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Role of gastric acid suppression in the treatment of gastro-oesophageal reflux disease

N J V Bell, R H Hunt

Abstract

Gastro-oesophageal reflux disease is a common condition with a complex pathophysiology. Despite the spectrum of abnormalities, gastric acid has a central role in mucosal damage, and the mainstay of medical treatment is suppression of gastric acid secretion. The results of antisecretory treatment as assessed by endoscopic healing are reviewed. H_2 receptor antagonists give more rapid symptom relief than placebo and can produce endoscopic improvement in 31–88% of cases depending on the severity of oesophagitis. Complete healing, however, is seen only in 27–45% of patients and these have mainly grades I–II disease. Improved healing rates can be obtained by increasing the degree of acid suppression or the length of treatment. The addition of a prokinetic agent may be beneficial. Omeprazole heals 67–92% of patients overall and although most successful in the lower grades of oesophagitis, can also heal 48–62% of patients with grade IV disease. The degree and rate of healing seem to be related to the reduction in oesophageal acid exposure and thus may correlate with the degree and duration of acid suppression over 24 hours obtained by the various treatments. The underlying pathophysiology is unchanged, however, and long term treatment may be needed to maintain remission.

Gastro-oesophageal reflux disease (GORD) is a very common condition in the western world with an estimated incidence of 7% of the adult population.[1] Reflux of gastric or duodenal contents into the oesophagus gives rise to symptoms of heartburn and regurgitation which are the principle reasons for the widespread consumption of antacid preparations.[2] While most patients with mild GORD present with symptoms of heartburn, in more severe cases reflux of gastric contents results in mucosal inflammation, ulceration, or stricture formation. Furthermore, protracted reflux over many years can result in metaplastic changes and the development of Barrett's epithelium.

The pathophysiology of GORD is complex and not yet fully understood. Defective lower oesophageal sphincter (LOS) motility may be the most important abnormality, of which two main types have been identified.[3] Transient relaxation of the lower oesophageal sphincter, lasting 5–35 seconds and independent of normal peristalsis, is seen in 60–83% of reflux episodes, and there is impaired suppression of these periods of sphincter relaxation in the supine position in patients with GORD when compared with healthy controls. Loss of the basal lower oesophageal sphincter tone is thought to account for up to 22% of reflux episodes especially in the more severe grades of oesophagitis.[4] Absence of basal LOS tone is rarely continuous but may last up to 10 minutes. Both forms of LOS dysfunction can occur in the same patient. Once reflux has occurred, impaired clearance of gastric contents from the oesophagus contributes to the exposure of the mucosa to damaging refluxate. Reduced gastric emptying, the presence of hiatus hernia, and impaired mucosal resistance to injury are also implicated in the pathogenesis of GORD.

Despite this spectrum of abnormalities, the role of gastric acid is considered essential to mucosal damage. Indeed, intraoesophageal acid perfusion has been used for diagnosis, as with the Bernstein acid perfusion test, and 24 hour intraoesophageal pH monitoring has become widely accepted as the standard test to detect reflux.

Thus, the mainstay of medical treatment for GORD has been aimed at eliminating oesophageal acid exposure, either by neutralisation with alkalies or by suppressing gastric acid secretion. The simple measures of weight loss, dietary control, abstinence from smoking, and raising the head of the bed remain important first line recommendations. Raising the bed head by 20 cm significantly augmented the symptomatic improvement seen with ranitidine from 77% to 87% in a group of 71 patients with grade III oesophagitis.[5]

Comparison of the various treatments used in GORD is complicated by the lack of agreed diagnostic criteria for oesophagitis, with some authors relying on symptomatology, radiological findings, or ambulatory pH monitoring, and others prefering endoscopic, histological, or acid perfusion studies. In order to assess the place of gastric acid suppression in the management of peptic oesophagitis, this paper reviews published studies that have used endoscopic healing as an end point for the evaluation of treatment regimens.

Unfortunately, the endoscopic diagnostic criteria also vary between trials, with several different grading systems used. There is agree-

Division of Gastroenterology, McMaster University Medical Centre, Hamilton, Ontario, Canada
N J V Bell
R H Hunt

Correspondence to:
Professor R H Hunt, Division of Gastroenterology, McMaster University Medical Centre, 1200 Main Street West, Room 4W8, Hamilton, Ontario L8N 3Z5, Canada.

