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A Review On PPI In The Treatment Of Gastroesophageal Reflux Disease (GERD)

Hasbi Habeeb[1]*, Alana Kalam S[1]

Dr. Subash Chandran M.P [2], Dr. Karthika Lal B [3], Dr. Prasobh G.R[4],

Dr. Nithin Manohar[5]

1. 5th Year Doctor of Pharmacy Student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.
2.Professor and Head of Department of Pharmaceutics, Sree Krishna College of Pharmacy and Research Centre,Thiruvananthapuram, Kerala, India.
3.Assistant Professor, Department of Pharmacy practice, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India.
4.Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.
5.HOD, Department of Pharmacy practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

ABSTRACT

The persistent, recurrent acid-peptic illness known as gastroesophageal reflux disease (GERD) is marked by a recurrence of bothersome reflux symptoms. Since it's a chronic illness, treatment must be ongoing. Patients usually start with simple lifestyle changes, and since they are easy to implement and inexpensive, they should be kept up even when more effective therapy are started. Currently, the most significant and effective medical treatment is powerful acid-suppressive medication. Whereas healing of the oesophageal mucosa is achieved with a single dosage of any proton pump inhibitor (PPI) in more than 80% of instances. PPI is still the best course of action, and it is "on-demand". PPIs have shown to be an affordable, long-term medication. By reducing the amount of acid in the stomach, PPIs lessen the symptoms of acid reflux into the oesophagus and heartburn. Studies with extended follow-up show that PPIs are a safe, effective, and acceptable treatment.

KEY WORDS

Gastroesophageal reflux disease (GERD); Proton pump inhibitors (PPI); Erosive reflux disease (ERD); Non-erosive reflux disease (NERD); Histamine Type-2 Receptor Antagonist (H2RA)

INTRODUCTION

The most prevalent upper gastrointestinal (GI) condition is known as gastroesophageal reflux disease (GERD), which is characterized by symptoms or lesions brought on by the retrograde movement of stomach contents into the oesophagus. It is a collection of diverse pathophysiologic conditions that cause the stomach's contents to easily pass into the oesophagus and cause uncomfortable symptoms or consequences.

Heartburn, which is a searing pain in the retro sternum that radiates up into the throat, and acid regurgitation, which is the sensation of stomach contents entering the mouth or hypopharynx, are the hallmark symptoms of GERD. There may also be unusual symptoms (such as belching, coughing, dysphagia, globus, chest pain, or throat symptoms) [1].

Furthermore, symptoms of GERD that resemble functional dyspepsia, such as fullness or early satiety, may be present. Greater transient lower oesophageal sphincter relaxations, which encourage greater acid and bile reflux, are one known underlying cause of GERD [2].

At the moment, PPIs are the most successful treatment for GERD and its aftereffects. The enteric-coated tablets or capsules containing proton pump inhibitors (PPIs), which are substituted benzimidazoles, are absorbed in the duodenum after passing through the stomach [3].

Proton pump inhibitors (PPIs) bind covalently to cysteine residues on the luminal surface of H+ /K+ ATPase proton pumps in the parietal cells, preventing ion transport and acid secretion following acid activation to sulphonamides. The efficacy of PPI therapy in healing oesophageal erosions is very high. In addition to curing reflux esophagitis, proton pump inhibitor therapy is a highly successful treatment for heartburn symptoms.[4]

Clinical investigations assessing PPI's effectiveness in symptom relief across various categories Patients with erosive reflux disease (ERD) and non-erosive reflux disease (NERD) typically have higher response rates due to reflux disease and oesophageal sensitivity.

The current systematic review set out to give an update on the effectiveness of proton pump inhibitors (PPIs) in acid suppression for both acute and long-term GERD treatment [5].

