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A COMPREHENSIVE REVIEW OF PROTON PUMP INHIBITORS IN MANAGEMENT OF GASTROINTESTINAL DISORDERS

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ABSTRACT

PPIs are among the most often given medications for infants and kids, and their use has dramatically increased over the past few decades. PPIs have been considered safe medications and are evidently successful when used as prescribed, however there is mounting evidence that they may have adverse effects. However, it is evident that many of these are also pertinent to pediatrics, primarily based on adult evidence. PPI use may have an impact on the composition and function of the gastrointestinal microbiota, reduce defences against pathogens, which increases the risk of infections, impede the absorption of minerals and vitamins, increasing the risk of certain deficiencies and bone fractures, and interfere with the digestion of proteins, increasing the risk of sensitization to allergens, the development of allergic diseases, and eosinophilic esophagitis. From adult data, a weak and unproven connection has also been inferred with pancreatic, liver, and stomach cancer. Overall, there is inconsistent and often weak data supporting these harmful effects. All things considered, there is considerable potential advantage to the selective use of PPIs for reasons with strong evidence, although babies and children should take them with greater caution. The worries about possible side effects linked to their use should be known by pediatricians.

KEYWORDS: Proton pump inhibitors, Indications, Antioxidant potential, Gastrointestinal disorders, Gastric acid.

1. INTRODUCTION

One of the most widely used drugs in the globe, if not the United States, is a proton pump inhibitor (PPI). Studies using observational data have shown that the usage of PPIs has grown over time, with 7%–15% of patients using them at any given time. For patients aged 70 years or above, this frequency rises to 40%, Roughly 25% of patients who are prescribed PPIs will keep using them for a minimum of a year. PPIs are the preferred course of treatment for acid-mediated upper gastrointestinal (GI) disorders like peptic ulcer disease and erosive esophagitis, but they are also being used more frequently for less obvious reasons and for ambiguous periods of time. Almost two thirds of PPI users in sizable observational research that looked at their ambulatory visits had no obvious reason to take PPIs. Several national gastroenterology organizations have advocated for restricting the use of PPIs in this particular scenario Furthermore, since PPIs have been sold over-the-counter in the US since 2003, doctors may not have a say in whether a patient decides to start treatment.[1] A class of substances known as proton pump inhibitors (PPIs) was created in the latter part of the 20th century. The first PPI to be introduced to the market in the late 1980s was omeprazole. Esomeprazole, lansoprazole, pantoprazole, and rabeprazole are a few examples of PPIs that feature the benzimidazole ring in their basic structures. The majority of PPIs are benzimidazole derivatives.[2] Esomeprazole, compared to other drugs that prevent the release of acid from the stomach, PPIs primarily reduce gastric acid discharges deeply, permanently, and for a respectably extended amount of time.[3] The mechanism of action of proton pump inhibitors (PPIs) is primarily characterized by the irreversible inhibition of the Hydrogen/Potassium adenosine triphosphate H^+/K^+ ATPase enzyme system. This system is found in the gastric parietal cells and acts by continuously promoting proton release into the gastric lumen. The H^+/K^+ ATPase system is commonly referred to as the proton pump because it is thought to be the last stage of stomach acid production, and inhibiting it will significantly lower the acid content of the stomach.[4]

The PPIs are given as prodrugs, which implies that they are inert and must be activated in order to start working fully. Before the rearrangement stage, which yields the compound's active state, the tertiary amines in the drug structure must be protonated in order for PPIs to be activated**.** Subsequently, the active medication forms an irreversible and covalent bond with the H^+/K^+ ATPase system, impeding its ability to pump protons. The H^+/K^+ ATPase enzyme and the active version of the PPI interact covalently to block stomach acid output for almost the whole day. PPIs are considered to stop their inhibitory impact by reactivating the

H^+/K^+ ATPase enzyme, which is assumed to happen when the medicine's antioxidant effect releases the sulphide bond between the enzyme and the drug. This process occurs naturally in the body. Due to its neutral charge and improved capacity to pass through the lipid bilayer membrane of cells, the inactive form of PPIs is more lipophilic. The PPIs have a short plasma half-life, ranging from one to two hours.[5] Proton pump inhibitors have a number of non-gastric acid suppression-related effects. By triggering endogenous protective antioxidant and lowering cytokine release, they have the potential to treat conditions involving endothelium dysfunction, such as preeclampsia, myocardial infarction, and Helicobacter pylori infections, respiratory tract disorders, viral infections, and tumours.[6,8]

Owing to this potential and their capacity to alter the expression of adhesion molecules, a number of studies have shown that PPIs also have anti-inflammatory properties. They can do this by directly influencing inflammatory cells like endothelial cells, neutrophils, and monocytes.[9,10] The ability of omeprazole, the PPI prototype, to suppress nuclear factor-B activation (NK-B), the release of inflammatory cytokines, and neutrophil chemotaxis has been confirmed by Chanchal et al. All things considered, these data suggest that omeprazole's cellular protective action is accomplished by preventing the production of proinflammatory cytokines, boosting the body's natural antioxidant defence system, and preserving the integrity of the injured tissue's internal structure.[11] It has been demonstrated that the degree of lesions is positively correlated with the increased quantity of intrinsic hydroxyl radicals, which, when scavenged by dimethyl sulfoxide, reduce lesions by approximately 90%, indicating a major involvement of hydroxyl radicals in stomach injury. Omeprazole significantly blocks gastric lesions in stress and indomethacin-induced ulcers at lower doses by suppressing stress-induced elevated production of hydroxyl radicals and related protein oxidation and lipid peroxidation, without reducing acid secretion, indicating that its antioxidant effect is crucial for gastro-protection and that its anti-ulcer activity has a separate purpose. In keeping with its antiapoptotic function in averting cell damage during ulceration, omeprazole also halts the stress-induced DNA fragmentation.[12] In addition to reviewing safety issues, this review article describes the current indications for PPIs in the therapeutic management of upper gastrointestinal problems.