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ment that confluent ulceration or stricture formation represent severe disease, but in lower grades there are considerable differences in the definition and application of criteria. Some authors accept mucosal erythema, oedema, or friability as mild oesophagitis whereas others require the presence of epithelial defects, as in the Savary-Miller classification.[6] This alone may account for the variability in healing rates between studies.

A further confounding factor is that most trials have allowed free use of antacids in addition to the treatment under investigation.

H_2 receptor antagonists

CIMETIDINE

Cimetidine has been compared with placebo in 10 trials.[7-16] These show a trend towards more rapid symptomatic relief compared with placebo groups, which was significant in five of the 10 studies. When endoscopic evaluation was considered, cimetidine produced an improvement in endoscopic grade, although this was significantly better than placebo in only three trials (Table I). Brown found a resolution of endoscopic changes in 55·6% with placebo against 81·8% with cimetidine 1 g per day, however 72·7% of these patients had minimal changes of mucosal friability or exudation at entry to the trial which would not be considered oesophagitis by more stringent criteria.[10] Cimetidine treated patients consumed significantly less antacid in five of eight studies, and in a randomised crossover trial using a double dummy technique, Petrokubi and Jeffries found a highly significant improvement in endoscopic oesophagitis with cimetidine 300 mg four times daily compared with antacid, with complete healing of mucosal erosions in 47% taking cimetidine compared with 7% taking regular antacid.[17]

In a dose ranging study, Kaul *et al* found no difference in endoscopic improvement with 800 or 1600 mg cimetidine daily or between six and 12 weeks' treatment.[18] Likewise, twice daily dosage was as effective as a four times a day regimen, with a healing rate of 55% in 118 patients receiving 1200 mg cimetidine daily.[19]

Cimetidine 300 mg four times daily was as effective as bethanecol 25 mg four times daily, with a six week healing rate of 68·2% for cimetidine compared with 52·4% for bethanecol.[20] Cimetidine also compared favourably with sucralfate in a study that showed an improvement of 67% for cimetidine 400 mg four times daily compared with 53% for sucralfate 1 g four times daily over an eight week period.[21]

RANITIDINE

In comparisons with placebo, ranitidine was superior in relieving symptoms of nocturnal and daytime heartburn and in reducing antacid consumption.[22-30] Ranitidine treatment is also associated with a significant improvement in the endoscopic grading of oesophagitis (Table II). When complete resolution of all epithelial defects is evaluated, however, healing occurred in only 33% (17–56) of ranitidine treated patients compared with 13% (3–41) with placebo. Goy *et al* found improvement in 88% of patients treated with ranitidine 150 mg twice daily, but observed complete healing in only 18%, none of whom had severe oesophagitis at entry to the study.[23]

Johansson *et al*, in a well designed double blind crossover study, looked at a group of patients who were unresponsive to first line measures including antacids. They found complete healing in 34% of ranitidine treated patients compared with 3% on placebo, but all of these were from the group with Savary-Miller grade I oesophagitis or less.[26] None of the patients with grades II or III disease had complete resolution of the endoscopic findings. The exclusion of patients who improved on first line methods and antacids from the study may partly explain the discrepancy between the findings in this trial and those of Grove *et al*[24] and Hine *et al*[25] who found no significant difference between ranitidine and 'antacid placebo.'

In an Italian multicentre study, Bovero *et al* showed that a bedtime dose of ranitidine 300 mg was as effective as ranitidine 150 mg twice daily,[31] a finding subsequently confirmed by Halvorsen *et al*.[32] Schaub *et al* found no significant benefit in increasing the dose to 300 mg twice daily,[33] although a recent study by Johnson has found that increasing the dose of ranitidine from 150 twice daily to 300 mg four times daily improved the healing of Savary-Miller grades II–III oesophagitis from 29% to 63% at four weeks ($p<0·0001$) with a further improvement from 54% to 75% at eight weeks.[34]

