pH, Healing Rate and Symptom Relief in Acid-Related Diseases

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Suppression of gastric acid secretion is widely used and logical for the treatment of acid-related diseases. Healing of duodenal ulcer, gastric ulcer and gastroesophageal reflux disease is correlated significantly with the degree and the duration of suppression of intragastric acidity over 24 hours and with the length of the treatment. To date, proton pump inhibitors are the most effective agents among the currently available antisecretory drugs in offering the highest healing rate and fastest resolution of symptoms. Combinations of an antisecretory drug with one or more antimicrobial agents accelerate healing of peptic ulcers.

INTRODUCTION

Gastric acid is considered an important physiological factor in maintaining normal upper gastrointestinal (GI)\(^b\) function. Gastric acid activates pepsin, modulates gastrin release, has a bactericidal action and facilitates calcium and iron absorption. Abnormalities of acid secretion are associated with a number of upper GI diseases. In patients with duodenal ulcer (DU), acid hypersecretion is seen commonly, and the concept of self-digestion by gastric juice became fashionable with the dictum of Schwarz "No acid — no ulcer." Gastroesophageal reflux disease (GERD), gastric ulcer (GU) and ulceration in hypersecretory conditions such as Zollinger-Ellison syndrome are also considered to result from an imbalance between intraluminal acid and mucosal defensive factors. Moreover, many patients with these conditions benefit from antisecretory therapy, and this supports the important role of gastric acid in the pathogenesis of these diseases.

Since the isolation of Helicobacter pylori more than a decade ago [1], our perception of the pathogenesis of gastroduodenal ulceration has been changed dramatically. To most, the evidence is now conclusive that this microorganism causes over 90 percent of duodenal ulcer and about 70 percent of gastric ulcer [2]. Many studies have shown that both healthy volunteers and duodenal ulcer patients with H. pylori infection have increased basal and maximum pentagastrin- and gastrin-releasing, peptide-stimulated acid secretion [3-5] and pepsin output [3]. Furthermore, eradication of H. pylori infection results in normalization of these abnormalities in acid secretion [3-5] and dramatically reduced DU recurrence [6]. Thus, eradication of H. pylori infection has important implications for the concept of controlling gastric acid secretion in H. pylori positive ulcer patients [7].

The healing of GERD, DU and GU by antisecretory drugs is each highly correlated with the control of gastric acid secretion [8-10]. The goals of treatment for these diseases are to relieve the symptoms, to heal the established lesions and to prevent the development of recurrence and complications. Many clinical trials have been carried out to achieve these goals; however, the results vary between drugs and regimens. This paper will focus

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\(^b\)Abbreviations: GI, gastrointestinal; DU, duodenal ulcer; GERD, gastroesophageal reflux disease; GU, gastric ulcer; PPI, proton pump inhibitors; AUC, area under the curve.
on the relationship of pH to ulceration and symptoms and to the control of intragastric pH and healing rate and symptom relief in patients with GERD and peptic ulcer diseases.

**PHYSIOLOGY OF SECRETION OF GASTRIC ACID**

Gastric acid is secreted from the parietal cells and pepsinogen from the chief cells in the gastric fundus. Under the activation of gastric acid, pepsinogens are transformed into the active enzyme, which initiates protein digestion. The peptic activity in gastric juice is pH-dependent with maximal activity at pH 1.5 to 2 [11]. When the pH is increased above 3, the activity of pepsin decreases markedly, and this correlates well with experimental esophagitis [11]. Under normal circumstances, secretion of gastric acid has a circadian rhythm, with a rise in gastric acid secretion during the day and decreasing secretion during the night [12]. Twenty-four hour intragastric pH monitoring studies show that ingestion of a meal has a major impact on intragastric acidity and results in an immediate rise of pH due to buffering by the meal. Subsequently a gradual fall of intragastric pH is seen as the neutralizing capacity of the meal is exceeded [13]. Thus the peak times of intragastric acidity occur when basal acid secretion is unaffected by meals in the postprandial period and during the night.

The regulation of acid secretion is complex. Classical physiological studies have shown that at least three types of receptor on the parietal cell are involved in the regulation of acid secretion. Receptors are stimulated by acetylcholine through the neurocrine pathway (M3 receptors), by gastrin through a hormonal pathway (gastrin receptors) and by histamine through a paracrine pathway (histamine receptors) [14]. The relevance and importance of post-receptor interactions between these receptors have been discussed for many years [15]; however, the H+/K+-ATPase or proton pump is recognized as the final common pathway to acid secretion for these three receptors [15].