2. Physiology of gastric acid secretion

Three phases have historically been identified in the regulation of gastric acid secretion: cephalic, gastric, and intestinal.[13] The food does not enter the stomach until the cephalic

phase has begun. The neurological system receives and processes stimuli from the senses of taste, smell, sight, and even idea of food. Gastric acid secretion is stimulated when the neurotransmitter acetylcholine, which is released by vagal efferent fibres, binds to muscarinic M_3 receptors on the parietal cells of the oxyntic glands. Pituitary adenylate cyclase-activating polypeptide (PACAP) can also directly upregulate histamine-producing enterochromaffin-like (ECL) cells by binding to its receptor, PAC1, which is present on ECL cells.[14] Both central and peripheral mechanisms control the stomach phase of acid secretion. The release of stomach acid is directly stimulated by the chemical makeup of food. For example, G cells release more glutathione when amino acids stimulate them, but fats and carbohydrates block them. Remarkably, research has shown that two active substances (A and B) in beer can activate parietal cell muscarinic M_3 receptors directly.[15] Depending on the degree of the distention, gastric distention can either stimulate or inhibit the release of stomach acid. Reduced gastrin production by G cells results from low-grade distention's activation of vasoactive intestinal peptide (VIP) neurons, which in turn stimulates somatostatin release. On the other hand, higher-grade distention causes cholinergic neurons to be recruited, which in turn causes stomach acid secretion to increase.[16] When chyme reaches the duodenum, the gastric acid secretion process shifts to the intestinal phase. It primarily stimulates the enterogastric reflex and has a negligible effect on the regulation of gastric acid secretion. Whether the metabolome or microbiome is involved in this process is unknown. The suppression of stomach acid secretion is the outcome of this reflex activation.[17] The parasympathetic nervous system primarily stimulates the body via connecting to M_3 receptors on parietal cells**.** Recent research has demonstrated that by blocking the release of somatostatin, stimulation of M_4 receptors on D cells which secrete somatostatin can indirectly increase stomach acid output.[18] The primary hormone that controls the secretion of gastric acid is called gastrin. It is released by stomach G cells that are exclusive to the antrum**.** The main ways that gastrin might increase the production of stomach acid. It primarily acts (indirectly) via interacting to the receptors for cholecystokinin-2 (CCK-2) on ECL cells. Furthermore, by interacting to CCK-2 receptors on parietal cells, gastrin can directly trigger the release of stomach acid. Histamine is the primary paracrine stimulant that stimulates the production of stomach acid. It is expelled by ECL cells found in the body mucosa or oxyntic region.[19]

3. Antioxidant potential of proton pump inhibitors

Numerous studies have looked at the antioxidant properties of different proton pump inhibitors, with varying degrees of success. Esomeprazole's potential anti-fibrotic and antioxidant effects in the treatment of liver fibrosis have been assessed by comparison with the well-known hepato-protective compound silymarin. Esomeprazole reduced fibrosis scores, repaired key histological abnormalities, reversed hepatocellular damage, attenuated lipid peroxidation, and increased antioxidant potential. Moreover, esomeprazole treatment led to the retrieval of the epithelial marker e-cadherin, along with the inhibition of inflammatory mediators like TGFβ, IL-6, and TNF-α and the up-regulation of Bcl_2 protein and down-regulation of hepatic Bax, indicating its role in preventing tissue damage.[20] Additionally, esomeprazole's antioxidant activity has been demonstrated to have a gastro-protective function via blocking the signalling pathway of NF-B and p38 MAPK. Along with lowering MDA levels and other invasive triggers like pepsin, stomach acid, and ROS-related inflammatory damage, esomeprazole treatment also boosted the expression of antioxidant components like GSH and SOD.[21]

Research has shown that lansoprazole has a protective effect against gastric ulcers and oxidative stress-induced liver damage. Pre-treatment with lansoprazole reduced the levels of oxidation drivers like MDA and increased antioxidant parameters like glutathione,[22] GST, SOD, GSH, and catalase, shielding the stomach mucosa and liver from oxidative damage. Similarly, Blandizzi investigated in 2005 potential mechanisms via which lansoprazole protects rats' gastrointestinal tracts from harm caused by several NSAIDs. The results show that lansoprazole protection against NSAID-induced stomach injury requires a reduction in mucosal oxidative damage in addition to preventing gastric acid secretion.[23] The primary cause of death for critically ill patients is stress-related mucosal injury, which causes gastrointestinal blood loss. Pantoprazole prophylaxis has demonstrated encouraging results in lowering clinically significant gastrointestinal bleedings because of its anti-inflammatory and antioxidant properties.[24] Previous research has consistently demonstrated the critical role that several PPI-class medications play in preventing oxidation, which aggravates mucosal injury in patients on the P.U. Whether various PPIs have comparable antioxidant qualities is still up for debate. In order to address this, Swamy and colleagues looked into the potential antioxidant properties of omeprazole, rabeprazole, and lansoprazole. They discovered that omeprazole has the strongest antioxidant potential when compared to other substances and

can significantly lower MDA levels by increasing SOD activity when compared to rabeprazole and lansoprazole.[25]

