pH, Healing Rate, and Symptom Relief in Patients with GERD

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Gastroesophageal reflux symptoms are common and occur in all of us from time to time. In others, reflux may be associated with ulcerative esophagitis. The symptoms may be aggravated by large meals, coffee, smoking and position. Physiological and pathological reflux can be separated by the frequency and duration of the exposure of the lower esophagus to acid. Pathological reflux results in symptoms and also esophagitis and ulceration in some patients. Although gastroesophageal reflux disease (GERD) is considered to result from a disorder of motility in the esophagus, gastric acid and peptic activity are deemed pivotal to the initiation and continuation of the esophageal damage and the development of symptoms. Acid exposure in the esophagus is normally less than 4 percent of the 24 hours with a pH below 4. An increase over 4 percent of the time with a pH less than 4 is considered pathological. Hence, ant-secretory drugs have become the principle approach to the treatment of reflux symptoms and esophagitis since they reduce the acidity of gastric juice and the activity of pepsin. Importantly, they also reduce the volume of gastric juice available for reflux into the esophagus.

There is a clear relationship between the degree and duration of acid suppression and the relief of heartburn and healing of esophagitis. Pharmacodynamic studies with different dose regimens of the H2-receptor antagonists and the proton pump inhibitors show a difference in the degree and duration of the ant分泌atory effect, and this correlates closely with the results of clinical trials with respect to the healing of esophagitis and the relief of symptoms. Proton pump inhibitors achieve healing rates by week four, which are not achieved by H2-receptor antagonists even after 12 weeks of treatment. The advantage of proton pump inhibitors over H2-receptor antagonists is due to the greater degree, longer duration of effect and more complete inhibition of acid secretion that maintains intragastric pH above 4 for a maximal duration. Although there is no significant difference between proton pump inhibitors with respect to healing of esophagitis, symptom relief occurs earlier with lansoprazole than omeprazole, and this is probably due to the greater oral bioavailability and faster onset of action of lansoprazole when compared to omeprazole.

INTRODUCTION

Gastroesophageal reflux disease (GERD) 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 [1]. 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 [2]. This results in prolonged exposure of the mucosa of the
lower esophagus to the damaging effects of acidic gastric contents. Despite the evidence of dysmotility and the defects in epithelial resistance in patients with GERD, gastric acid is considered of central importance to the initiation and continuation of the esophageal damage and the development of symptoms in patients with GERD and has been recognized as an independent pathophysiological factor in esophagitis [3]. Moreover, the successful results of antisecretory therapy in patients with erosive esophagitis support this view [4, 5].

It is well accepted that the suppression of 24-hr gastric acid secretion significantly correlates with the healing rates of duodenal ulcer, gastric ulcer, and erosive esophagitis [4-7]. Three primary parameters determining the effect of antisecretory treatment have been derived from antisecretory data. These are the degree of suppression of acidity, the duration of suppression of acidity over 24 hours and the duration of antisecretory treatment [7-10]. Proton pump inhibitors (PPIs) produce a greater and longer-lasting degree of suppression of acidity than standard or higher doses of H2-receptor antagonists (H2RAs) in 24-hr pH studies. This significantly correlates with the speed of healing and relief of reflux symptoms in patients with grade II to IV esophagitis as shown in a recent meta-analysis of randomized controlled clinical trials consisting of 95 treatment arms and 7,635 patients with almost two times more patients healed and symptom-free per week when treated with PPIs than with H2RAs [11]. In patients refractory to standard doses of H2RAs, poor or no inhibition of gastric acid secretion has been considered the reason for the treatment failure [12]. Therefore, suppression of intragastric acidity over 24 hours plays a crucial role in the healing of esophagitis [6]. The longer and the greater the suppression of gastric acid secretion, the more esophagitis is healed [6].

