Review paper

The role of pH in symptomatic relief and effective treatment of gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is a condition in which gastroduodenal contents pass into the oesophagus and cause troublesome symptoms and complications. The aetiopathogenesis of gastroesophageal reflux disease is complex and multifactorial. Acid reflux plays an important role in the GERD pathogenesis, both in erosive and non-erosive reflux disease. Reduction of GERD symptoms and mucosal healing correlates with the number of hours that intragastric acid is suppressed to a pH > 4.0. Mucosal healing was achieved in most of patients who received different types of proton pump inhibitors, but only in 50% of those who received H2 blockers. These findings seem to be best accounted for by differences in the duration and degree of acid suppression achieved by different classes of drugs and perhaps between agents within those classes.

Gastroesophageal reflux disease (GERD) is a condition in which gastroduodenal contents pass into the oesophagus and cause troublesome symptoms and complications. The current GERD classification distinguishes syndromes from symptoms, and further separates the categories into oesophageal and extraoesophageal. Symptomatic oesophageal syndromes include a typical reflux syndrome with predominant heartburn and acid regurgitation. Symptoms of a typical reflux syndrome also include upper abdominal pain and reflux-induced sleep disturbances. The second oesophageal symptomatic syndrome is a chest pain syndrome where pain is the only symptom of the disease or predominates over typical symptoms of GERD. A separate group are syndromes with oesophageal injury. These include reflux esophagitis, reflux stricture, Barrett's oesophagus, and oesophageal adenocarcinoma. Extraoesophageal syndromes include reflux cough, reflux laryngitis, reflux asthma, and reflux dental erosion, for which association with reflux was established, and another group with only suggested causality [1].

Gastroesophageal reflux disease is one of the most common diseases of the digestive tract in the world. It is estimated that the prevalence is highest in Europe and North America, where at least weekly reflux symptoms range from 8.8% to 27.8% [2].

The aetiopathogenesis of gastroesophageal reflux disease is complex and multifactorial. Mechanisms contributing to the development of GERD include both transient lower oesophageal sphincter relaxations (TLOSRs) and different lower oesophageal sphincter (LOS) pressure abnormalities. Other factors contributing to the pathophysiology of GERD include hiatal hernia, poor oesophageal clearance, delayed gastric emptying, and impaired mucosal defensive factors. These elements promote recurrent reflux of gastric contents into the oesophagus and impaired oesophageal clearance, leading to increased mucosal injury [3].

Acid reflux plays an important role in the GERD pathogenesis, both in erosive and non-erosive reflux disease. Acid-mediated reflux episodes may last minutes or longer, depending on various factors such as time of the day, body position, physical activity, and meals. Most reflux symptoms are related to the degree and duration of oesophageal acid exposure.

The primary goal of treatment for patients with gastroesophageal reflux disease is to eliminate symptoms, improve quality of life, and reduce the risk of complications resulting from prolonged contact with reflux. Successful treatments are those that focus on symptom relief, mucosal oesophageal inflammation healing, and prevention against disease recurrence. These goals

can be achieved through methods that involve the use of well-tolerated drugs administered in a simple dosing regimen and which also facilitate doctor-patient cooperation [4].

The results of previous studies confirm unequivocally that proton pump inhibitors (PPIs) are the most effective agents in reducing symptoms in patients with gastroesophageal reflux disease [1, 5]. Proton pump inhibitors are derivatives of benzoimidazoles, whose mechanism of action is to block the hydrogen-potassium ATP-ase enzyme (proton pump) located at the secretory surface of the parietal cells. These compounds are prodrugs and their active form is produced in acidic environments. Blocking ATP-ase is stable and makes the enzyme irreversibly active. To restart the H^+ production in the cell, the new pump must be synthesised. Proton pump inhibitors block the activity only of proton pumps that have previously recruited and stimulated hormonal stimuli released during a meal. The antisecretory effect of PPIs is initially suboptimal because not all proton pumps are activated in postprandial secretion. Additional proton pumps may be inhibited within the subsequent 3–5 days, but after this time a balance between active and blocked proton pumps is created. After 5 days of PPI at a single daily dose, a reduction in maximum gastric acid secretion of 66% is observed. All currently available PPIs have a short half-life of 1–2 h, but their inhibitory effect on gastric acid secretion persists much longer. The clinical effect largely depends on the stability of covalent bonds between the drugs and the proton pump molecules. Because proton pump cells display the highest availability for IPP at maximum stimulation of acid secretion, these drugs most effectively inhibit its secretion when taken 30–60 min before breakfast. An additional significant consequence of the use of drugs that inhibit hydrochloric acid secretion is to reduce the volume of gastric juice and, consequently, to reduce the volume of the contents of the oesophagus. It is recommended to take PPI while fasting and about 30–60 min before a meal, because the presence of food in the stomach reduces its absorption. Furthermore, fasting administration makes the peak plasma concentration match the maximum number of activated proton pumps. The inhibition of gastric acid secretion by PPIs is influenced by individual characteristics like variation in the metabolism of PPIs regarding polymorphisms and P2C19 cytochrome CYP3A4, as well as external factors like *Helicobacter pylori* infections.