In a similar vein, research has been done on the potential antioxidant capacity of pantoprazole, omeprazole, esomeprazole, and lansoprazole in order to assist medical professionals in recommending a PPI that possesses both high antioxidant potential and acid-suppression capabilities. According to the study, omeprazole and esomeprazole may provide considerable antioxidant benefits in addition to their acid-suppressive effects when compared to other medications in their class. This could provide the gastrointestinal tract with twofold protection. The chemical structures of the various PPIs were found to be responsible for the variations in antioxidant potential; omeprazole and esomeprazole, in particular, have the strongest electron-donating groups attached to their pyridine and benzimidazole moieties when compared to other drugs. As a result, these agents have the ability to react with free radicals and stabilize them by donating one of the unshared electrons attached to their nitrogen's.[26] Furthermore, an investigation into the variations in the antioxidant effect of different brands of esomeprazole sold in community pharmacies has shown that these variations may exist within the antioxidant potential of the same agent, and more research is required to fully understand this difference.[27]

4. Pharmacology

4.1 Mechanism of action

The fundamental chemical structure of all PPIs is the same as that of substituted benzimidazoles; variations in the type and location of the substituted group account for the variations in the pharmacokinetic and pharmacodynamic properties of individual drugs. Nevertheless, the fundamental mode of action is nearly the same.[28] The main mechanism of action of PPIs is the irreversible inhibition of the hydrogen/potassium adenosine triphosphate (H^+/K^+ ATPase) enzyme system. This system is found in the gastric parietal cells and acts by continuously releasing proton into the gastric lumen; this action is the basis for the system's common name, the proton pump. Since proton pumping is thought to be the last stage of stomach acid production, inhibiting this process will significantly lower the amount of gastric acid produced. Since the PPIs are supplied as prodrugs, their inactive form must first be activated in order for them to start working fully. Prior to the rearrangement step, which yields the compound's active state, the tertiary amines in the drug structure must be protonated in order for PPIs to be activated. Subsequently, the active medication attaches

itself covalently and irreversibly to the H^+/K^+ ATPase machinery, preventing it from pumping protons.[29]

PPIs have an established anti-secretory impact in addition to a direct anti-inflammatory mode of action. By preventing transcriptional activation, they prevent eotaxin-3 production by esophageal epithelial cells stimulated by T_H2 cytokines pathway (STAT6). This PPI mechanism is most likely more significant in the treatment of eosinophilic esophagitis (EoE), but it also shows up in the epithelial cultures obtained from patients with GERD (Gastric Reflux Disease) as well as from EoE patients.[30]

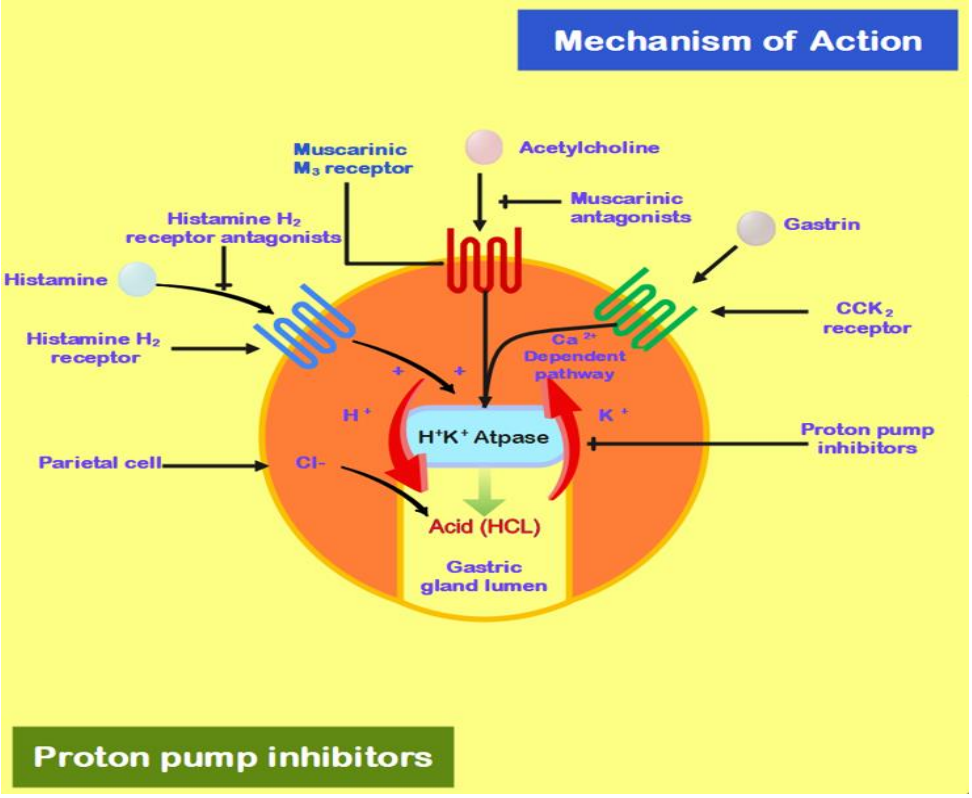

Table 1: The most commonly used Proton pump inhibitors for Ulcer treatment with Mechanism of action, Dosage and their adverse effects.[29]

Category	Drugs	Dosage (mg)	Mechanism of Action (MOA)	Adverse effects
Proton pump inhibitors	Omeprazole	10,20,40	Inhibition of the proton pump (gastric H^+/K^+ ATPase) enzyme system	Headache, stomach discomfort, diarrhoea, nausea, vomiting, constipation, flatulence, Vitamin B12 deficiency, and osteoporosis are among the Adverse effects.
	Lansoprazole	15,30		
	Rabeprazole	20		
	Pantoprazole	20,40		

4.2 Pharmacokinetics

PPIs differ in their pKa, bioavailability, peak plasma levels, and excretion route, but they are similar in structure and mode of action. These variations are not statistically significant, and it is unclear whether they have any clinical significance. When the parietal cell is primed to release acid postprandially, PPIs work best; this association has significant clinical implications for when to provide PPIs. PPIs should be given before to the first meal of the day since the parietal cell has the highest concentration of H^+K^+ ATPase following a prolonged fast. The majority of people only require one daily dosage to achieve the required degree of acid inhibition, and if a second dose is occasionally required, it should be given before dinner.[31]