In comparisons with prokinetic agents, ranitidine 150 mg twice daily was shown to be superior to metoclopramide 10 mg three times daily,[35] and more recently, equivalent to cisapride 10 mg four times daily for Savary-Miller grades I–II oesophagitis.[36]

Ranitidine and cimetidine have been compared directly in only one published study in which the investigators found no difference between ranitidine 150 mg twice daily and cimetidine 400 mg twice daily at eight weeks, although the study was limited to a small number of patients.[37]

FAMOTIDINE

In an open trial in patients with grades I or II oesophagitis, famotidine 40 mg at night resulted in symptomatic relief in 81% of patients within four weeks and endoscopic healing in 82% at 12 weeks.[38] Berenson *et al* have recently reported the results of a controlled study of 318 patients with grades II–IV oesophagitis in which famotidine 40 mg twice daily healed 48% patients at six weeks compared with 18% with placebo.[39] These figures increased to 69% and 29% respectively at 12 weeks. A lower dose of 20 mg twice daily healed 54% of patients at 12 weeks but at six weeks was not significantly better than placebo. These results reflect the findings of 24 hour oesophageal pH monitoring. Famotidine 20 mg twice daily was more effective at reducing the total percentage of reflux time than a single 40 mg dose of famotidine given at bedtime, but only 40 mg twice daily was significantly superior in

TABLE I *Comparison of cimetidine (CIM) and placebo (PLAC) in improvement of endoscopic grade of reflux oesophagitis*

Author	Year	Dose (mg/day)	Weeks	% Improved CIM	% Improved PLAC	p value
Behar[7]	1978	1200	8	45	37	NS
Breen[8]	1983	1000	8	31	42	NS
Bright-Asare[9]	1980	1200	8	78	78	NS
Brown[10]	1979	1000	8	82	56	N/A
Ferguson[11]	1979	1600	26	63	31	<0·05
Festen[12]	1980	1600	8	46	14	NS
Fiasse[13]	1980	1600	8	53	33	NS
Greaney[14]	1981	1600	6	N/A	N/A	NS
Powell-Jackson[15]	1978	1600	6	47	40	NS
Wesdorp[16]	1978	1600	8	67	0	<0·01

TABLE II *Comparison of ranitidine (RAN) and placebo (PLAC) in improvement of endoscopic grade of reflux oesophagitis*

Author	Year	Dose (mg/day)	Weeks	% Improved RAN	% Improved PLAC	p value
Berstad[22]	1982	300	6	71	32	<0·01
Goy[23]	1983	300	6	88	28	<0·01
Grove[24]	1985	300	6	N/A	N/A	NS
Hine[25]	1984	300	6	48	25	NS
Johansson[26]	1986	300	8	49	6	<0·01
Lehtola[27]	1986	450	6	60	26	<0·05
Sherbaniuk[28]	1984	300	6	61	48	<0·05
Sontag[29]	1987	300	6	63	46	=0·06
Wesdorp[30]	1983	300	6	79	24	<0·01

TABLE III *Four week endoscopic complete healing rates for omeprazole (OH) v ranitidine (RAN) 300 mg/day*

Author	Year	Dose omeprazole (mg)	% Healed OM	% Healed RAN	p value
Zeitoun[53]	1987	20	81	45	<0·001
Sandmark[54]	1988	20	67	31	<0·0001
Ruth[55]	1988	20	92	40	N/A
Havelund[56]	1988	40	77	39	<0·001
Vantrappen[57]	1988	40	85	40	<0·0001
Klinkenberg-Knol[58]	1987	60	76	27	<0·002

reducing the number of reflux periods longer than five minutes occurring in the upright position. All three treatment regimens successfully decreased the nocturnal percentage of acid contact time, the number of reflux episodes, and the number of episodes lasting more than five minutes in the supine position.[40]

NIZATIDINE

Nizatidine has been evaluated in three trials. Twice daily dosage with 150 mg was significantly superior to placebo in reducing endoscopic oesophagitis, but 300 mg given once a day failed to show any significant benefit.[41] Similar findings were reported by Quik *et al* from a study of 325 patients. Nizatidine 300 mg twice daily healed 50% of the patients at 12 weeks compared with 34% on placebo, but once daily dosage with 300 mg was not significantly better than placebo. When assessed by entry grade, however, the advantage of twice a day as opposed to a single daily dose was apparent for severe oesophagitis only.[42] Berges *et al* also found that the twice daily dose gave significantly better 12 week healing rates than the once a day regimen.[43]

The implication in the findings for both of the newer H_2 receptor antagonists (famotidine and nizatidine) is that reflux oesophagitis of grades II–IV requires prolonged acid suppression for healing whereas mild disease (grade I) will respond to nocturnal acid inhibition alone.