**GASTRIC ACID SECRETION IN PATIENTS WITH GERD**

Whether gastric acid hypersecretion exists in patients with GERD is controversial [13-16]. The results from the critical analysis by Hirschowitz show no difference in basal and maximal gastric acid secretion between patients with endoscopically defined esophagitis and controls without esophagitis [13]. However, this study suffered from several methodological problems including possibly different techniques used for gastric analysis over the 14-year retrospective period and a questionable definition of hypersecretion (greater than 15 meq/hr was used) [17, 18]. The study by Collen et al. shows that a subgroup of patients were gastric acid hypersecretors although this result might be confounded by the inclusion of patients previously on H2-receptor antagonists studied during the period they might have acid rebound [14]. In a more recent large prospective study involving 228 patients, there was a significant difference in the mean basal acid output between patients with GERD (6.5 ± 5.6 meq/hr) and 65 normal controls (3.0 ± 2.7 meq/hr, p < .0001) [16]. Although 48.7 percent of the patients had a previous history of H2RA therapy, only 14.5 percent were taking H2RA during the two months prior to the gastric analysis [16]. Hypersecretion also was reported in the study of Johansson, who excluded patients taking H2RA [15]. Thus, there may be a subset of patients with GERD who are acid hypersecretors.

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

**Symptoms, mucosal damage and esophageal acid exposure**

There are a number of studies showing that the severity and frequency of
symptoms and endoscopic esophagitis correlate significantly with the duration of gastroesophageal reflux, the degree of esophageal exposure to gastric acid, and the pH of the refluxate [19-22]. The results reported by Joelsson et al. have shown that the severity and frequency of reflux symptoms were associated significantly with the median duration of esophageal acid exposure (pH < 4) in 190 patients with and without endoscopic esophagitis when compared with 50 asymptomatic controls [19]. In asymptomatic subjects, the median acid exposure time was 1.1 percent, while in symptomatic patients without endoscopic esophagitis, the acid exposure time was 1.9 percent for patients with occasional symptoms (grade 1), 3 percent for those with one to three times occurrence of symptoms daily (grade 2) and 3.8 percent for patients with constant symptoms (grade 3), respectively. In patients with endoscopic esophagitis, the corresponding median acid exposure time was 6 percent, 10 percent and 11.2 percent for patients with symptom grades 1, 2 and 3, respectively [19]. The longer the duration of acid exposure, the more severe were the symptoms and the esophagitis.

**pH 4 as a threshold between pathological and physiological reflux**

Animal studies have demonstrated that esophageal mucosal injury is highly pH-dependent [21, 23]. Perfusion of the esophagus over a one-hour period with hydrochloric acid at varying pH induced esophagitis only when solutions of pH below 1.6 were used. The addition of porcine pepsin to the perfusate increased the severity of esophagitis and produced mucosal inflammation with solutions of between pH 1.3 and 2.3 [23].

Distal intraesophageal pH varies from 5 to 7. A threshold of pH 4 has been suggested by most investigators as the optimal pH to discriminate aggressive and non-aggressive reflux [6, 20, 24] although this may underestimate the number of reflux episodes detected by manometry [25]. Why is pH 4 chosen as the pH threshold? Historical 24-hr pH studies have shown that heartburn occurred in patients only when intraesophageal pH monitoring dropped below 4 [24, 26]. Furthermore, this pH has proved to be the optimal threshold in more recent studies. By applying discriminant analysis and receiver-operating-characteristic analysis, Schindlbeck et al. evaluated this threshold comprehensively to define the optimal threshold for assessing pathological reflux and found a maximum sensitivity of 93.3 percent and specificity of 92.9 percent by considering the percentage of time above pH 4 in both the upright and supine positions [27]. Although other pH thresholds may be useful to differentiate between normal and pathological reflux for the individual patient, this threshold has proved to be the optimal and more reproducible [28, 29]. 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 by using integrated acidity, expressed as the area under the curve, to represent total hydrogen activity (H+ and hence true acid exposure [30]. A significant correlation has been shown between area under the curve for H+ and all grades of esophagitis [30].