Approximately 66% of the maximal stomach acid output is inhibited by five days of once-daily PPI medication. Activated enzyme in the canalicular membrane is the only enzyme that PPIs inhibit, hence the reduction of stomach acid secretion following an initial dose is likely to be less than ideal. As when an inactive enzyme is brought into the secretory canaliculus, acid secretion will start up again, albeit more slowly. further H^+K^+ ATPase will have been recruited and then blocked after the second dose, which is administered the next day. next the third dose, further recruitment and likely acid inhibition will take place. In contrast to H_2 antagonists, which operate more quickly, the infrequent use of a PPI taken "as needed" does not consistently result in enough acid inhibition or a consistent or satisfying clinical response**.** After stopping PPIs, the biological reversibility of the disulfide link and enzyme turnover determine whether acid secretion can resume. It could take up to 48 hours for the maximal acid secretory capacity to return.[31]

4.3 Metabolism

Hepatic cytochrome P_{450} enzymes are responsible for the metabolism of PPIs; CYP_2C_{19} plays a major role in this process. Nevertheless, there are notable differences in the PPIs' ability to suppress other pathways in favour of CYP_2C_{19}. Genetic variations also influence CYP_2C_{19} activity to some degree. As a result, two inactivating variants have been identified; in these people, PPI metabolism via this pathway may be delayed.[32,33] These medications are quickly metabolized by homozygotes for the wild type gene, whereas heterozygotes metabolize them more slowly.

PPI metabolism and plasma levels are correlated, and variations in these parameters may account for dose needs and clinical effectiveness variations. For instance, one study looked at

the impact of omeprazole's varied metabolism when treating 62 Japanese patients for H. pylori.[32] All individuals homozygous for a CYP_2C_{19} mutation (i.e., slow metabolizers) had their mutation eradicated, whereas only sixty and twenty-nine percent of heterozygotes and wild type homozygotes, respectively, had successful therapy. In a different study, slow metabolizers had a significantly higher likelihood of being asymptomatic (85 versus 68 and 46 percent, respectively) when compared to heterozygotes and wild type homozygotes in the treatment of 65 patients with gastroesophageal reflux disease (GERD).[34] Just 16 percent of wild type homozygotes with severe GERD showed a response. Moreover, the wild type homozygotes (quick metabolizers) exhibited the lowest levels of lansoprazole in their plasma.

5. Indications for PPI use

5.1 Gastroesophageal reflux disease

The Montreal Consensus Group described gastroesophageal reflux disease (GERD) as a disorder that arises when stomach acid reflux produces uncomfortable symptoms and/or problems.[35] GERD is defined by the American College of Gastroenterology (ACG) as symptoms or difficulties brought on by the reflux of stomach contents into the esophagus, mouth, throat, or even the lungs.[36] Further classification of GERD can be made based on whether erosions are present or absent (erosive reflux disease vs. nonerosive reflux disease, respectively). Pharmacologic alternatives such as PPIs, antacids, and histamine-2 receptor antagonists (H_2RAs) are available for the treatment of GERD. In comparison to H_2RAs or placebo, PPI therapy has regularly shown greater healing rates and decreased relapse rates in cases of erosive esophagitis.[37] PPIs have been shown to have quicker healing rates in cases of erosive esophagitis when compared to H_2RAs or placebos (12% weekly vs. 6% weekly and 3% weekly, respectively). Furthermore, PPIs had the highest cumulative healing rate (84%) across all treatment durations when compared to H_2RAs (52%) and placebo (28%).[38]

PPIs reduce symptoms in about 60% of patients with nonerosive reflux disease and 80% of individuals with erosive esophagitis.[39,40]

For the initial management of erosive esophagitis, the ACG treatment guidelines strongly recommended an 8-week course of PPI therapy in order to promote healing and control symptoms.[36] The guidelines also stated that there was no variation in the way that different PPIs treated erosive esophagitis or its healing process. Esomeprazole was found to have a 5% greater chance of healing erosive esophagitis after 8 weeks and an 8% greater relative improvement in GERD symptom relief at 4 weeks, according to a meta-analysis of 10 trials

involving over 15,000 patients,[41] however, the clinical significance of these findings is unknown. PPIs should be taken one hour before meals to ensure maximum efficacy, with the exception of dexlansoprazole (Dexilant, Takeda Pharmaceuticals) and immediate-release omeprazole with sodium bicarbonate. It is quite effective to use immediate-release omeprazole with sodium bicarbonate before bed to decrease nocturnal acidity.[42] Regardless of when food is consumed, Dexlansoprazole, a dual delayed-release version of R-lansoprazole, can be taken at any time.[43]

In patients with nonerosive reflux disease, PPIs were found to be more efficacious than H_2RAs (related risk, 0.66; 95% CI, 0.60-0.73) and prokinetics (relative risk, 0.53; 95% CI, 0.32-0.87) in a Cochrane systematic review.[44] PPI-assisted continuous maintenance therapy is suitable for individuals with Barrett esophagus or erosive esophagitis who experience a clinical recurrence after stopping therapy. The patient group with nonerosive reflux disease may benefit from intermittent or on-demand PPI medication, as over 60% of them have a return of GERD symptoms over time.[45] In patients with nonerosive reflux disease, on-demand PPI therapy did not result in lower patient satisfaction, according to a systematic study comparing it to continuous PPI therapy.[46] For this patient group, on-demand PPI medication is not, however, FDA-approved. The existence of a hiatal hernia, noncompliance, prolonged illness duration, inadequate dosage, and extraesophageal symptoms are risk factors for inadequate management of GERD symptoms[47] Patients with uncontrolled GERD have few treatment options. While moving to a different PPI is standard clinical procedure, there is no evidence to support this decision. If an H_2RA is added at night, the pH may be more easily controlled during the night. However, this benefit is only momentarily sustained because the H_2RA can cause tachyphylaxis.