COMBINATION THERAPY

In an attempt to improve the healing rates in reflux oesophagitis, the effect of gastric acid suppression with the H_2 receptor antagonists in combination with other agents has been studied. Lieberman and Keefe, in a double blind trial, treated 25 patients resistant to cimetidine alone with cimetidine 1200 mg per day in combination with metoclopramide 40 mg per day or placebo. They found that 9 of 12 (75%) patients improved endoscopically as well as symptomatically on combination therapy compared with 4 of 12 (33%) treated with cimetidine alone. However, side effects caused by the dopaminergic antagonist action of metoclopramide such as intermittent fatigue and increased anxiety were common.[44] Against this, Temple *et al* reported no benefit from the combination, but found that side effects necessitated withdrawal in one third of the patients.[45]

The newer prokinetic agent cisapride has also been used in combination with H_2 antagonists. Cisapride 10 mg twice daily, when given together with ranitidine 150 mg twice daily showed a trend towards improvement over ranitidine 150 mg twice daily alone at 12 weeks, but the difference failed to reach statistical significance.[46] When combined with cimetidine 1 g daily, cisapride 40 mg per day improved endoscopic healing at 12 weeks from 46% to 70% compared with cimetidine 1 g per day alone in patients with Savary-Miller grades II or III oesophagitis.[47] In this small study of 24 patients, there were no serious side effects reported, suggesting that there is a place for a larger controlled trial.

Colloidal bismuth 120 mg four times daily has been used in combination with cimetidine 800 mg at night for severe (Savary-Miller grades III–IV) oesophagitis.[48] Together, they gave significantly better results than cimetidine alone. Seven of the 10 patients on double therapy had complete resolution of their oesophagitis, the other three improving by at least two grades. In comparison, none of the 10 patients treated with cimetidine alone returned to grade 0 during the three weeks of the trial. It is not known whether this action is due to the cytoprotective properties of colloidal bismuth or to its action on *Helicobacter pylori*, which was found in the oesophagus in 9 of 20 patients.

Sucralfate also acts as a mucosal protective agent. In contrast to colloidal bismuth, however, the combination with cimetidine was not significantly different to treatment with sucralfate alone.[49]

ACID PUMP INHIBITION

Omeprazole is the first of a new class of drugs that specifically blocks the enzyme H^+/K^+-ATPase in the parietal cell, and effectively inhibits gastric acid secretion.

In an open study, Dent showed that 30 mg omeprazole daily could heal oesophageal ulceration in 6 of 8 patients within four weeks and in 7

of 8 at eight weeks, with the remaining patient having a 95% reduction in area of ulceration.[50] When compared with placebo, omeprazole produced healing in 81% of the patients at four weeks *v* 6% for placebo. Symptomatic improvement was just as impressive with complete relief from all symptoms being achieved in 39% of patients at only two weeks compared with 3% in the placebo group.[51] Hetzel *et al* went on to compare two different dosages in 164 patients: omeprazole 40 mg resulted in 82% healing at four weeks in contrast to 70% with the 20 mg dose. At eight weeks the cumulative healing rates were 85% and 79% respectively.