**ACID IN GASTROESOPHAGEAL REFLUX DISEASE**

Gastroesophageal reflux disease is considered to be primarily a motility disorder characterized by abnormally frequent transient relaxations of the lower esophageal sphincter and loss of lower esophageal sphincter tone in the basal state [16]. Both of these abnormalities facilitate reflux of acidic gastric contents into the lower esophagus. Furthermore, clearance of the acidic refluxate from the esophagus is impaired in about 50 percent of patients with GERD [17]. This results in prolonged exposure of the mucosa of the lower esophagus to the damaging effects of acidic gastric contents. In some patients, delayed gastric emptying [18] and abnormal duodeno gastric reflux [19] may make the refluxate, containing duodenal contents, more irritant to the esophageal squamous mucosa.

*Gastric acid and Symptoms in GERD*

Despite the evidence of dysmotility, gastric acid is considered of central importance to the initiation and continuation of the esophageal mucosal damage and the development of symptoms in patients with GERD. The question of acid hypersecretion has been examined by Hirschowitz, who compared 155 patients with endoscopically defined esophagitis and 508 controls without esophagitis [20]. There was no significant difference in basal or maximal gastric acid secretion between the groups, and the severity of esophagitis was not related to any parameters of acid secretion. However, there are a number of studies showing that the severity and frequency of symptoms including heartburn, regurgitation and pain significantly correlate with the duration of gastroesophageal reflux, the degree of esophageal exposure to acid, and the pH of the refluxate [21, 22]. The longer the duration of acid exposure, the more severe were the symptoms. Furthermore, it has been shown that the esophageal mucosa is sensitive to acid both in humans [22] and in an animal model [11].
Using intraesophageal perfusion of hydrochloric acid (HCl) at different pH values, Smith et al. evaluated the sensitivity of the esophageal mucosa in 25 symptomatic patients with GERD [22]. All subjects experienced pain when the perfusate had a pH between 1 and 1.5. Eighty percent had pain at pH 2.0, and half experienced pain with the pH between 2.5 and 6.

**Importance of Pepsin in GERD**

Pepsin is one of the major components of the refluxate in patients with GERD [23]. Active pepsin can be found in almost all reflux episodes detected by pH monitoring. The concentration of pepsin in the refluxate correlates significantly with severe esophagitis, particularly at night [23]. Symptoms, especially dysphagia, also have a significant correlation with pepsin concentration [23]. This evidence confirms early experimental observations that pepsin can cause esophageal mucosal damage in an acidic medium [11, 24]. However, since the peptic activity is pH dependent [11], it is possible, pharmacologically, to reduce the damaging effect of pepsin on the esophageal mucosa by increasing the pH of the refluxate above 4 to inhibit the activity of pepsin. The less effective control of the diurnal intragastric pH during the treatment with H₂RA still allows pepsin to have proteolytic activity, while the mean pH achieved with proton pump inhibitors (PPIs) is high enough to virtually abolish peptic activity [25]. Thus, acid suppression is appropriate for patients with GERD to minimize the injurious effect of both acid and pepsin.

**Bile Acids**

The damaging effect of bile acids on the esophagus and the mechanism of pathogenesis is not well documented. Bile may have a role in the development of so-called alkaline reflux esophagitis in achlorhydric patients [26], or in a subgroup of patients with complicated GERD [27, 28], or in patients with a history of gastric surgery [29]. Recent studies have shown that esophageal exposure to bile acids is not common in normal subjects, while patients with erosive esophagitis and Barrett’s metaplasia have increased esophageal exposure to a refluxate containing duodenal juice [30, 31]. Simultaneous 24-hr pH measurement and bile monitoring of the distal esophagus found a close association between duodeno-gastro-oesophageal reflux and the total proportion of time the pH was less than 4 (p < .001) but not greater than 7. This suggests that acid reflux is the primary factor in the development of Barrett’s metaplasia and that bile reflux may have a synergistic role in the progression of the severity of the esophagitis [28].