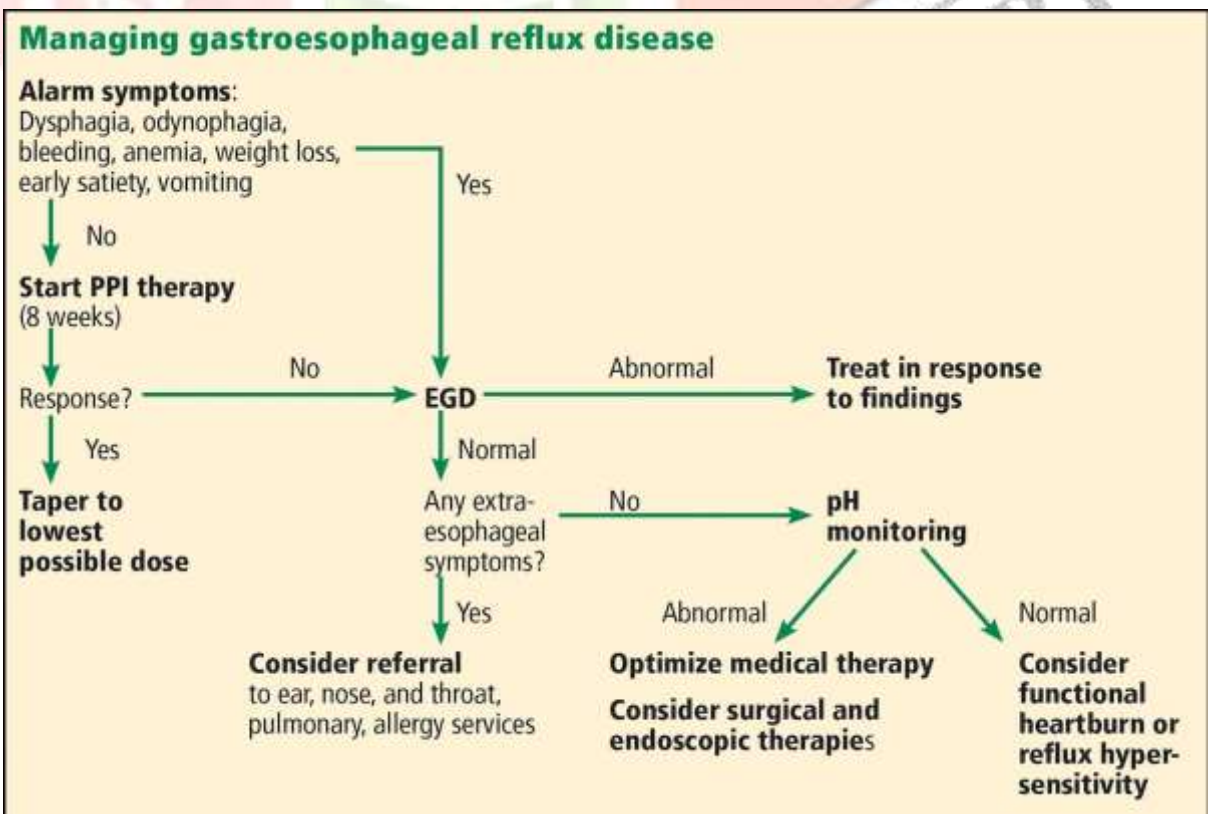

figure 1; approach to gastroesophageal reflux disease (PPI = proton pump inhibitor, EGD = esophagogastroduodenoscopy)

PATHOPHYSIOLOGY

The disorder known as gastroesophageal reflux disease (GERD) is brought on by the retrograde reflux of stomach contents into the oesophagus. One of the main symptoms is a searing discomfort in the chest that usually gets worse when you lie down after eating. The pathophysiology of gastro-oesophageal reflux disease is multifaceted, involving transient lower oesophageal sphincter relaxations and various lower oesophageal sphincter pressure anomalies. Oesophageal mucosal damage results from the reflux of acid, bile, pepsin, and pancreatic enzymes [2].