5.2 Barrett esophagus

Age over 50, male sex, smoking, central obesity, male sex, and chronic GERD (>5 years) are known risk factors for the development of Barrett esophagus.[48-50] Practically all Barrett esophagus patients receive PPI therapy because it successfully manages reflux symptoms and keeps the esophagitis in these patients from getting worse. According to studies, PPI medication administered continuously may be able to halt the evolution of Barrett's esophagus.[51-54] Regular once-daily PPI medication is advised by the ACG recommendations for the management of Barrett esophagus.[55] Twice-daily dose is not advised until reflux symptoms are not adequately controlled.

5.3 *Helicobacter pylori* Infection

One of the main causes of stomach cancer and peptic ulcer disease is Helicobacter pylori. All individuals who test positive for the illness should get therapy, according to the updated ACG clinical guidelines[56] for the management of H pylori infection. All of which involve the use of a PPI. H pylori infection cannot be completely eradicated by PPI monotherapy. On the other hand, eradication rates are higher when a PPI is added to an antibiotic combination than when antibiotics are used alone.[57] PPIs increase the pH within the stomach and maximize the antibiotics' antibacterial effects when taken concurrently. Moreover, PPIs raise the concentration of antibiotics within the stomach because they reduce the volume of gastric secretory secretions.

5.4 Peptic ulcer bleeding

Among all GI-related conditions, GI bleeding was the most frequent diagnosis for hospital admission in 2012.[58] The most frequent cause of upper gastrointestinal bleeding is still peptic ulcer disease. Intravenous PPI medication is now routinely started for upper gastrointestinal bleeding after the hemodynamic status has been determined and any required resuscitation actions have been carried out. In a randomized experiment, Lau and colleagues[59] found that giving patients an omeprazole infusion continuously after a high-dose bolus was beneficial before they had an endoscopy. Among patients who took omeprazole, 19.1% needed endoscopic therapy, while 28.4% of patients who got a placebo needed it (P=.007). Similarly, among patients with peptic ulcer disease, clean-based ulcers were discovered more frequently (64.2% vs. 47.4%; P=.001) and active bleeding was considerably less common in patients who received omeprazole (6.4% vs. 14.7%; P=.01). The use of PPIs before to endoscopic examination was evaluated in six randomized studies involving 2223 patients,[60] and the results of the review revealed that PPI medication did not significantly lower mortality before endoscopy (odds ratio [OR], 1.12; 95% CI, 0.72-1.73), the need for surgery (OR, 0.96; 95% CI, 0.68-1.35), rebleeding (OR, 0.81; 95% CI, 0.61-1.09). On the other hand, there were significantly fewer endoscopic treatment rates (OR, 0.68; 95% CI, 0.50-0.93) and a significantly lower proportion of peptic ulcers with high-risk stigmata at endoscopy (OR, 0.67; 95% CI, 0.54-0.84). A bolus PPI and continuous infusion are advised by the ACG recommendations for peptic ulcer bleeding[61] in order to reduce the number of patients who have ulcers with high-risk stigmata and the need for endoscopic therapy. If an endoscopy reveals that the patient's bleeding is not due to a peptic ulcer, PPI medication may be stopped. To lower the risk of further bleeding, intravenous PPI

medication should be maintained if endoscopic assessment must be postponed or is not possible.

The use of intravenous PPI therapy (high-dose bolus and continuous infusion) for 72 hours following successful endoscopic treatment of high-risk peptic ulcers is advised by the 2012 ACG recommendations[61] Following an endoscopic assessment of peptic ulcer bleeding, a Cochrane meta-analysis of 22 randomized studies[62] examined the use of an intermittent PPI therapy vs a high-dose bolus PPI with continuous infusion. Risk ratio [RR], 0.85; 95% confidence interval [CI], 0.47-1.54); risk of rebleeding (RR, 1.27; 95% confidence interval, 0.96-1.67); surgery (RR, 1.33; 95% confidence interval, 0.663-2.77); duration of hospital stays (mean difference, 0.26; 95% confidence interval, -0.08 to 0.6); and need for blood transfusion (mean difference, 0.05; 95% confidence interval, -0.21 to 0.3) did not differ significantly. Similarly, a 2014 systematic review[63] comparing intermittent PPI therapy to high-dose PPI therapy following successful endoscopic treatment of high-risk peptic ulcers found that in terms of mortality, need for blood transfusions, and rebleeding within 7 or 30 days, intermittent PPI therapy was not inferior to high-dose PPI plus continuous infusion therapy. However, as the majority of the data favours the use of a continuous infusion, intermittent PPI therapy is not currently advised following endoscopic treatment of peptic ulcers with high-risk stigmata. Lastly, because the risk of significant rebleeding is so minimal, individuals with peptic ulcers with flat, pigmented patches or clean bases just need to take oral PPI medication.[61,64]

5.5 Reducing Gastrointestinal Bleeding Associated with Antiplatelet Therapy and NSAIDs

A crucial component of patients' preventative care when they are at risk of subsequent cardiovascular events is antiplatelet therapy. Aspirin therapy reduced all major cardiovascular events in a meta-analysis of secondary prevention studies, but it also increased the incidence of extracranial bleeding considerably.[65] The risks of upper and lower GI bleeding (RR, 2.3 and 1.8, respectively) were shown to be elevated even with low dose aspirin.[66,67] Patients with acute coronary syndrome are often treated with clopidogrel and aspirin. When compared to aspirin alone, dual antiplatelet treatment (DAPT) decreased the risk of cardiac mortality, myocardial infarction, and stroke in one study; however, it also raised the risk of bleeding from 2.7% to 3.7%.[68] A major randomized trial indicated that DAPT increases the risk of GI bleeding by two to three times; the number needed to harm was 130, and the relative risk