Since the introduction of the first PPI (omeprazole) in 1988, pantoprazole, lansoprazole, rabeprazole, esomeprazole, and dexlansoprazole have also been made available. Inhibition of hydrochloric acid secretion by PPIs is more effective than H_2 blockers, lasts longer, and is not associated with tachyphylaxis. In the treatment of GERD in patients with typical symptoms of the disease and no evidence of clinical alarm, empirical treatment with a standard dose PPI for 2–4 weeks is recommended.

Numerous randomised trials, which included over 3000 patients, have shown that PPIs are more effective in reducing the symptoms in patients with erosive esophagitis than both placebos and H_2 blockers [6]. Mucosal healing was achieved in 78% of patients who received proton pump inhibitors, 50% of those who received H_2 blockers, and in 24% of patients treated with placebo. These findings seem to be best accounted for by differences in the duration and degree of acid suppression achieved by different classes of drugs and perhaps between agents within those classes. Healing of erosive oesophagitis correlates with the number of hours that intragastric acid is suppressed to a pH > 4.0.

Various randomised trials have compared the efficacy of different PPIs. In patients with GERD, faster clinical improvement is seen during the first 5 days with esomeprazole 40 mg versus omeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg; however, these differences are not maintained from the fifth day of treatment [7].

Eggleston *et al.* compared rabeprazole 20 mg with esomeprazole 20 mg and 40 mg in the treatment of GERD. No significant differences in the resolution of symptoms between rabeprazole 20 mg, esomeprazole 20 mg, and esomeprazole 40 mg were identified [8].

There are different parameters that must be taken into consideration when the available PPIs are compared. Among them, the average time during which intragastric pH is greater than 4 is relatively sensitive to changes in pH within 24 h and easily understood [9]. In patients with GERD it is necessary to obtain an intragastric pH above 4 for at least 16 h/day [10].

Previous data suggest that symptom response to a PPI once daily (4 weeks treatment) in patients with non-erosive reflux disease (NERD) is correlated with the extent of oesophageal acid exposure although GERD symptoms are often more difficult to control in patients without oesophageal lesions [11].

With regard to the differences in time action, it has been found that standard-dose rabeprazole, was as effective as high-dose omeprazole in reducing symptoms of severe GERD in the first 3 days of treatment, but had faster onset of action in patients with severe heartburn [12].

In many patients with erosive GERD, PPIs fail to achieve complete healing of oesophageal lesions. Over 20% of patients with GERD have an inadequate response to taking omeprazole 20 mg twice per day. A higher dose of omeprazole (80 mg/day) improves the

symptoms in refractory patients [13]. One of the probable causes of failure in the effectiveness of standard dose is night-time acid reflux, when suitable acid inhibition does not occur for long periods [14]. However, even today the clinical significance of this phenomenon remains unclear, and it is unknown whether it is related to the lack of therapeutic response to these medications. Other causes of refractoriness to the treatment include poor compliance, hypotensive lower oesophageal sphincter, and ineffective oesophageal peristalsis [15].

The measurement of intragastric pH is a well-accepted method for the assessment of the pharmacodynamic effects of proton pump inhibitors. Regarding the duration of gastric acid inhibition, Miner *et al.*, in a randomised, crossover study, evaluated and compare intragastric pH (measured on day 5 at steady state) following standard doses of esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole in patients with symptoms of GERD. They found that intragastric pH was maintained above 4.0 for a mean range of 10.1–14.0 h in 24 h when various PPIs were given once daily, before the morning meal [16]. Esomeprazole, at a standard dose of 40 mg, provided a significantly higher percentage of patients with an intragastric pH greater than 4.0 for more than 12 h relative to the other proton pump inhibitors ($p < 0.05$).