**DIFFERENCES BETWEEN ANTISECRETORY TREATMENTS IN SUPPRESSING GASTRIC ACID SECRETION**

**H₂RAs**

As described above, the frequency of acid reflux and the exposure time of the esophagus to acid in patients with GERD are both increased and correlate with the severity of the disease. Since most reflux occurs post-prandially and in the early evening, treatments to reduce acid reflux should target both basal acid secretion as
well as meal-stimulated acid secretion. Pharmacologically, \( H_2 \)RAs are unable to overcome the integrated stimulus to acid secretion produced by a meal [31-34]. Results from a 24-hr pH monitoring study have shown that neither ranitidine 150 mg twice daily, nor an increased dose of 300 mg twice daily altered the 22-hour intravesophageal pH profile when compared with pretreatment recordings [35]. Attempts to improve the effect of \( H_2 \)RAs on reducing evening reflux, by dosing immediately after the evening meal have also been unsuccessful in reducing meal-stimulated acid secretion albeit better than dosing at bedtime [34, 36]. The percentage of time with intravesophageal pH above 4 over 24 hours is about 10 hours for this dose regimen [34, 36]. Increasing doses of ranitidine from 150 mg three times a day to 300 mg three times a day significantly reduced the exposure time of the esophagus to acid from 6.8 percent to 2.5 percent [37]. This correlates significantly with the reduction in the frequency and the severity of heartburn. Furthermore, there is a correlation between basal acid secretion in patients with GERD and the dose of ranitidine required for healing esophagitis [16, 38]. However, increasing doses of ranitidine above 600 mg/day only increased modestly the antisecretory effect achieved with ranitidine 300 mg twice daily [39]. This may be due to the rapid development of tolerance to \( H_2 \)RAs as seen in normal volunteers [40] and in patients with reflux esophagitis [41].

**PPIs**

PPIs are strong acid suppressing agents that specifically inhibit the enzyme of \( H^+K^+ \)-ATPase and block the final common pathway for acid secretion. This is a prolonged and highly effective inhibition of both basal and stimulated gastric acid secretion to all known stimuli including meals. In comparison with placebo, omeprazole 10, 20 and 40 mg/day given in the morning significantly decreases the frequency of reflux episodes/hr and the mean percentage of total reflux time over the 24-hr period from 16.3 percent for the placebo treatment to 6.3 percent with omeprazole 10 mg, 0.9 percent with omeprazole 20 mg and 0.6 percent with omeprazole 40 mg/day [42].

There are numerous comparative studies showing that PPIs are superior to \( H_2 \)RAs in the suppression of gastric acid secretion in patients with peptic ulcer and in the reduction of acid reflux in patients with GERD. In a randomized comparative study in patients with active gastric ulcer, lansoprazole 30 mg daily has been shown to be significantly more effective than famotidine 20 mg twice daily in maintaining intragastric pH above 3 throughout the 24-hr period (99 percent vs. 68 percent) with more ulcers healed with lansoprazole than with famotidine [43]. In another randomized, double-blind study in patients with grade II to IV esophagitis, Ruth et al. have shown that omeprazole 20 mg daily was significantly better than ranitidine 150 mg twice daily in reducing the total reflux time over the 24-hr period (2.5 percent vs. 6.3 percent, \( p = .02 \)) and the frequency of reflux episodes (20 vs. 49, \( p = .003 \)) [44]. This correlated with a higher healing rate of esophagitis seen in patients treated with omeprazole than with ranitidine [44]. Even when compared with higher doses of \( H_2 \)RAs (e.g., ranitidine 300 mg or famotidine 40 mg twice daily), omeprazole 20 mg daily offers better results in the reduction of total reflux time (pH < 4) and the number of reflux episodes [45, 46], two important determinants for healing GERD.

The suppression of gastric acid secretion has an important impact on the activity of pepsin as shown in animal studies. Although the relationship between hypersecretion of gastric pepsin and the severity of GERD is controversial [47, 48], to inactivate peptic activity by suppressing gastric acid secretion is a well-accepted approach for the treatment of acid-related diseases. In analysis of 24-hr pH studies, Hirschowitz has shown that the diurnal intragastric pH during treatment with cimetidine 1000 mg/day or ranitidine 300 mg/day still allows pepsin to maintain
significant proteolytic activity, whereas the pH achieved with omeprazole 30 mg/day is high enough largely to abolish peptic activity [49]. This may partly explain the superiority of PPIs over H₂RAs in the treatment of acid-related diseases because of the successful elimination of an additional aggressive factor — the peptic activity.