(RR) was 1.78 (95% confidence interval [CI], 1.25-2.54). A history of GI bleeding and complications from peptic ulcer disease are the biggest risk factors for GI bleeding in patients on DAPT. Additional variables include advanced age, concurrent use of NSAIDs or anticoagulant medications, and H pylori infection.[69-73] Aspirin can directly harm the mucosa lining the stomach, but its main impact comes from inhibiting cyclooxygenase systemically, which lowers prostaglandin synthesis.[67] Although clopidogrel is not ulcerogenic, its antiplatelet properties may encourage bleeding at the locations of pre-existing ulcers.[74]

PPIs reduce the production of stomach acid for a maximum of 36 hours,[75] which facilitates the healing of ulcers and erosions, stabilizes thrombi, and lowers the incidence of GI bleeding in DAPT patients. PPIs reduced the incidence of upper gastrointestinal bleeding by 50% in patients using clopidogrel and by 2.8% annually in patients with more than three risk factors, according to research by Ray and colleagues[76] PPI use in addition to clopidogrel decreased gastrointestinal bleeding when compared to clopidogrel alone in observational research involving 8311 participants (RR, 0.19; 95% CI, 0.07-0.49).[77] Fewer GI events were recorded in the DAPT plus PPI arm in a randomized trial[78] comparing patients on DAPT plus PPI to patients taking clopidogrel alone (hazard ratio [HR], 0.34; 95% CI, 0.18-0.63). Consequently, there is evidence to suggest that PPI medication may help patients on DAPT avoid upper gastrointestinal haemorrhage. Nevertheless, a few studies suggested that PPIs might reduce clopidogrel's effectiveness, which would raise the risk of cardiovascular events. Patients on clopidogrel had a higher incidence of cardiovascular events when they used PPIs, according to the CREDO (Clopidogrel for Reduction of Events During Observation) trial.[79] The use of PPIs was not linked to an elevated risk of major cardiovascular events in a retrospective analysis of a randomized study involving 13,608 patients who had percutaneous coronary intervention and were given prasugrel or clopidogrel.[80] There has only been one randomized, controlled study that assessed clopidogrel's effectiveness when used with a PPI 3761 patients with percutaneous coronary intervention or acute coronary syndrome were randomly assigned to receive either clopidogrel alone or clopidogrel and omeprazole at a fixed dose in this trial. Low-dose aspirin was also given to each patient.[78] The incidence of major cardiovascular events did not differ between the two groups (HR, 0.99; 95% CI, 0.68-1.44); however, patients who received omeprazole in addition to clopidogrel experienced a lower rate of gastrointestinal events (HR, 0.34; 95% CI, 0.18-0.63). PPI usage is advised in patients undergoing DAPT who have a history of GI bleeding or numerous risk factors for the condition, according to a joint consensus statement from the American Heart Association, the

American College of Cardiology Foundation, and the American Society of Cardiologists.[81] Patients without GI bleeding risk factors shouldn't take PPIs on a regular basis. As of right now, the FDA advises against giving omeprazole or esomeprazole to anyone taking clopidogrel.[82]

In order to lower the risk of duodenal and stomach ulcers as well as complications brought on by NSAIDs, daily PPI use is advised by the ACG guidelines for the prevention of NSAID-related ulcer complications.[83] In patients on NSAIDs or cyclooxygenase-2 inhibitors, a multicentre, randomized trial comprising 844 participants compared two dosages of esomeprazole (20 and 40 mg) with placebo.[84] If a patient had a history of stomach or duodenal ulcers or was older than 60, they were deemed to be at high risk for developing ulcers. After eight weeks, 5.3%, 4.7%, and 20.4% of patients receiving 20 mg, 40 mg, and placebo, respectively, had ulcers recorded. A comparison was made between a propensity-matched group of 2777 patients who had endoscopic evidence of upper gastrointestinal haemorrhage and 5532 controls.[77] PPI use was linked to a significant reduction in the incidence of bleeding in patients on NSAIDs (RR, 0.30; 95% CI, 0.17-0.53). In order to reduce the risk of upper gastrointestinal bleeding and ulcer formation in at-risk individuals using NSAIDs, PPI use is supported by data from randomized, controlled trials and observational research.

5.6 Dyspepsia

Approximately 20% of persons worldwide suffer from dyspepsia, which is particularly common in women, smokers, and NSAID users.[85] While dyspepsia is expected to cost the US health care system around $18 billion annually, it has a major negative impact on quality of life and individuals in these populations have normal life expectancies.[86,87] The ACG guidelines for dyspepsia suggest that patients under 60 years old who are H pylori-negative or who have had their H pylori eliminated undergo an empirical trial of PPI medication. In individuals with dyspepsia, data compiled from six trials revealed an RR of 0.75 (95% CI, 0.64-0.88) favouring PPI medication over antacid therapy and placebo. PPIs were reported to be superior to H_2RAs in trials comparing the two treatments for dyspeptic patients under 60 years of age (pooled RR, 0.81; 95% CI, 0.72-0.91). The PPI medication was administered once daily in each of these trials. Strong data from randomized trials supported the recommendation of PPI treatment for dyspepsia. For eight weeks, patients with functional dyspepsia who are H pylori-negative or who have had H pylori eliminated should also take

once-daily PPI medication. When PPI therapy was compared to placebo in individuals with functional dyspepsia, pooled data from 15 studies with 5853 patients showed an RR of 0.87 (95% CI, 0.82-0.94) in favour of PPI therapy (number needed to treat = 10).[88]