Factors known to contribute to GERD include:

• Transient relaxation of the lower oesophageal sphincter (LES)

• Sliding hiatal hernia

• Low pressure in the LES

• Development of acid pockets in the proximal stomach due to inadequate mixing of acid with chyme

• increased distensibility of the gastroesophageal junction

• Delayed gastric emptying

• Obesity

The abnormal reflux of stomach contents into the oesophagus is the primary cause of gastro-oesophageal reflux disease (GERD). It is sometimes linked to abnormal lower oesophageal sphincter (LES) function or pressure. Reduced gastro-oesophageal sphincter pressure in patients may be caused by

a) Spontaneous transient LES relaxations

b) Transient increases in intra-abdominal pressure

An atonic LES, all of which have the potential to cause reflux disease of the stomach. GERD may also develop as a result of issues with other normal mucosal defence mechanisms, such as abnormal anatomy of the oesophagus, improper clearance of gastric fluids by the oesophagus, decreased mucosal resistance to acid, delayed or ineffective gastric emptying, insufficient production of epidermal growth factor, and decreased acid-buffering capacity of saliva.[3][7]

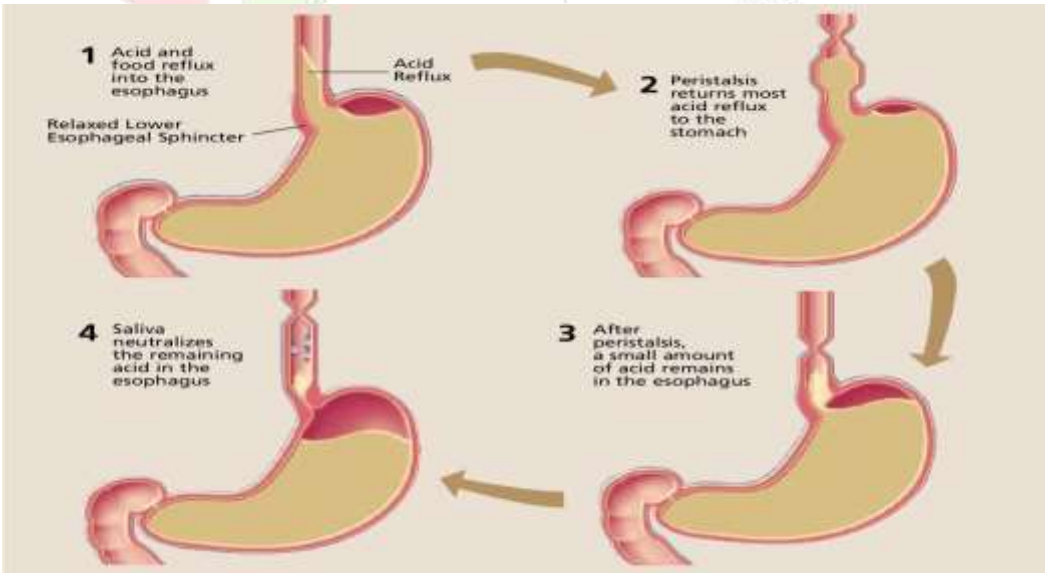

figure 2; pathogenesis of GERD

Acid reflux into the oesophagus can cause damage to the lining of the stomach, pepsin, bile acids, and pancreatic enzymes. The refluxate's composition and volume, along with the length of exposure, are therefore significant aggravating factors that impact the outcomes of gastro-oesophageal reflux. When treating gastro-oesophageal reflux, rational therapeutic regimens aim to minimize aggravating variables while optimizing the mucosal defence mechanisms [2].