It is known that lansoprazole has a better bioavailability than omeprazole after oral administration as shown in double-blind, randomized cross-over studies [50, 51]. After the first dose, the bioavailability of lansoprazole is greater than 85 percent and remains constant after repeated dosing [51]. This has been confirmed in our recent study in healthy volunteers in whom once daily lansoprazole 30 mg was used on four days, and the maximum antisecretory effect was obtained six hours after the first dose and was consistent with repeated dosing [52], whereas the bioavailability of omeprazole is only 35 percent after the first dose and rises to about 60 percent after repeated dosing [53]. The plasma half-life of lansoprazole also is longer and the $t_{\text{max}}$ is significantly shorter and, hence, lansoprazole has a faster onset of action than omeprazole [51, 54]. The pharmacokinetic differences between these two PPIs may explain the different effect of these two drugs on inhibiting gastric acid secretion and, thus, improvement of symptoms and possibly healing of GERD. In a placebo-controlled study, both lansoprazole 30 mg/day and omeprazole 20 mg/day were significantly better than placebo in increasing 24-hr intragastric pH and decreasing basal and pentagastrin-stimulated acid secretion [50]. However, the effect of lansoprazole on intragastric pH was consistently better than omeprazole. Lansoprazole had a significantly longer effect than omeprazole on maintaining the intragastric pH above 3 over the 24-hr period [50]. In a comparative study, Dammann et al. have shown that, when compared with placebo, lansoprazole 30 mg/day decreased meal-stimulated acid secretion over a 24-hr period on the first day by 45.1 percent, followed by omeprazole 40 mg/day by 41.7 percent, lansoprazole 15 mg/day by 34.6 percent and omeprazole 20 mg/day by 15.6 percent [51]. There is a dose-dependent effect for lansoprazole and omeprazole on the suppression of intragastric acidity with a potency order of lansoprazole 60 mg > lansoprazole 30 mg = omeprazole 40 mg > lansoprazole 15 mg = omeprazole 20 mg [51, 54, 55].

CLINICAL TRIALS IN THE TREATMENT OF GERD

The aims of medical treatment of GERD are to relieve the symptoms, to heal established esophageal mucosal damage and to prevent the development of complications. In order to achieve these goals, treatment needs either to prevent the reflux of acidic gastric contents into the esophagus or to reduce the injurious action of acid to a level that will allow healing of the esophageal mucosa to occur. Currently, there are no effective agents that can restore fully the motor defects that lead to pathological acid exposure in patients with GERD. Therefore, suppression of acid secretion remains the mainstay of medical treatment for patients with GERD.

H₂RAs

The effect of H₂RAs on the healing of erosive esophagitis has proved disappointing [11, 56]. Complete healing of severe esophagitis is rare although patients generally benefit from symptomatic improvement. It is known that H₂RAs have certain pharmacokinetic and pharmacodynamic characteristics that limit the effect, such as short duration of effect, incomplete suppression of acid secretion, particularly that stimulated by meals [31-33], the development of tolerance [41] and acid rebound [57].

In a meta-analysis, We have show that early studies with standard dose of ranitidine 150 mg twice daily healed 38.6 percent of the patients with grades II to IV at four weeks and 54.3 percent at eight weeks
Complete symptom relief is seen in 42.4 percent of the patients at four weeks and 50.6 percent at eight weeks [11, 59, 61, 63, 69, 72]. In a placebo-controlled study, Robinson et al. showed that famotidine 20 mg twice daily improved symptoms in 69.9 percent of the patients without erosive esophagitis at two weeks and 81.8 percent at six weeks, which was significantly better than famotidine 40 mg no. and placebo [73]. The modest effect on erosive esophagitis seen with standard doses of H2RAs may result from its relatively weak effect on the suppression of gastric acid secretion as discussed above.