An initial trial comparing omeprazole and ranitidine suggested a significant difference in favour of omeprazole.[52] These findings have subsequently been confirmed in several studies (Table III). The results for omeprazole are particularly impressive since they represent complete healing, not just improvement, and the study groups included those with severe (grades III–IV) oesophagitis. Not surprisingly, better healing rates were achieved in those with lower grades of disease; 90–100% of patients with grades I–II oesophagitis healed within four weeks compared with 53–55% of those treated with ranitidine.[56 57] Even at 12 weeks, the results for ranitidine showed healing in only 88% for grades I–II. For grade III disease, healing takes slightly longer. Omeprazole achieved 70% healing at four weeks and 90% healing at 8 to 12 weeks. Omeprazole is also effective in the treatment of grade IV oesophagitis, with healing observed in 48% at four weeks increasing to 62% at eight weeks.[51]

The improved healing rates achieved by omeprazole over the H_2 antagonists, seem to be directly related to the greater degree and duration of acid suppression provided by inhibition of the acid pump. Using 24 hour intraoesophageal pH monitoring, Pasqual showed that omeprazole could reduce reflux, as measured by the time the pH was below 4, from mean (SEM) 11·2 (4·5)% to less than 5% over the 24 hour period.[59] Omeprazole 40 mg resulted in a significantly shorter time below pH 4 than 20 mg (0·7 (1·3)% *v* 3·1 (4·1)%). Ruth *et al* compared the effects of ranitidine and omeprazole on oesophageal pH.[55] They found that 20 mg omeprazole significantly reduced all reflux variables when analysed according to body position and total values, except for the duration of the longest reflux period which was significantly improved only in the upright position. Ranitidine 150 mg twice daily, however, was only significant in reducing the total reflux time.

In a double blind comparison with cimetidine, omeprazole 40 mg provided complete healing in 71% of patients at eight weeks compared with 23% healing on cimetidine 400 mg four times daily. Patients with grades III–IV oesophagitis comprised more than 60% of both study groups. Twenty four hour oesophageal pH was recorded in 18 of the 67 patients. Both day and night oesophageal acid exposure, as defined by reduction of the oesophageal pH to 4 or less, was abolished by omeprazole 40 mg in those patients with healed oesophagitis, whereas 3 of 5 patients healed on cimetidine had daytime acid exposure of greater than 5%. Those patients who failed to heal on omeprazole had no change in their mean night time acid exposure.[60]

Klinkenberg-Knol *et al* performed ambulatory 24 hour oesophageal pH monitoring in a small group of patients on 60 mg omeprazole. They found that acid reflux was not entirely abolished by even such high doses of omeprazole. Two of their seven patients had pathologically long supine reflux periods.[61] This may account for the few patients who fail to heal despite such high dose treatment.

Discussion

The above studies clearly show that increasing the degree of gastric acid suppression increases the healing of reflux oesophagitis in the short term. This does not, however, alter the natural history of the disease. Relapse is common on stopping treatment, with some 20% only remaining in remission at six months and approximately 50% relapsing in under two months.[14 51 56]

Maintenance treatment with reduced doses of antisecretory drugs seems to have no advantage over placebo.[18 62] Sherbaniuk, however, found that longterm treatment with full dose ranitidine could maintain the improvements obtained over one year.[28] Omeprazole 10 or 20 mg once daily has been used for maintenance therapy and at 20 mg daily reduces the relapse rate to 20% at one year. Weekend only dosage regimens have been studied but have not proved to be of benefit.[63 64]

The disappointing results obtained by the H_2 receptor antagonists may be partly explained by the pathophysiology of the condition. Johansson and Tibbling performed gastric secretion tests and 24 hour pH monitoring in a group of 42 patients with reflux oesophagitis.[65] They found gastric hypersecretion in 76%, and that basal and peak acid output, number of reflux episodes, and total supine reflux time were significantly more reduced in symptomatic responders than in non-responders. The basal acid output has also been shown to correlate with the severity of reflux disease; patients with erosive oesophagitis and Barrett's oesophagus have significantly higher basal acid outputs than those with heartburn alone.[66] Serum gastrin values are also higher in resistant cases.[67]