**RATIONALE OF ACID SUPPRESSION IN THE MANAGEMENT OF GERD**

Despite abnormal motor function in the lower esophagus of patients with GERD, gastric acid is deemed essential to the development of symptoms and mucosal damage. Intraesophageal acid perfusion, as with the Bernstein test, has been used for the diagnosis of patients with symptoms suggestive of GERD, and 24-hr intra-esophageal pH monitoring is widely accepted as a standard test to detect reflux of acidic gastric contents into the esophagus [32]. The time course of reflux is different between patients with mild erosive esophagitis or normal endoscopic appearances and patients with more severe erosive esophagitis. Daytime reflux alone, which is often closely related to symptoms, is seen more commonly in mild cases, while patients with more severe grades of esophagitis have frequent nocturnal reflux and long-lasting acid exposure [21, 33-36], which also may be associated with the development of complications of GERD [33].

However, data on the relationship between acid secretion, acid exposure time and the severity of esophagitis and symptoms have been conflicting [21, 37-39]. One large study from Sweden compared 24-hr pH monitoring from 190 symptomatic patients and 50 normal
controls [21]. Reflux symptoms correlated well with the duration of acid exposure (see Table 1).

A threshold of pH 4.0 has been suggested by most investigators as the optimal pH to differentiate physiological and pathological reflux [22, 32, 40]. If the pH is above 4, only a small proportion of patients experience esophageal pain during the Bernstein test [22]. This threshold has a maximum sensitivity of 93.3 percent and specificity of 92.9 percent [40]. Thus, if the intraesophageal pH of the refluxate can be maintained at or above 4 over the 24-hr period, a majority of patients will remain symptom free and undergo healing of esophagitis [9]. More recently, we have suggested a new analysis of 24-hr pH recording as a clinical predictor of esophageal mucosal damage and endoscopic grade of esophagitis [41]. We took data from 33 continuous 24-hr esophageal pH recordings performed in patients with varying grades of esophagitis, and calculated the area under the curve to represent total hydrogen activity (H+) and hence acid exposure. A significant difference was seen between AUC for H+ activity and all grades of esophagitis (see Table 2). This predictor might prove to be more accurate than the broad criteria of damage associated with the pH 4 threshold and four percent acid exposure time and could be used as a predictive model of esophageal mucosal damage and endoscopic grades of esophagitis.

**CLINICAL TRIALS OF ANTISECRETORY DRUGS IN GERD**

Many studies with conventional doses of cimetidine and ranitidine have not shown much superiority over placebo in relieving symptoms and healing esophageal mucosal lesions in patients with GERD (for review see Reference 42). This has been considered due to inadequate doses chosen for the treatment of GERD. Recent trials comparing ranitidine at higher doses with placebo indicate that there is a significant difference in symptomatic relief and healing of erosive esophagitis with two high doses of ranitidine (150 mg qid and 300 mg qid, respectively) compared to placebo over 12 weeks with the highest healing gain of 35 percent and 37 percent in one study [43], and 41 percent and 34 percent at eight weeks in another [44]. These data suggest that healing of esophagitis requires more effective suppression of acid secretion since increasing doses of ranitidine from 300 mg bid to 300 mg six times a day correlates dose-dependently with the reduction in the number and the duration of reflux episodes in GERD [45].

**Table 1. Correlation between severity of symptoms and acid exposure time.**

| Groups (no.) | Acid exposure time (percent)* | Reflux symptoms (≥ grade 2) |
|--------------|-----------------------------|-----------------------------|
| Normal controls (50) | 1.1 | 0 |
| Patients with no esophagitis (127) | 3.4† | 63/127 (50%) |
| Patients with esophagitis (63) | 10.6† | 42/63 (67%) |

Data from Joelsson and Johnsson [21].

*Percent of 24-hr recording.
†Significant difference vs. controls.

**Table 2. Predictive model of mucosal damage and endoscopic grades of esophagitis.**

| AUC* (min x mmol/L) | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---------------------|---------|---------|---------|---------|
| 67.1 ± 19          | 142.6 ± 38 | 473.5 ± 76 | 868.1 ± 170 |

Table modified with permission from Barrientos et al. [41].