5.7 Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is defined as a unique clinicopathologic ailment that satisfies the following criteria by the ACG guidelines for the therapy of EoE[88] First signs of esophageal dysfunction; second, eosinophil-predominant inflammation on esophageal biopsy, with a peak value of at least 15 eosinophils per high-power field; third, mucosal eosinophilia isolated to the esophagus that endures following a PPI trial; fourth, ruling out other potential causes of esophageal eosinophilia; and fifth, reaction to treatment (e.g., dietary restriction, topical corticosteroids). PPI-responsive esophageal eosinophilia (PPI-REE) could be a distinct clinical condition. After receiving a course of PPI therapy, patients with PPI-REE experience a remission of their esophageal eosinophilia and symptoms suggestive with EoE, including possible endoscopic signs of the condition. Consequently, all patients with EoE symptoms who are diagnosed with isolated esophageal eosinophilia should have an 8-week PPI trial before undergoing a repeat endoscopy and biopsies, according to the ACG guidelines.[89] Esophageal eosinophilia resolution is categorized as PPI-REE as opposed to EoE. PPI therapy will be beneficial for more than one-third of individuals with esophageal eosinophilia.[90] In this aspect, the working mechanisms of PPIs remain poorly understood. According to one theory, GERD patients' exposure to acid weakens the tight connections between the esophageal epithelium and the stomach, which permits allergen entry and eosinophil recruitment.[91] Alternatively, by preventing the release of eotaxin, which attracts eosinophils, PPIs may directly reduce inflammation on the esophageal epithelium.[92]

6. Clinical limitations of proton pump inhibitors

Given the widespread availability of PPIs in both prescription and over-the-counter versions, along with their shown clinical superiority over H_2RAs, it is reasonable to conclude that these medications cannot be made much better. Conversely, because of unresolved symptoms, up to 50% of patients on PPIs for nonerosive GERD are unsatisfied with their treatment.[93] The short plasma half-life and the requirement for pre-prandial dosing are serious issues, even though a number of non-PPI related factors (such as UGI motility disorders, duodenogastric-esophageal reflux, visceral hypersensitivity, and patient hypervigilance) may also play a role in this insufficient response. Approximately 40% of patients who were using PPIs twice a day

raised their dosage due to persistent symptoms that occurred at night.[94] When taking single release PPIs once daily in the AM, patients often experience "nocturnal acid breakthrough," or an overnight recovery of stomach acid secretion.[95] Following the practice guidelines of the American College of Gastroenterology[96] and the American Gastroenterology Association**,** the dosage is commonly increased twice daily. Even with this frequent intervention, many patients still experience breakthrough symptoms when taking the medication twice daily.[97] Pharmacologically, intragastric pH below 4 occurs 15% of the time when healthy volunteers receive 40 mg of esomeprazole twice a day.[98]

There is a serious lack of understanding regarding the significance of when to take medication. As was previously mentioned, in order for PPIs to bind, the parietal cell canaliculi membrane must express the proton pump. Since cytosolic pumps—those found inside lipid rafts-are inaccessible, they won't be impacted. About half of patients don't take their PPIs within an hour after breakfast[94,97] and it's possible that their doctor or pharmacist didn't tell them to[99] One major factor contributing to PPI failure may be poor compliance coupled with a limited window of efficacy because of plasma half-life.[93]

6.1 Long term use of proton pump inhibitors

Because acid promotes the digestion and ionization of less soluble forms of dietary calcium as well as the release of food-bound vitamin B12, chronic high-dose PPI use is thought to have an impact on the absorption of calcium, magnesium, and vitamins B12.[100] A nested, case-controlled series conducted in 2006 with over 13,000 patients from the UK revealed that the risk of hip fracture rose with the length of PPI use (OR, 1.44), and it increased more in patients who had taken high-dose PPIs (OR, 2.65).[101] This study, while significant, has drawn a lot of criticism due to patient heterogeneity among study arms and varying PPI usage prevalence (e.g., PUD among fracture patients), which could account for observed fracture differences without establishing causality. A subsequent investigation that excluded patients with significant hip fracture risk factors found no correlation between PPI use and suggested that the prior results might have been influenced by confounding.[102] In the end, it appears that there is still uncertainty regarding the danger associated with PPI use, despite the literature's continuous trend of retrospective assessment and analysis.[103] However, the U.S. FDA mandated in 2010 that all PPI manufacturers update the warning on their product labels regarding the potential risk of hip, wrist, and spine fractures when using the drug at high doses (More than once daily) or for an extended period of time (More than a year).

A possible connection between the emergence of community-acquired pneumonia and PPI use has also been shown by retrospective observational studies and their meta-analyses.[104,105] According to a meta-analysis incorporating eight observational studies, the use of PPIs was linked to a 27% higher risk of pneumonia, either obtained in a hospital or the community (OR, 1.27). However, the highest risk was observed within 7 days after starting PPI medication (OR, 3.95).[104] This early risk was previously shown to exist.[106] It's noteworthy that the result happens before PPIs reach their maximum efficacy. There was no higher risk of pneumonia, according to a more recent systematic evaluation of studies that included only patients who were prescribed PPI medication for NSAID usage that had just started. The authors of this study contend that protopathic bias-arising from the inclusion of individuals with GERD, a risk factor for pneumonia-or from the misdiagnosis of early pneumonia symptoms mistaking for GERD, may have contributed to the previously noted connection.[105] This association is speculative in the lack of prospective, high-quality evidence, and it has no bearing on our decision to prescribe antisecretory medicine to patients who have a clear indication.