In order to increase the effect of healing esophagitis and relief of symptoms, higher doses of H2RAs and or more frequent dosing have been used and show better results than those achieved with standard doses [74-77]. It is known that higher doses or more frequent dosing with H2RAs is associated with an increased suppression of gastric acid secretion over 24 hours, including meal-stimulated integrated acid secretion [75, 78]. This correlates with higher healing rates in patients with esophagitis and faster relief of symptoms than with standard doses of H2RAs in head-to-head comparison studies [58, 72, 74, 77]. The results of Johnson et al. show that, in patients with grade II to III esophagitis, treatment with ranitidine 300 mg four times a day healed 63 percent of the patients after four weeks and 75 percent after eight weeks, whereas in patients receiving ranitidine 150 mg twice daily, the healing rates were 29 percent at four weeks and 54 percent at eight weeks, respectively. The differences were highly significant (both p < .01) [58]. Significantly more patients had complete symptomatic relief on treatment with the higher dose of ranitidine at four and eight weeks (67 percent vs. 46 percent and 84 percent vs. 64 percent, both p < .05). In several other studies involving ranitidine 150 mg four times a day [72, 79-81], an approved healing dose of ranitidine for esophagitis in the USA, the healing rates of esophagitis ranged from 37 to 49 percent at four weeks and 62 to 69 percent at eight weeks, respectively. Therefore, with higher doses of H2RAs, faster healing of esophagitis and more rapid relief of reflux symptoms can be achieved.

**Studies comparing H2RAs with PPIs**

As shown above, PPIs have a greater inhibitory effect on gastric acid secretion than H2RAs. This is reflected in the results of numerous clinical trials showing that significantly more patients with esophagitis are healed with PPIs than H2RAs. In five head-to-head comparative studies carried out in the USA and Europe [64, 82-85], lansoprazole 30 mg daily was consistently and significantly better than a standard dose of ranitidine 150 mg twice daily in healing esophagitis and relief of reflux symptoms. In a randomized, multicenter, comparative study, 229 patients with grades I to III esophagitis were randomized to receive lansoprazole 30 mg daily, 60 mg daily or ranitidine 150 mg twice daily for up to eight weeks [64]. At four weeks, by intention-to-treat analysis, healing was achieved in 84 percent and 72 percent of the patients receiving lansoprazole 30 mg and 60 mg, respectively, whereas only 39 percent of the patients were healed with ranitidine 150 mg twice daily. There was a significant difference between the two doses of lansoprazole and ranitidine in the healing rates (p < .01). After eight weeks, the corresponding figures were 92 percent, 91 percent and 53 percent, respectively, with significantly more patients healed with lansoprazole than with ranitidine (p < .01). These differences were not influenced by smoking, drinking, patient age or sex and were seen across all grades of esophagitis [64]. Heartburn was significantly reduced in more patients treated with lansoprazole than with ranitidine at the four- and eight-week assessments either by physicians or by patients. Furthermore, patients receiving lansoprazole took less antacids on fewer days than those treated with ranitidine (p < .01) [64]. In a more recent study, Sontag et al. reported, in a randomized, double-blind
study that the superiority of lansoprazole over ranitidine is also seen in healing erosive esophagitis in patients with Barrett’s esophagus [82]. A total of 105 patients were randomly allocated to lansoprazole 30 mg daily and ranitidine 150 mg twice daily for eight weeks. A large and significant difference in healing rates was found between patients treated with lansoprazole and ranitidine being 32 percent at 2 weeks, 37 percent at four weeks and 33 percent at eight weeks, respectively (all p < .001) [82]. Significantly fewer patients in the lansoprazole group had heartburn during treatment than those in the ranitidine group [82].

Similar results have also been reported in early studies comparing omeprazole with standard dose of H2RAs [86, 87]. In a double-blind, multi-center, comparative study, Sandmark compared the effect of omeprazole 20 mg daily with ranitidine 150 mg twice daily on endoscopic healing of esophagitis and relief of symptoms in 144 patients with grades II to IV GERD [61]. The healing rates were 67 percent and 31 percent at four weeks in the omeprazole and ranitidine groups by per-protocol analysis, and 85 percent and 50 percent at eight weeks, respectively. Both differences were highly significant (p < .0001) [61]. More interestingly, 51 percent patients in the omeprazole group experienced substantial symptom improvement at the end of the first week of treatment, compared with only 27 percent of those receiving ranitidine (p = .009). Adverse events were comparable between these two groups [61]. A recent article combining two individual comparative studies with a total of 550 patients showed that omeprazole 20 mg daily is significantly more effective than standard-dose H2RAs in healing grade I to IV esophagitis and relieving reflux symptoms [88]. Moreover, the advantage of omeprazole over H2RAs was not influenced by patient age. Therefore, in comparison with standard doses of H2RAs, omeprazole has proved consistently more effective in providing faster relief of reflux symptoms and rapid healing of esophagitis.