*p < .001 between grades.
The PPIs have been studied in many well-designed clinical trials, which show a consistent and significantly better effect than H₂RA for healing esophagitis and relieving symptoms (for reviews, see References 42, 46 and 47). In two comprehensive meta-analyses, Chiba et al. combined data from forty-three randomized, endoscopically controlled studies involving 3710 patients with esophagitis of grades II-IV [48, 49]. The results showed that omeprazole is significantly more effective both in relieving the symptoms and in healing esophagitis [48, 49]. Furthermore, the healing-time curve shows that a significantly greater proportion of patients were healed with omeprazole at two and four weeks than H₂RAs at eight to 12 weeks [46]. This is also seen with lansoprazole studies in a more recent review and update of the previous meta-analysis [46]. Although there are few published studies available regarding the effect of pantoprazole [50], a recent double-blind multicenter study showed that pantoprazole has a similar effect to omeprazole in the treatment of GERD [51]. Moreover, PPIs have been used successfully to heal patients refractory to standard or even high doses of H₂RA [52-55]. The more effective healing of esophagitis achieved with the PPIs is related directly to the greater degree and the longer duration of acid suppression. Omeprazole 20 mg/day reduced 24-hr intragastric acidity by 95 percent, while ranitidine 150 mg bid, having a weak effect on food-stimulated gastric acid secretion during the day, reduced 24-hr intragastric acidity by only 55 percent [56]. Furthermore, the higher dose of omeprazole 40 mg almost completely eliminates acid reflux episodes in patients of GERD [57].

In a simple meta-analysis of the published trials of the PPIs in esophagitis of grades II-IV, healing at four weeks correlates with the various doses of the PPIs. Thirty mg lansoprazole healed 79 percent of patients with esophagitis, while 71 percent, 69 percent and 66 percent of patients were healed by 20 mg omeprazole, 40 mg pantoprazole and 15 mg lansoprazole, respectively. However, 40 mg omeprazole healed 76 percent of patients, a rate that is close to 30 mg lansoprazole (79 percent) (see Figure 1). These data probably

![Figure 1. Dose comparisons and healing rates at four weeks with various PPIs in patients with esophagitis grades II-IV.](image-url)
reflect the inhibition of 24-hr acid secretion achieved by different doses of the PPIs [57, 58, 59].

A dynamic relationship between the duration of intragastric pH above 4 and healing of esophagitis has been shown in our previous study [9]. Treatments that maintain intragastric pH above 4 for 96 percent or more of the 24-hr period normalize the time of esophageal exposure to acid and are associated with the highest healing rates [9, 46]. Eight-week healing of esophagitis correlates inversely with esophageal acid exposure. Thus, the healing rate of esophagitis can be predicted by the duration of suppression of intragastric acidity above pH 4 which is achieved by any antisecretory drugs [9].

**ACID CONTROL FOR SYMPTOM RELIEF AND HEALING IN DU**

**Acid profile**

Patients with DU generally secrete more gastric acid than normal subjects both at night and during the day [60, 61]. Historically, studies indicated that basal and maximal acid output in DU patients was about twice normal, especially in male patients [62]. However, more recent reviews show that there is a considerable overlap between DU patients and controls [63, 64], and the considerable variation between individuals implies that 24-hr intragastric pH measurements are not capable of identifying predictably individuals at risk of developing DU [46].

**Acid, duodenal ulcer and pain**

The pathogenesis of ulcer pain is not well understood and has been poorly investigated. Three main factors have been discussed: acid, motility and inflammatory reaction surrounding the ulcer [65]. Gastric acid is still considered to play a major role in the causation of mucosal injury in DU patients. The lack of DU in achlorhydric patients and the severe peptic ulceration seen in patients with Zollinger-Ellison syndrome also support the importance of acid in the development of an ulcer. A low intragastric and intraduodenal pH correlates significantly with epigastric pain in DU patients [66]. More convincing evidence for the role of acid in DU pain comes from a controlled double-blind study that demonstrated that, in contrast to controls, typical DU pain can be reproduced by direct acidification of an ulcer crater with hydrochloric acid [67]. The development of acid-induced pain was seen more commonly in patients with symptoms. Furthermore, the administration of an anticholinergic agent did not prevent pain, suggesting a mechanism other than muscular spasm in this group of patients [68]. However, DU pain cannot be explained entirely by the effect of acid on the ulcer crater alone, since a contrasting report regarding the relationship between intraduodenal pH and DU found no significant difference in gastric and duodenal bulb acidity between hypersecretory DU patients and normosecretory controls [69]. Thus, other factors must contribute to the ulcer pain, such as erosive duodenitis or dysmotility of the duodenum and pylorus in some patients [66, 70].

**RATIONALE OF ACID SUPPRESSION IN THE MANAGEMENT OF DU**

Treatment of DU has been focused on suppressing the secretion of gastric acid. This has been achieved traditionally by surgery [71], radiotherapy [72] and a spectrum of pharmacological agents [73]. Elective surgery has declined dramatically since the introduction of effective drugs of the H₂RA class in 1970s, and more recently the H⁺/K⁺-ATPase PPIs [73].