One limitation on the use of PPIs on a once-daily basis is incomplete acid suppression over the 24-hour post-dose interval. Therefore, the next step to improve the efficacy of PPIs is to increase the dose to twice daily. Johnson *et al.*, performed a study comparing the effectiveness of once and twice-daily dosing of lansoprazole and esomeprazole in controlling intragastric acidity over a 24-hour period. Esomeprazole 40 mg taken twice daily controlled acid for 19.46 h daily, which provided superior control of intragastric pH compared with either once or twice daily dosing of lansoprazole (respectively, 12.28 h and 15.74 h) and once daily dosing of esomeprazole (14.54 h; $p < 0.01$). This procedure results in partial improvement because it only prolongs acid suppression by another 5 h [17].

The new proton pump inhibitor dexlansoprazole is a modified-release R-enantiomer of lansoprazole, which employs Dual Delayed Release (DDR) technology. There are two types of coated microgranules in the capsule, which release active agents depending on the pH value. A quarter of the dose of dexlansoprazole is released at pH 5.5 in the proximal part of the duodenum. The remaining 75% of the dose is released in the distal small intestine at pH 6.75 [18]. This mechanism of release leads to two peaks in serum drug concentration and subsequently prolonged exposure of proton pumps to the drug. As a result, serum dexlansoprazole reaches twice the maximum: 1–2 h and 4–5 h after drug intake. Consequently, dexlansoprazole modified release ensures the longest period of drug retention in the circulation and the most powerful inhibitory effect on the proton pump of all available PPIs [19].

An important condition for effective PPI therapy is the patient's compliance in the timely taking of the medication. Because the absorption and bioavailability of PPIs have been shown to diminish when they are administered with food, it is recommended that PPIs should be administered 30–60 min before meals to optimise antisecretory effects and minimise the possibility of a negative pharmacokinetic food interaction. Lee *et al.* evaluated the effect of dosing time relative to food intake on the pharmacokinetics and pharmacodynamics of dexlansoprazole. There was no statistically significant difference in mean 24-h intragastric pH under fasted and various fed conditions (5 and 30 min before or 30 min after meal), which suggest that dexlansoprazole can be administered without regard to meals [20]. In another study, the effect of dexlansoprazole on serum concentrations and pH in the stomach was examined during four different times of day, 30 min before one of three meals or an evening snack. There were no statistically significant differences in mean 24-h intragastric pH between dosing before dinner or an evening snack vs. breakfast; however, there was a small but statistically significant difference between lunch and breakfast. The authors concluded that dexlansoprazole provides comparable pH control when administered at different times of the day [21].

Another clinical trial assessed the effect of dexlansoprazole on gastric pH value over the course of 24 h. A comparative study was performed in healthy volunteers to determine the effect of a single dose of dexlansoprazole 60 mg and esomeprazole 40 mg on the mean intragastric pH value over 24 h and the percentage of time with pH > 4 [22]. A mean percentage of time with intragastric pH > 4 revealed the following statistically significant differences: 58% for dexlansoprazole and 48% for esomeprazole ($p < 0.003$). Additionally, the average of mean intragastric pH for dexlansoprazole was 4.3 compared with 3.7 for esomeprazole ($p < 0.001$). 24-hour intragastric pH for dexlansoprazole was higher, particularly in the second part of the day. This study indicated that dexlansoprazole technology leads to an extended duration of gastric acid control compared with esomeprazole. By extending the duration of acid suppression, a single daily dose of dexlansoprazole can potentially replace twice-daily dosing of other PPIs.

Other studies examined the effects of different doses of the dexlansoprazole vs. lansoprazole on 24-hour intragastric pH values. Dexlansoprazole (60 mg,

90 mg, and 120 mg) achieved significantly higher mean 24-hour intragastric pH values and percentage of time intragastric pH > 4 as compared with lansoprazole 30 mg [23]. Mean intragastric pH values increased by more than 0.5 and the percentage of time intragastric pH > 4 by more than 10% during the 16–24-hour interval for all the studied regimens, as compared with standard dose of lansoprazole [24]. Additionally, as the authors have shown, a plasma dexlansoprazole MR concentration of 125 ng/ml corresponds with the longest time during which intragastric pH is greater than 4 over a 24-hour period, which confirms that dexlansoprazole MR provided extended acid suppression as compared with lansoprazole [25]. The greater intragastric pH achieved after dexlansoprazole is associated with high rates of healing erosive esophagitis [26].

Another important problem in patients with GERD is night-time reflux. Patients with reflux during sleep are more likely to develop more severe conditions such as oesophageal inflammation, peptic stricture, oesophageal ulceration, Barrett's oesophagus, and even adenocarcinoma of the oesophagus. Additionally, these patients have a higher prevalence of oropharyngeal, laryngeal, and pulmonary manifestations [27]. Sleep may alter physiological mechanisms responsible for normal oesophageal clearance, resulting in increased oesophageal acid exposure. For example, episodes of gastroesophageal reflux occurring during sleep are less frequent than in the daytime, but last significantly longer, which increases acid mucosal contact time. Moreover, the rate of swallowing is reduced during sleep and primary oesophageal peristalsis and emptying of the stomach is decreased. In addition, the reduction of saliva secretion during sleep is responsible for delaying the neutralisation of acidic in the oesophagus. All these mechanisms lead to decreases in acid clearance and increases in acid mucosal contact time [28].