Collen *et al* have recently published a study of patients resistant to conventional doses of ranitidine.[68] The non-responders had significantly higher basal acid outputs than those who experienced complete symptomatic relief, and 9 of 12 were true hypersecretors (basal acid output >10 mEq/hour). Symptomatic relief was achieved in 10 of 12 using increased doses of ranitidine (up to 1800 mg/day). They found that basal acid output had to be almost completely suppressed (to below 1 mEq/hour) for heartburn to be relieved. The longest period of unbuffered basal acid output occurs at night, and studies have shown that the degree of supine reflux correlates with the severity of oesophagitis to a greater extent than day time reflux.[69] This may reflect the impaired clearance of acid from the oesophagus and diminished neutralisation by salivary bicarbonate at night, as well as the potency of the refluxate. The healing rates of the various drugs

seem to reflect their ability to inhibit gastric acid production, as has been shown for duodenal and gastric ulcer disease.[70 71] A recent meta-analysis has shown that duodenal ulcer healing not only correlates with the degree of acid suppression but also with the duration of acid suppression and the length of treatment.[72] Furthermore, there is no benefit from increasing the suppression to above a gastric pH of 3·0, but increasing the duration of the antisecretory effect is more important. As oesophageal reflux can occur throughout the whole 24 hours, a similar relation to that seen for duodenal ulcer disease may exist. The ability of omeprazole to achieve a longer duration of acid suppression presumably accounts for its success in treating oesophagitis resistant to H_2 receptor blockade.

As stated previously, GORD is a multifactorial condition. The presence of a competent lower oesophageal sphincter mechanism is important. Leiberman found oesophageal sphincter pressures to be lower in his group of relapsing patients than in those in prolonged remission.[73] Although LOS hypotonia can be induced by peptic oesophagitis, healing of oesophagitis with antisecretory agents fails to improve LOS motility[50] and relapse is the rule on withdrawal of treatment. The addition of cisapride may well allow a bimodal approach to therapy.

In contrast to most pharmacological treatments, the surgical approach to GORD has been aimed at improving LOS function. Anti-reflux surgery has been directly compared with medical treatment in three trials. Behar, before the advent of the H_2 antagonists, reported an excellent result in 73% of patients after fundoplication, with a minimum follow up of 20 months. In contrast, only 19% of those maintained on antacids had a satisfactory response.[74] Posterior partial (270°) fundoplication has been compared with long term treatment with ranitidine 150 mg twice daily.[75] Initial eight week treatment with ranitidine produced some improvement, but no further benefit was obtained from extending treatment to six months. After surgery, performed in a group showing no improvement with ranitidine, all patients had a normal endoscopic appearance at six months. Only 1 of 15 patients experienced mild symptoms involving an inability to belch, a relatively common problem after a 360° Nissan procedure. Spechler *et al* have shown that the improved results of surgery over medical treatment with ranitidine are maintained at one year's follow up.[76]

Long term profound acid suppression with either high dose H_2 receptor antagonists or with omeprazole may be necessary to obtain lasting symptomatic relief and endoscopic healing equivalent to that obtained surgically, especially for grades III and IV ulcerative oesophagitis. The safety of such a life time of acid suppression is uncertain, although 15 years post marketing surveillance of cimetidine has proved it to be remarkably safe and omeprazole has been used compassionately for up to six years without significant adverse effect.[77] While enterochromaffin like cell hyperplasia and gastric carcinoid formation have been reported in rats given long term high dose omeprazole, these changes have since been shown to occur with H_2 receptor antagonists such as ranitidine and loxtidine, the hypolipidaemic compound ciprofibrate or after partial fundectomy.[78–80] This phenomenom seems to be due to the hypergastrinaemia associated with acid suppression achieved by a variety of means, rather than a direct effect of any of the agents, and furthermore is reversible by antrectomy.[81 82] Prolonged hypochlorhydria, however, may predispose to late gastric carcinoma as observed some 20 years after surgery for benign peptic ulcer disease.[83 84] Experimentally, at least, operations resulting in duodenogastric bile reflux increase the susceptibility of the gastric mucosa to neoplastic change.[85] It is thought that a high intragastric pH promotes bacterial overgrowth which converts dietary nitrates and nitrites into carcinogenic *N*-nitroso compounds. Bile reflux seems to be involved in carcinogenesis, but whether by the formation of cocarcinogens or as a promoter by increasing mucosal permeability to initiating carcinogens is uncertain.[86] Until these matters are resolved, particularly for the younger patient, there remains a role for surgery in the management of GORD.

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