Patients with an active DU generally secrete more acid during the 24-hr period than controls [60, 61]. Nocturnal acid secretion has been considered an important pathophysiological factor in the development of DU [74] and is a major component of basal acid secretion, a target time for pharmacological control by the H₂RAs [75]. H₂RAs predominantly
lower basal acid secretion rather than meal-stimulated acid secretion and, thus, have been
targeted at bedtime dosing for healing DU to optimize the effect on the longer period of
basal acid secretion. Several clinical trials have shown that the inhibition of nocturnal acid
secretion obtained by large single bedtime doses of \( \text{H}_2 \)RAs yield healing rates of DU com-
parable to or better than those achieved with dose regimens that are aimed at suppressing
acid secretion over the 24-hr period [75-78].

Two models of the relationship between ulcer healing and acid suppression by dif-
ferent regimens of antisecretory drugs have been established by our group [8, 79].
Suppression of 24-hr intragastric acidity by \( \text{H}_2 \)RAs correlates significantly with DU heal-
ing at four weeks. Reduction of nocturnal acidity is primarily responsible for the signifi-
cant correlation [79]. However, when all drug classes studied including omeprazole were
used for analysis, a more significant correlation is shown between the suppression of over-
all 24-hr acidity and healing rates at four weeks. Thus, suppression of nocturnal acidity is
increased from 30 percent to about 95 percent by \( \text{H}_2 \)RA, and a therapeutic gain of some
20 percent DU healing can be expected at four weeks. However, when suppression of
overall 24-hr acidity is increased from 40 percent to almost 100 percent by inclusion of
the PPI effect, the therapeutic gain is almost doubled to 40 percent [79]. Thus, inhibition
of 24-hr acid secretion is more important than suppression of nocturnal acid secretion
alone in determining DU healing. In contrast to \( \text{H}_2 \)RAs, the PPIs provide a significantly
greater degree and longer duration of inhibition of acid secretion regardless of the stimu-
lus. However, it is important to emphasize that the duration of treatment is also a critical
determinant, and the healing rate achieved by omeprazole 20 mg at four weeks can be
approached by \( \text{H}_2 \)RAs if the treatment is extended to eight weeks [79].

Further analyses identified the three key parameters determining healing of DU by
antisecretory drugs: the degree of suppression of acid secretion, the duration of acid sup-
pression over the 24-hr period and the length of therapy in weeks [8]. Thus, if intragastric
\( \text{pH} \) can be maintained above 3 for a period of 18 to 20 hours per day, a 100 percent
healing rate of DU can be predicted at four weeks [8]. This probably explains why the PPIs
heal DU more effectively than \( \text{H}_2 \)RAs, since 24-hr intragastric acidity studies indicate that
a longer duration and greater degree of acid suppression is achieved by the PPIs, omepra-
zeole [80], lansoprazole [58] and pantoprazole [59] when compared to \( \text{H}_2 \)RA.

**CLINICAL TRIALS IN DUODENAL ULCER**

Several well-designed, controlled clinical trials have demonstrated the superiority of
PPIs over \( \text{H}_2 \)RAs in the treatment of duodenal ulcer, and these studies have been analyzed
recently by different reviewers [8, 50, 64, 79, 81-83]. In a meta-analysis, Eriksson et al.
show a significant difference in healing of DU between omeprazole 20 mg o.d. and the
\( \text{H}_2 \)RAs ranitidine and cimetidine, at regular doses [82]. A total of 3,504 DU patients from
16 double-blind clinical studies were included for analysis. On an intention-to-treat basis,
omeprazole 20 mg o.d. healed 61.7 percent and 87.4 percent DU patients at two and four
weeks, while ranitidine 150 mg b.i.d. or 300 mg h.s. healed 46.5 percent and 76.5 percent
at two and four weeks, respectively (both \( p < .001 \)). When omeprazole was compared with
cimetidine 400 or 600 mg b.i.d. or 800 mg h.s., the differences were similar. Another two
meta-analyses revealed the similar healing differences between \( \text{H}_2 \)RA and the newer PPIs
lansoprazole 30 mg o.d. [83] and pantoprazole 40 mg o.d. [50], confirming that faster
healing is a characteristic of PPIs in the treatment of DU. Furthermore, a more compre-
hensive meta-analysis pooled data from 279 randomized, double-blind, endoscopically
controlled clinical trials involving 44,870 patients, comparing healing rates of DU by dif-
ferent drug classes [84]. Among six different drug classes, the PPIs, represented in this
analysis by omeprazole, gave the highest overall healing rate at 80.8 percent, irrespective
of treatment duration. The speed of healing calculated as the average slope of the healing
time curve was 22.3 percent ulcers healed per week. However, all classes of drugs have the potential to approach 100 percent healing if the length of treatment is continued for long enough [85].