Treatment of night-time reflux is a real challenge for physicians and is more difficult than reducing daytime symptoms. Pathological night-time reflux is also an important cause of resistance to treatment in patients with GERD. After a morning PPI dose, only activated pumps are blocked, and both resting and newly synthesised pumps are not inhibited and therefore have the capacity to secrete acid. Most PPIs have a short plasma half-life (1–2 h), and a second dose before the evening meal has no effect on episodes of reflux during the night-time hours. Most patients will reflux after midnight because the supine time is associated with more reflux events, and even delayed release-PPIs *b.i.d.* may still not control night-time acidity [29].

Analysis of the intragastric profiles of pH in patients treated with PPI twice daily showed that they effectively control acid secretion during the day, but at night the pH falls below 4 for at least 1 h. This phenomenon, called nocturnal acid breakthrough (NAB), can affect some patients with GERD for relapse.

Miehlke *et al.* compared the effect of esomeprazole 40 mg twice daily and pantoprazole 40 mg twice daily on intragastric pH and showed that at night the proportion of time with intragastric pH > 4 was 85.4% with esomeprazole and 63.6% with pantoprazole ($p < 0.0001$). Despite the improved effect after *b.i.d.* esomeprazole, the intragastric pH may remain less than 4 for up to a third of the night [30].

Other studies found that 60–80% of patients have persistent gastric acidity at night despite *b.i.d.* PPIs, and approximately 25% of reflux patients fail to respond to *b.i.d.* PPI for 4–8 weeks [31]. Therefore, acid secretion after midnight is not controlled even with the most aggressive acid-suppressive therapy. Thus, nocturnal acidity remains an issue in patients, who have the capacity to reflux, despite taking a PPI either once daily or *b.i.d.*

In these cases, a better alternative is the use of novel PPI, which can reliably control nocturnal acid secretion and night-time symptoms – dexlansoprazole MR.

The dual system of dexlansoprazole MR release from capsules inhibits overnight gastric acid secretion in the stomach. As a result, it is effective in the treatment of night-time heartburn, regurgitation and related sleep disorders. In a randomised study of 305 patients with night-time GERD, dexlansoprazole MR was shown to be significantly more effective in reducing night-time symptoms compared with a placebo. Taken once daily, in the morning, within 4 weeks, dexlansoprazole MR led to significantly greater improvements in sleep quality and work productivity. Additionally, dexlansoprazole MR 30 mg, compared with placebo, significantly increased the percentage of nights without nocturnal GERD from 35.7% to 73.1% and was superior in reducing night-time symptoms and sleep disturbance [32].

Proton pump inhibitors are currently the most effective treatment for GERD and its complications, but a significant proportion of patients, particularly non-responders, have symptoms that are inadequately controlled with a single dose of PPI. This is due to the fact that standard-dose PPI does not provide complete control of gastric acid secretion over a period of 24 h. Further improvement in acid inhibition can be achieved by increasing the residence time of PPIs in the systemic circulation, resulting in much more prolonged acid suppression. Therefore, dexlansoprazole, due to the new drug release formula that affects bioavailability and pharmacokinetic and pharmacodynamic parameters, has a beneficial effect on the management and

improvement of GERD symptoms. In addition, the drug can be administered independently of meals and the time of day, and is particularly important in the treatment of night-time reflux. It seems that dexlansoprazole demonstrates a unique pharmacodynamic profile, which probably translates to improved clinical efficacy in GERD patients.

Conflict of interest

The author declares no conflict of interest.

