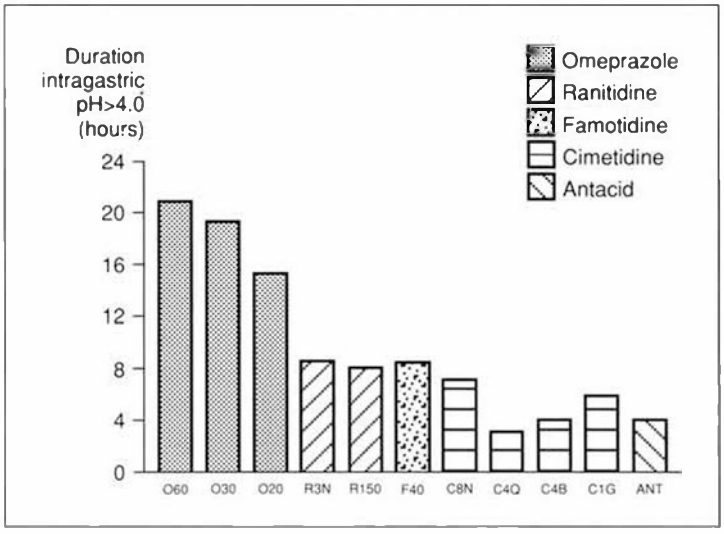

Fig. 4. Duration, in hours, of the 24-hour period that the intragastric pH is raised above 4.0 for some commonly prescribed drugs. O60, omeprazole, 60 mg once daily; O30, omeprazole, 30 mg once daily; O20, omeprazole, 20 mg once daily; R3N, ranitidine, 300 mg at bedtime; R150, ranitidine, 150 mg twice daily; F40, famotidine, 40 mg at bedtime; C8N, cimetidine, 800 mg at bedtime; C4Q, cimetidine, 400 mg four times daily; C4B, cimetidine, 400 mg twice daily; C1G, cimetidine, 200 mg three times daily and 400 mg at bedtime; ANT, antacid, 150 mmol seven times daily.

Preliminary results show a correlation coefficient of 0.87 ($p<0.05$) between the healing rate of oesophagitis at 8 weeks and the duration, in hours, that the intragastric pH is maintained above 4.0 (fig. 1). A similar finding is seen with pH thresholds of 3.0 and 5.0, but the relationship is not so strong. Eight-week healing of GORD follows an inverse relationship with oesophageal acid exposure ($r=0.83$; $p<0.05$) (fig. 2). This finding is not surprising,

given the close relationship between the duration of suppression of intragastric acidity to above pH 4.0 and the inhibition of oesophageal acid exposure, as expressed as time below pH 4.0 (fig. 3). This is despite the variability in oesophageal pH studies, owing to electrode position or day-to-day variation in the degree of reflux [47, 48].

The response to antisecretory drugs can therefore be predicted by the duration of suppression of intragastric acidity to above pH 4.0, over a 24-hour period, achieved by each treatment regimen. Figure 4 shows some commonly prescribed treatments that achieve this goal. As can be seen, omeprazole has a clear advantage, and this is reflected in its ability to heal reflux oesophagitis.

Conclusion

The extent of oesophageal mucosal injury is determined by the degree and duration of oesophageal acid exposure, which, in turn, is related to the pH of the gastric contents. The effect of antisecretory therapy on GORD can be predicted from the duration of suppression of intragastric acidity to above pH 4.0 achieved by each drug regimen, and the length of treatment.

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