In addition to effective healing of DU, PPIs also provide faster relief of symptoms than H₂RAs [50, 82, 86, 87]. One recent meta-analysis reported that in 1,948 patients, almost 60 percent patients were symptom free after two weeks treatment with H₂RAs, while in 1,921 patients treated with omeprazole, over 70 percent patients were free of epigastric pain [82]. Our unpublished analysis shows that 91 percent DU patients were symptomatic at entry to clinical trials. After treatment with omeprazole, the proportion of patients with symptoms dramatically declined to 31 percent at two weeks and 20 percent at four weeks. A similar effect on symptom relief was seen with H₂RA and antacids if the duration of the treatment was long enough (see Table 3). Of particular interest is the observation that some 20 percent of DU patients still complain of symptoms at the end of treatment even when almost all (over 95 percent) ulcers are healed by omeprazole [8, 84].

Comparative healing studies with PPIs indicate that lansoprazole 30 mg/day may be more effective than omeprazole 20 mg/day in healing duodenal ulcer as reflected by a greater proportion of ulcer healed at an earlier time point [81, 88]. In a recent review, two of three comparative studies showed that, at recommended doses, lansoprazole 30 mg healed significantly more proportion of DU patients than omeprazole 20 mg after two weeks (a therapeutic gain of 16 and 19 percent, respectively). However, there was no significant difference between these two PPIs after four weeks [81]. Pantoprazole 40 mg/day did not show much difference from omeprazole 20 mg/day in healing DU and relief of symptoms [89, 90]. The difference in DU healing seen between lansoprazole and omeprazole may be due to a more rapid onset of the antisecretory effect of lansoprazole 30 mg since the oral bioavailability of lansoprazole is higher than that of omeprazole [91]. In addition, 30 mg/day lansoprazole is more effective in increasing intragastric pH above 3 for the 24-hr period than omeprazole 20 mg/day [58]. When compared to H₂RAs, both lansoprazole and pantoprazole are significantly more effective than H₂RA in healing DU and relief of symptoms [50, 86, 87]. The higher proportion of symptom-free patients seen with PPI treatment could be explained by the greater and more prolonged suppression of acid secretion over the 24-hr period achieved by PPI as compared to H₂RA [9, 58].

### IMPORTANCE OF H. PYLORI ERADICATION IN DU HEALING

With the recent appreciation of the role of H. pylori infection in the pathogenesis of duodenal ulcer, many clinical trials have been carried out to heal duodenal ulcer with antisecretory drugs and simultaneously to cure the infection with antimicrobials [92-94]. Thus, the combination of antimicrobials with antisecretory drugs might be expected to accelerate DU healing. In a randomized, controlled study, Graham et al. compared the effect of ranitidine plus tetracycline, metronidazole and bismuth subsalicylate, with ranitidine alone

### Table 3. Percentage of DU patients with symptoms over time by drug classes.

| Drug (arms)   | Entry (%) | 2 weeks (%) | 4 weeks (%) | 6 weeks (%) | 8 weeks (%) |
|--------------|-----------|-------------|-------------|-------------|-------------|
| Placebo (29) | 340/366*  | 318/460 (69)| 523/914 (57)| 37/72 (51)  | 11/22 (52)  |
| Omeprazole (13) | 663/754 (91) | 333/1075 (31) | 118/597 (20) | —           | —           |
| H₂RA (110)   | 2737/2816 (84) | 1599/4133 (39) | 1196/5553 (22) | 195/1176 (17) | 68/375 (18) |
| Antacids (12) | 114/162 (70) | 93/204 (46)  | 75/338 (22)  | 6/30 (20)   | 9/40 (23)   |