References

1. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014; 63: 871-80.
2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence based consensus. Am J Gastroenterol 2006; 101: 1900-20.
3. Castell DO, Murray JA, Tutuian R, et al. Review article: the pathophysiology of gastro-oesophageal reflux disease – oesophageal manifestations. Aliment Pharmacol Ther 2004; 20: 14-25.
4. Kahrilas P, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008; 135: 1392-413.
5. Coron E, Hatlebakk JG, Galmiche JP, et al. Medical therapy of gastroesophageal reflux disease. Curr Opin Gastroenterol 2007; 23: 434-9.
6. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Practice Parameters Committee of the American College of Gastroenterology. Arch Intern Med 1995; 155: 2165-73.
7. Zheng RN. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol 2009; 15: 990-5.
8. Eggleston A, Katelaris PH, Nandurkar S, et al. Clinical trial: the treatment of gastro-oesophageal reflux disease in primary care – prospective randomized comparison of rabeprazole 20 mg with esomeprazole 20 and 40 mg. Aliment Pharmacol Ther 2009; 29: 967-78.
9. Calvet X, Gomollon F. What is potent acid inhibition, and how can it be achieved? Drugs 2005; 65: (Suppl 1): 13-23.
10. Hatlebakk JG. Review article: gastric acidity – comparison of esomeprazole with other proton pump inhibitors. Aliment Pharmacol Ther 2003; 17 (Suppl 1): 10-5.
11. Dean BB, Gano AD, Knight K, et al. Effectiveness of proton pump inhibitors in non-erosive reflux disease. Clin Gastroenterol Hepatol 2004; 2: 656-64.
12. Holtmann G, Bytzer P, Metz M, et al. A randomized, double-blind, comparative study of standard-dose rabeprazole and high-dose omeprazole in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2002; 16: 479-85.
13. Leite LP, Johnston BT, Just RJ, et al. Persistent acid secretion during omeprazole therapy: a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. Am J Gastroenterol 1996; 91: 1527-31.
14. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther 2014; 5: 105-12.
15. Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. Gastroenterol Rep 2015; 3: 41-53.
16. Miner P, Katz PO, Chen Y, et al. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003; 98: 2616-20.
17. Johnson DA, Stacy T, Ryan M, et al. A comparison of esomeprazole and lansoprazole for control of intragastric pH in patients with symptoms of gastro-oesopahgeal reflux disease. Aliment Pharmacol Ther 2005; 22: 129-34.
18. Metz DC, Vakily M, Dixit T, et al. Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. Aliment Pharmacol Ther 2009; 29: 928-37.
19. Hershcovici T, Jha LK, Fass R. Dexlansoprazole MR: a review. Ann Med 2011; 43: 366-74.
20. Lee RD, Vakily M, Mulford D, et al. Clinical trial: the effect and timing of food on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR, a novel Dual Delayed Release formulation of a proton pump inhibitor – evidence for dosing flexibility. Aliment Pharmacol Ther 2009; 29: 824-33.
21. Lee RD, Mulford D, Wu J, Atkinson SN. The effect of time-of-day dosing on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR: evidence for dosing flexibility with a dual delayed release proton pump inhibitor. Aliment Pharmacol Ther 2010; 31: 1001-11.
22. Kukulka M, Eisenberg C, Nudurupati S. Comparator pH study to evaluate the single-dose pharmacodynamics of dual delayed-release dexlansoprazole 60 mg and delayed-release esomeprazole 40 mg. Clin Exp Gastroenterol 2011; 4: 213-20.
23. Zhang W, Wu J, Atkinson SN. Pharmacokinetics, pharmacodynamics, and safety evaluation of a single and multiple 60 mg, 90 mg, and 120 mg oral doses of modified-release TAK-390 (TAK-390MR) and 30 mg oral doses of lansoprazole in healthy subjects. Gastroenterology 2007; 132 (suppl 52): A487.
24. Bell NJ, Burget D, Howden CW, et al. Appropriate acid suppression for the management of gastrooesophageal reflux disease. Digestion 1992; 51 Suppl 1: 59-67.
25. Wu J, Vakily M, Witt G, et al. TAK-390 MR vs. Lansoprazole (LAN) for maintenance of drug concentration above a threshold which corresponds to higher%-time pH>4. Am J Gastroenterol 2007; 102 (Suppl 2): 124.
26. Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation – results from two randomized controlled studies. Aliment Pharmacol Ther 2009; 29: 731-41.
27. Fass R. Effect of gastroesophageal reflux disease on sleep. J Gastroenterol Hepatol 2010; 25 Suppl 1: S41-4.
28. Pasricha PJ. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. Am J Med 2003; 115: 114S-8S.

29. Orr WC. Reflux events and sleep: are we vulnerable? Curr Gastroenterol Rep 2006; 8: 202-7.
30. Miehlke S, Madisch A, Kirsch C, et al. Intragastric acidity during treatment with esomeprazole 40 mg twice daily or pantoprazole 40 mg twice daily – a randomized, two-way crossover study. Aliment Pharmacol Ther 2005; 21: 963-7.
31. Richter JE. How to manage refractory GERD. Nat Clin Pract Gastroenterol Hepatol 2007; 4: 658-64.
32. Fass R, Johnson DA, Orr WC, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol 2011; 106: 421-31.

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