Additionally, research suggests that the use of PPIs may increase a patient's vulnerability to a variety of enteric infections, such as Salmonella, Campylobacter jejuni, Clostridium difficile, and small intestinal bacterial overgrowth.[106,107] C. difficile (CDI) infection is particularly significant because of the increased health burden and related morbidity that this issue poses. A meta-analysis of 42 observational studies involving approximately 313,000 patients in 2012 discovered a correlation between PPI usage and incident (OR,1.7) and recurrent (OR,2.5) CDI. The U.S. FDA released a medication safety communication as a result of this observation, highlighting the significance of PPI exposure. However, it is still unclear how the dosage and duration of PPI treatment affect this association. As was previously mentioned, the cytochrome P450 isozyme 2C19 metabolizes all PPIs to some degree. Although this PPI pharmacological characteristic has long been understood, it has only lately drawn a great deal of attention. PPI-induced enzyme inhibition specifically has the potential to prevent clopidogrel (Plavix®) from activating, which has prompted a rush of modifications, articles, and warnings. This interaction was initially noticed in in vitro experiments that showed simultaneous omeprazole treatment reduced clopidogrel's efficacy on platelet inhibition.[108]

The FDA advised against taking both medications at once in 2009. Despite this first worry, there is no in vivo evidence linking the use of clopidogrel with omeprazole to worse clinical outcomes. Furthermore, it has not been consistently shown that this in vivo connection exists with other PPIs whose metabolism is less reliant on 2C19.[109] Despite this, we avoid using omeprazole (and its stereoisomer, esomeprazole) in patients on clopidogrel, preferring to use pantoprazole, lansoprazole, or dexlansoprazole instead, given our understanding of the pharmacodynamics. Based on 61 unique case reports, the FDA released a class warning in 2011 suggesting that long-term PPI usage may cause low magnesium levels. Although the exact cause and frequency of PPI-associated hypomagnesemia are unknown, the FDA advises monitoring magnesium levels on a regular basis in patients who may require long-term PPI treatment, who take PPIs along with digoxin, or who take medications that have the potential to cause hypomagnesemia, such as diuretics.[111] Additional recent FDA-mandated PPI class warnings include the risk of vitamin B12 insufficiency with chronic (more than three years) daily PPI usage and PPI-associated acute interstitial nephritis.

6.2 Advances in PPI technology

Many attempts have been undertaken to address the pharmacologic constraints that come with the present PPIs, including their requirement for pre-prandial dose and short plasma half-life, which results in a brief duration of impact. The first imidazopyridine PPI, tenatoprazole, has shown to have a much longer half-life (8 hours after a single dose and 14 after several doses) than PPIs that are currently on the market. It has also shown greater inhibitory effect on H+/K+ ATPase. The area under the plasma concentration curve (AUC) rises by more than 20 times as a result of this half-life increase, indicating higher tissue exposure and an extended duration of impact at the parietal cell canaliculus.[112-114] Although there are currently no conclusive therapeutic efficacy trials available, this modification to the PPI structure holds exciting possibilities for the future. The issues presented by short serum half-life have also been addressed by modifications in the formulation of already marketed PPIs. Five separate 10 mg tablets that are intended to be broken down and absorbed gradually throughout the small intestine and colon are contained in each 50 mg capsule of rabeprazole-ER. When compared to esomeprazole and traditional delayed-release rabeprazole, rabeprazole-ER demonstrated better control of nocturnal stomach acid secretion in research including healthy participants. However, rabeprazole-ER was not found to be superior to esomeprazole in two parallel double-blind trials for the treatment of severe erosive

esophagitis (classified as Los Angeles Classification grade C or D) and the alleviation of concomitant heartburn100. As a result, the compound's clinical development was stopped.[115]

The purpose of dual-release dexlansoprazole is to release the medication in two distinct, pH-controlled phases. At a pH of 5.5, 25% of the medication dose is released in the proximal small intestine. Pharmacokinetics (peak plasma concentration in 1–2 hours) are comparable to those of conventional enteric coated PPIs. Five to six hours after delivery, a second release of 75% of the drug dose occurs in the more distal small intestine at a pH of 6.75, producing a second peak in the serum. Similar to tenatoprazole, this drug raises the mean 24-hour intragastric pH and increases the AUC overall compared to its stereoisomer lansoprazole. Patients who have to take their medication twice a day to regulate their symptoms, who have trouble adhering to mealtime schedules, or who have persistent nocturnal symptoms may benefit from this.[116]

An alternative approach to circumvent the requirement for premeal dosage would be to combine the PPI with a stomach acid secretion stimulant. Succinic acid is a pharmaceutical excipient that has FDA approval and works similarly to Penta gastrin. This compound is "generally recognized as safe" and has been used as an acidity regulator in the food and beverage industry in the past. Omeprazole (Vecam®) and succinic acid together showed noticeably superior nocturnal intragastric pH regulation than omeprazole alone in a preclinical investigation with 36 healthy participants. There is presently a Phase IIb clinical trial ($NCT_{01059383}$) assessing participants who have heartburn.[117]

7. CONCLUSION

PPIs are a vital component of the gastroenterologist's armament for handling common clinical issues in the modern era. They are quite effective in treating diseases connected to acid reflux in general. Despite this, the widespread use of PPIs and their careless use have prompted insurers to exercise more monitoring and legitimately express concern over the possibility of persistent hypochlorhydria and drug interactions. When using any medication, including PPIs, responsibly, the doctor must carefully evaluate the patient's cofactors, the right indication, the predicted dosage, and the length of the recommended course of treatment. PPIs are very useful medications, although they have flaws because of their pharmacologic restrictions, to some extent. The creation of a non-benzimidole PPI and advanced delivery methods to lessen the issues related to their brief half-life and required pre-prandial dose are two innovative strategies being investigated to get around these restrictions.

It is yet to be shown whether these methods have a definite clinical benefit or bring unexpected issues.

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