High doses or frequent dosing regimens of H2RAs have been studied in order to increase the effect of H2RAs on healing esophagitis. Ranitidine 150 mg four times a day and 300 mg four times a day or 300 mg twice daily were used in three randomized, comparative studies showing similar results in healing esophagitis between these dose regimens [79-81]. Ranitidine 150 mg four times a day is as effective as ranitidine 300 mg four times a day in healing esophagitis of grades II to IV. Although significantly more patients were healed with higher doses of H2RAs than with the standard doses, about 30 percent of patients did not respond to these dose regimens after eight weeks of treatment. Furthermore, these doses were not effective in patients with severe esophagitis with an average of 50 percent unhealed at eight weeks, and treatment is not cost-effective when compared with lansoprazole 30 mg daily or omeprazole 20 mg daily [89, 90].

In numerous clinical trials, PPIs have proved more effective in healing erosive esophagitis than H2RAs with either standard or higher doses in patients with esophagitis and especially in those with severe disease or refractory to H2RAs. In a double-blind, randomized, multi-center study comparing the effect of lansoprazole 30 mg daily and ranitidine 300 mg twice daily on healing of patients with moderate and severe esophagitis, four and eight weeks of treatment with lansoprazole healed 79.4 percent and 91.2 percent patients by intention-to-treat analysis, respectively, while the corresponding figures for patients receiving ranitidine were 41.5 percent and 66.2 percent, respectively. There was a significant difference in healing rates between the two groups at both 4 and 8 weeks (p < .001) [91]. Symptom improvement as evaluated on a visual analog scale (VAS) was significantly better in patients treated with lansoprazole as compared to those on ranitidine.
The VAS decreased from 65.1 mm at entry to 13.5 mm at 4 weeks and 11.3 mm at 8 weeks in the lansoprazole group. In the ranitidine group, the corresponding figures were 63.5, 22.8 and 18.5 mm, respectively. Adverse events were comparable in both groups [91]. Therefore, even with a higher dose of H₂RAs, PPIs proved to be consistently and significantly better for healing all grades of esophagitis and for the relief of reflux symptoms.

In another randomized, double-blind, multicenter study Bate et al. compared the differences between omeprazole 20 mg daily and cimetidine 400 mg four times a day in healing esophagitis and relief of symptoms in patients with grade I to IV esophagitis [92]. After four weeks of treatment, 56 percent of the patients in the omeprazole group were healed, whereas complete healing occurred in only 26 percent of the patients treated with cimetidine. The corresponding figures at eight weeks were 71 percent and 35 percent in patients treated with omeprazole and cimetidine, respectively. The difference was significant at both four and eight weeks between the two groups (p < .001) [92]. Moreover, healing was consistent at four and eight weeks among all grades of esophagitis in patients treated with omeprazole, while in the cimetidine group there was a significantly inverse correlation between endoscopic grades at entry and the healing rates at four and eight weeks (r = -0.98 and -0.99, respectively), and no patients with grade IV esophagitis at entry were healed after four and eight weeks. Increasing treatment duration from four weeks to eight weeks only healed 9 percent more patients with cimetidine, while the therapeutic gain was 15 percent with omeprazole [92]. Furthermore, significantly more patients became asymptomatic in the omeprazole group than in the cimetidine group at both four and eight weeks (46 percent vs. 22 percent and 66 percent vs. 41 percent, both p < .001).

**Studies comparing lansoprazole with omeprazole**

Four head-to-head studies have compared the effects of lansoprazole and omeprazole in the treatment of esophagitis. The recursive search found another abstract meeting the inclusion criteria, and this has been included for analysis with a total of 1013 patients. Lansoprazole 30 mg daily was used in all five studies. Omeprazole 20 mg daily was used in four studies and 40 mg daily in one study. The pooled results show that healing rates at four weeks are 73.7 percent for lansoprazole and 71.5 percent for omeprazole, respectively, with an odds ratio of 1.12 (95 percent CI: 0.92 – 1.37; Mantel-Haenszel 2 x 2 tables, d.f. = n – 1). At eight weeks, the pooled healing rates are 83 percent for lansoprazole and 81.7 percent for omeprazole, respectively, with an odds ratio of 1.09 (95 percent CI: 0.86 – 1.4).