MANAGEMENT

The goal of therapy is to increase the body's defensive systems against reflux and/or lessen the aggressive elements that aggravate reflux or damage to the mucosa. The goal of therapy is to

- Reduction of refluxate acidity
- Decreasing the gastric volume available to be refluxed
- Improving gastric emptying
- Elevation of LES pressure
- Enhancing esophageal acid clearance
- Preservation of the esophageal mucosa [9]

NON-PHARMACOLOGICAL TREATMENT

Suggested lifestyle changes for all GERD sufferers

- Raise the bed's head to improve esophageal clearance. Place bricks measuring 6 to 8 inches beneath the bed's head. Take a nap on a foam wedge.
- Weight reduction (reduces symptoms) in obese patients [10]

Recommended lifestyle modifications that should be individualized to specific patients

- Steer clear of meals that could lower the lower esophageal sphincter pressure, such as alcohol, chocolate, fats, and peppermint and spearmint.
- Eat meals high in protein to help decrease the pressure at the lower esophageal sphincter.
- Steer clear of meals that directly irritate the mucosa lining the esophagus. (Spicy food, coffee, orange juice, and tomato juice)
- Behaviors that may reduce esophageal acid exposure
    - Eat in moderation and try not to eat just before bed (within three hours, if feasible; reduces stomach volume).
    - Give up smoking (reduces the relaxation of the esophageal sphincter spontaneously).
    - Avoid alcohol (increases amplitude of the lower esophageal sphincter, peristaltic waves, and frequency of contraction)
    - Avoid tight-fitting clothes
    - Take medications that have a direct irritant effect on the esophageal mucosa with plenty of liquid if they cannot be avoided. (Tetracyclines, Quinidine, and Potassium chloride, aspirin, Non-Steroidal Anti-Inflammatory Drugs) [13]

PHARMACOLOGICAL TREATMENT

Antacids

E.g.: Aluminum hydroxide gel, Calcium Carbonate, Milk of Magnesia

For occasional and relatively rare reflux symptoms, over-the-counter antacids are the most effective treatment option. Regular use of antacids can exacerbate the issue. They swiftly exit the stomach, which paradoxically causes your stomach to produce more acid.

MOA: - Antacids work by neutralizing stomach acid and preventing the proteolytic enzyme pepsin from working. Because antacids neutralize stomach acid, they lessen the amount of acid that reaches the duodenum and expose the lining of the esophagus to less gastric acid.[8]

Histamine blockers

E.g.: Ranitidine, Famotidine, Cimetidine

Drugs known as histamine 2 (H2) blockers are effective in reducing acid output. About 50% of individuals with esophageal erosions recover with H2 blockers.

MOA: - H2RAs block the binding and function of the endogenous ligand histamine by reversibly binding to histamine H2 receptors on gastric parietal cells, which reduces stomach acid output.[12]

Prokinetic agents

E.g.: Metoclopramide

Prokinetic agents are medications that increase your gastrointestinal tract's smooth muscle activity. These medications work a little less well than PPIs. It could be taken along with medication that suppresses acid production.

MOA: - Medication known as prokinetics, or prokinetic agents, aids in the management of acid reflux. Prokinetics facilitate a quicker emptying of the stomach by strengthening the lower esophageal sphincter (LES). As a result, acid reflux can happen faster.[15]

Proton Pump Inhibitors

E.g.: Pantoprazole, Esomeprazole, Omeprazole

When it comes to treating erosive esophagitis and its consequences, erosive and nonerosive GERD symptoms, and preventing GERD-related symptom recurrence, PPIs are superior to H2RAs. PPIs are modified benzimidazoles that bind H+, K+-ATPase, the last common step in acid secretion, permanently.[10]

Pantoprazole, rabeprazole, lansoprazole, omeprazole, and esomeprazole are the five PPIs that are currently marketed. The FDA has approved doses of omeprazole (20 and 40 mg), lansoprazole (15 and 30 mg), rabeprazole (20 mg), pantoprazole (40 mg), and esomeprazole (40 mg) that are to be taken once daily. These doses are adequate to treat the majority of patients. In roughly 78% of instances (range, 62–94%), symptoms should subside, and in 83% of cases (range, 71–96%), esophagitis should recover.[1]

It's debatable which PPI is better than the others. Every study demonstrating the superiority of one PPI over another is countered by another. Overall, all first-generation PPIs (omeprazole, lansoprazole, rabeprazole, and pantoprazole) can be regarded as having equivalent effectiveness based on comparable intragastric pH profiles after 7 days of dosage and comparable oesophageal healing rates of over 80% after 8 weeks (Figure 3).