Table modified with permission from Morgan et al., unpublished data

*Number with symptoms/number evaluated
on DU healing [95]. The results showed that DU healing was more rapid in patients receiving ranitidine plus triple therapy than in those given ranitidine alone. Lifetable analysis demonstrated a leftward shift of the healing curve. More recently, PPIs combined with one or more antimicrobials have been accepted increasingly as effective, safe and simple regimens to heal *H. pylori* positive DU patients, to cure the infection and to prevent ulcer recurrence [96-98]. Omeprazole plus clarithromycin dual therapy healed 98 percent of DU patients at four weeks [96, 97]. When metronidazole was added, 100 percent of patients were healed [98]. These healing rates are superior to the use of either omeprazole (94 percent) [96, 97] or clarithromycin alone (71 percent) [96]. The accelerated healing environment achieved by combined therapy may result from a synergistic effect between antisecretory drugs and antimicrobials since PPIs such as omeprazole or lansoprazole reduce intragastric acidity, which allows acid-labile antibiotics to work more effectively [99]. Moreover, eradication of *H. pylori* results in normalization of acid secretion [5, 100-102] and pepsin output [101] although it takes time to return, and the reduction of acid secretion and pepsin output may eventually reduce the risk of ulcer recurrence.

Data on the effect of antisecretory and antimicrobial drug combination therapy on symptom relief in DU patients are scant. Many regimens, *per se*, especially bismuth triple therapy, have poor tolerability and cause symptoms themselves [103]. Compliance has a significant influence on the success rate of treatment [103]. Since the PPIs are the best agents for rapid ulcer healing and fast relief of symptoms, dual or triple antimicrobial therapy including a PPI is a logical choice for ulcer healing and resolution of symptoms in *H. pylori*-positive DU patients.

**Influence of other factors on DU healing**

Smoking, ulcer size, and prior ulcer history have generally been considered as risk factors delaying duodenal ulcer healing [104-106]. The presence of these risk factors affect length of antisecretory treatment and healing of duodenal ulcer [105]. In a prospective multicenter study, Armstrong et al. showed that the speed of DU healing correlates closely with a number of risk factors [105]. In the absence of risk factors, the mean DU healing time achieved with ranitidine 300 mg daily was 3.3 weeks, rising to 3.7 weeks for one, 4.4 weeks for two, and 5.1 weeks for three to five risk factors [105]. The effect of these risk factors is cumulative. At four weeks, 82.7 percent of patients with none of the risk factors were healed, whereas healing rates decreased to 50 percent from 64.9 percent in patients with two more risk factors. Thus, patients with additional risk factors require a longer period of antisecretory treatment with H2RA to achieve ulcer healing. It is not clear whether smoking affects acid secretion [107]. However, in animal studies, smoking aggravates acetic acid-induced peptic ulcers [107-108]. Furthermore, PPIs such as omeprazole and lansoprazole have been shown more effective than H2RA in healing duodenal ulcer in smokers [86, 109]. Thus, acid suppression has an important implications in the treatment of peptic ulcers in smokers.

**ACID CONTROL FOR SYMPTOM RELIEF AND HEALING IN GU**

**Rationale of Acid Suppression in the Management of GU**

Most GU patients are normosecretors or hyposecretors as determined by basal or stimulated gastric acid secretion compared to controls [13, 110]. Twenty-four-hour intragastric pH measurements show that the median integrated acidity in GU patients is lower than healthy subjects [13]. Nevertheless, gastric acid is still necessary for the formation of a gastric ulcer. If the mucosal integrity is impaired, as in gastritis, acid back diffusion may occur, disrupting the mucosa and predisposing to ulceration even with normal or low levels of acidity. As with DU, the mechanism of GU pain is not clear. It seems that gastric
mucosal inflammation may be more relevant than gastric acid in pain development since symptomatic GU patients may be hypochlorhydric [111].

Despite these observations, suppression of gastric acid secretion has remained the mainstay of treatment for gastric ulcer, although the relationship between acid suppression and gastric ulcer healing is not as clear-cut as for DU [112]. The results of a meta-analysis from our group reported that the primary variables determining the healing of gastric ulcer are similar to those for duodenal ulcer although the duration of treatment is the most important determinant [10]. Suppression of 24-hr intragastric acidity also correlates significantly with GU healing; however, the therapeutic gain from increasing the suppression of acidity is not as relevant as for DU [112]. The results of a meta-analysis from our group reported that the primary variables determining the healing of gastric ulcers are similar to those for duodenal ulcer although the duration of treatment is the most important determinant [10]. Suppression of 24-hr intragastric acidity also correlates significantly with GU healing; however, the therapeutic gain from increasing the suppression of acidity is not as relevant as for DU [112].