There are four studies in the literature with data for evaluation of symptoms. Three have shown that lansoprazole is superior to omeprazole in the relief of symptoms as assessed by patients and investigators [93-95]. In a large U.S. multi-center, randomized, double-blind and placebo-controlled study involving 1284 patients with grade II to IV esophagitis, Castell et al. compared two different doses of lansoprazole (15 mg and 30 mg daily) with omeprazole (20 mg daily) in healing esophagitis (above grade II) and relief of reflux symptoms [94]. By intention-to-treat analysis, both lansoprazole 30 mg daily and omeprazole 20 mg daily were significantly more effective than lansoprazole 15 mg daily in healing esophagitis at both four and eight weeks. The healing rates were almost identical between lansoprazole 30 mg daily and omeprazole 20 mg daily (79.6 percent vs. 79.6 percent at four weeks and 87.2 percent vs. 87 percent at eight weeks, respectively). However, there was a significant difference in symptom relief between these two
groups. After the first day of treatment, significantly fewer patients in the lansoprazole group experienced daytime and nighttime heartburn than patients receiving omeprazole (38 percent vs. 48 percent, p < .05). This advantage was maintained throughout the duration of the eight-week treatment with a significant reduction in antacids use in patients treated with lansoprazole. The incidence of adverse events was comparable between the two groups [94].

Another large study consisting of 604 patients from the U.K. showed similar results [95]. After three days of treatment, significantly greater symptom relief of daytime heartburn was achieved in patients treated with lansoprazole 30 mg daily (median change in VAS: -20.2 mm) when compared to those receiving omeprazole 20 mg daily (median change in VAS: -15.3 mm) as indicated by a greater change in VAS score from baseline [95]. Similar results also were reported in a Scandinavian multi-center, randomized trial in which significantly more patients treated with lansoprazole 30 mg daily experienced a greater improvement in heartburn than those receiving omeprazole 20 mg daily [93].

Mulder et al. reported a Dutch multi-center study showing that there was no significant difference in terms of healing of esophagitis and relief of symptoms at both four and eight weeks between patients treated with lansoprazole or omeprazole [96]. Since omeprazole 40 mg daily was used to compare with lansoprazole 30 mg daily in this study, it is difficult to make a comparison on a dose-by-dose basis.

As discussed earlier in this paper, reflux symptoms are significantly associated with esophageal acid exposure time (pH < 4). Since lansoprazole 30 mg daily has a rapid onset and longer-lasting suppression of acid secretion than omeprazole 20 mg daily [50, 51, 54, 55], it is understandable why lansoprazole is superior to omeprazole in relieving reflux symptoms in patients with GERD.

SUMMARY AND CONCLUSIONS

Although GERD is recognized as a motility disorder, gastric acid together with pepsin have been considered as key factors in initiating and perpetuating the mucosal damage to the esophageal mucosa and the development of symptoms in patients with esophagitis. There is a dynamic relationship between the degree and duration of esophageal acid exposure and healing of esophagitis. The longer the intragastric pH is above 4, the more patients will be healed at any arbitrary time-point. Treatments to relieve reflux symptoms and heal esophagitis with H₂RAs have been surprisingly unsuccessful. This correlates with the ineffectiveness of H₂RAs in suppressing gastric acid secretion. High-dose H₂RAs are more effective than standard doses in reducing acid secretion, but the advantage is modest in improving healing rates in esophagitis, and they are ineffective in patients with severe esophagitis; moreover, there is a higher cost. PPIs are very effective acid-suppressing agents under all conditions and are effective in healing all grades of esophagitis. In comparison with other medical treatments, PPIs produce the fastest healing and relief of reflux symptoms. The advantage of PPIs over H₂RAs is associated with the greater degree, longer duration and more complete inhibition of acid secretion, which provides a longer effect in maintaining intragastric pH above 4. Lansoprazole has a better bioavailability and a longer effect on suppressing acid secretion than omeprazole after oral administration. In clinical trials, significantly more patients have reflux symptom relief after treatment with lansoprazole than with omeprazole, although there is not significant difference in healing esophagitis between these two PPIs. This suggests that, overall, greater acid suppression may result in greater improvement of quality of life in patients with erosive esophagitis [97].
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