There are slight variations in pricing and pharmacodynamics. Individual differences in a patient's reaction to PPI, however, might be rather significant. As a result, if a patient is not responding to one PPI, we advise moving on to another one as soon as possible.[1]

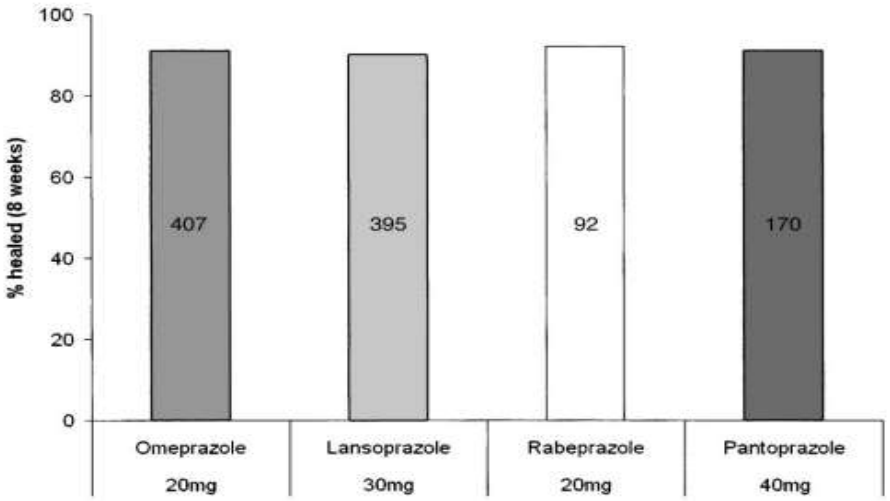

figure 3; comparison of first-generation PPIs for short-term treatment healing rates. bars indicate percentage healing after 8 weeks of treatment. numbers indicate patients in respective studies.

According to reports, esomeprazole, the active S-isomer in omeprazole's racemic combination and the most current "second-generation" PPI, has a little superior effect on GERD.

It's crucial to consider when to administer the PPI in relation to meals. The best time to take the PPI is between fifteen and thirty minutes before a meal. In this way, the drug can be absorbed and made available to the proton pumps for use when the meal activates them. When PPIs are administered before meals, intragastric pH regulation is better than when they are taken after. Clinically, insufficient timing is often observed, particularly when patients are provided PPI twice daily without additional instructions; these patients often take the drug in the morning and right before bed (without eating).[1]

Single-dose proton pump inhibitors are effective in reducing intragastric acidity, alleviating symptoms, and healing erosive esophagitis; however, some individuals may not heal as well and may need higher dosages. Furthermore, in order to effectively control their symptoms, patients with extra-oesophageal presentations (such as cough, laryngitis, or asthma) might need to take higher doses. Giving the PPI twice a day is preferable to double the single dose quantity. This advice is supported by research done on healthy participants that showed 20 mg of omeprazole before breakfast and before dinner controlled intragastric pH better than 40 mg of the drug in those same periods.

More recently, it has been found that Nocturnal acid breakthrough can be decreased with a single dosage of H2RAs administered to the PPI before bed (Figure 4). Concerns that combination of PPI and H2Ras would diminish the efficiency of PPIs were resolved by studies revealing identical intragastric acid control on daily PPI following placebo or H2RAs the night before. Therefore, H2RAs are still potentially beneficial medications for on-demand management of both daytime and nocturnal GERD symptoms.[1]