In contrast to H2RA, the PPI regimens, such as omeprazole 20 mg to 40 mg o.d., which have the greatest effect on 24-hr intragastric acidity, provide the highest healing rates at two, four and eight weeks [113]. However, the difference between these two drug classes tends to become smaller as the duration of treatment extends from two weeks to eight weeks. If intragastric pH can be maintained at or above 3 for 18 to 20 hr of the day, almost 100 percent of gastric ulcer can be predicted to heal at eight weeks, while this can be achieved at four weeks for duodenal ulcer [8]. This is in accordance with clinical observations that gastric ulcers take a longer time to heal than duodenal ulcers and that persistence with effective treatment is an important factor to ensure complete ulcer healing [8, 10].

Clinical Trials in GU

In comparative studies, PPIs have produced consistently higher rates of GU healing over H2RAs [114-118]. A meta-analysis of trials comparing the effect of omeprazole 20 mg o.d. with ranitidine 150 mg b.i.d or 300 mg h.s. on healing of GU showed a therapeutic gain of 9.9 at 4 weeks (p = .005) and 6.7 at 8 weeks (p = .02) for omeprazole over ranitidine [82]. Similarly, pooled results of two studies indicates a significant difference in ulcer healing between pantoprazole 40 mg o.d. and ranitidine 300 mg h.s. at four and eight weeks yielding a therapeutic gain of 32 percent and 15 percent respectively (both p < .001) [50]. Lansoprazole 30 mg o.d. also showed a superiority of healing GU over ranitidine 300 mg h.s. or 150 mg b.i.d. at four and eight weeks [116,117], but on an intention-to-treat basis, there is no significant difference in healing between lansoprazole and ranitidine at eight weeks (81 percent vs 76 percent [116], 98.6 percent vs 91.4 percent [117]). In contrast to omeprazole, the newer PPIs, pantoprazole 40 mg o.d. and lansoprazole 30 mg o.d. seem to be more effective than omeprazole 20 mg o.d. at four weeks in healing GU but results are similar at eight weeks [90, 119]. These clinical observations may reflect the pharmacodynamic differences between the PPIs since lansoprazole 30 mg o.d. has a higher oral bioavailability and a more rapid onset of antisecretory effect than omeprazole [91]. In addition, lansoprazole 30 mg o.d. is more effective in increasing gastric pH above 3 and maintaining this over a longer duration of the 24-hr period than omeprazole 20 mg o.d. [58].

PPIs show a less dramatic effect on symptoms and are only marginally better than ranitidine in relieving symptoms in patients with gastric ulcer [82, 116-118]. One meta-analysis shows that 65.3 percent of patients treated with omeprazole 20 mg o.d. were symptom-free at 2 weeks compared to 56.4 percent of patients treated with ranitidine 150 mg. b.i.d. or 300 mg h.s. (p < .05) [82]. The resolution of day-time pain contributes mainly to this difference because there is no significant difference in relieving nocturnal pain between the groups [82]. In contrast to ranitidine 300 mg h.s. or 150 mg b.i.d., initial studies with pantoprazole 40 mg o.d. or lansoprazole 30 mg o.d. have not shown any significant differences in improving GU symptoms [116-118]. These clinical observations could suggest that, as with healing of gastric ulcer, the length of treatment with antisecretory agents is the major factor determining the relief of GU symptoms.
The association between *H. pylori* infection and gastric ulcer is less clear than with duodenal ulcer. It is not clear whether *H. pylori* infection affects acid secretion in GU patients. However, eradication of *H. pylori* infection still has important implications for the treatment of gastric ulcer. Clinical trials have not shown that antimicrobials increase the speed of GU healing achieved by antisecretory agents alone, but eradication treatment dramatically reduces the recurrence rate of gastric ulcer in the same way as is seen with duodenal ulcer [120-122].

Smoking and ulcer size are also risk factors for slow healing of gastric ulcer [104]. However, concomitant use of a non-steroidal anti-inflammatory drug is more closely related with slowed GU healing than with DU [103]. Gastric ulcers heal faster if the drug is stopped [123].

**CONCLUSIONS**

Gastric acid secretion is important for maintaining normal gastrointestinal function. Suppression of gastric acid secretion has proved very effective in the treatment of acid-related disorders and remains the major form of treatment. Three key parameters determine the effect of treatment with antisecretory drugs: the degree and the duration of acid suppression and the length of treatment. The PPIs have been considered the best agents for healing esophagitis and peptic ulcers. Moreover, symptom relief is well correlated with the degree of suppression of gastric acid secretion in patients with GERD but correlates less well for symptom relief of DU and GU. The combination of antimicrobials with antisecretory drugs appears to accelerate the healing of duodenal ulcer.

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