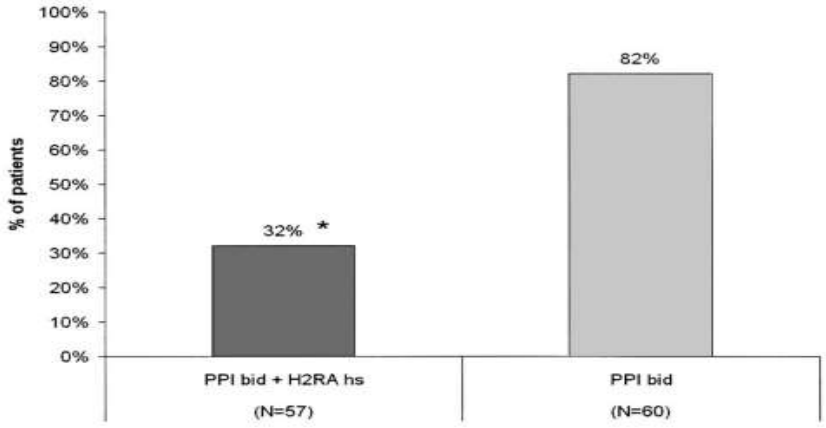

figure 4; Proportion of patients with nocturnal acid breakthrough (defined as intragastric pH<4 for at least 60 continuous minutes) on

PPI bid+ H2RA at bedtime versus PPI twice per day alone.

table 1; suggested approach to acid suppressive therapy

Step	Medical regimen
1	Single-dose PPI (AM before meals)
2	Switch to another PPI
3	PPI AM plus evening (or bedtime) H2RA
4	PPI twice daily before meals
5	PPI twice daily before meals plus H2RA at bedtime

We suggest the step-up therapy approach to acid suppression, as shown in Table 2, based on the available evidence. A common recommended diagnostic strategy for GERD is now the symptom response to a PPI therapy trial ("PPI-trial"). Reflux testing should be done on patients who fail PPI trials or do not react to PPI therapy in order to assess the severity of reflux and how it relates to symptoms [1]. Oesophageal pH testing has been the recognized gold standard for diagnosing GERD for over 20 years. Before conducting oesophageal pH testing, patients should be off PPI treatment for a minimum of 7 days in order to optimize study interpretation. During this time, GERD patients who did not respond to traditional PPI treatment due to inadequate dosage may experience a worsening of their symptoms, which could aid with diagnosis clarification.[1]

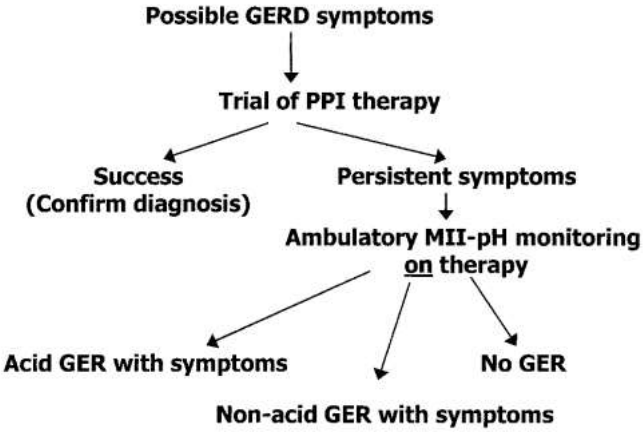

figure 5; suggested diagnostic GERD algorithm

CONCLUSION

Treatment for gastroesophageal reflux disease (GERD) must be ongoing because it is a chronic illness. Patients begin with simple lifestyle changes, and because these are inexpensive and easy to implement, they should be kept up even when more effective therapy are started. Currently, the most significant and effective medical treatment is powerful acid-suppressive medication. More than 80% of the time, a single dose of any PPI can repair the oesophageal mucosa; however, controlling the symptoms is more challenging. It may be necessary to administer more doses or use H2RA in combination therapy to control symptoms. Patients who are still experiencing symptoms after starting treatment should have testing to see if their symptoms are related to acid reflux disease (GER), non-acid reflux disease, or neither. Studies with extended follow-up show that PPIs are safe, effective, and well-tolerated drugs.

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