JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

UNDERSTANDING AND APPROPRIATE USE OF PPIs

URVASHI GARG*[1], SUSHIL SINGHAL [2], PRIYANSHU TANGRI [3]

1 Student Of Department Of Pharmacology M.Pharm 4Th Sem,GRD PG IMT Dehradun Uttarakhand, India Pin-248009

2 Assosiate Professor GRD PG IMT Dehradun Uttarakhand, India Pin-248009

3 Professor GRD PG IMT Dehradun Uttarakhand, India Pin-248009

ABSTRACT

Drug usage is common because of usefulness, safety profile, effectiveness, and tolerability. At a cost of GBP 82 million annually and with nearly 35 million prescriptions filled, omeprazole was the second most distributed item in England in 2020.PPIs are the mainstay in the treatment of dyspepsia, GERD, ZE syndrome, Helicobacter pylori (H. pylori) eradication, gastric and duodenal ulcers, dyspepsia, and the management and avoidance of ulcers linked to non-steroidal anti-inflammatory drugs (NSAIDs).The survey highlights the importance of communication between patients and healthcare providers, with many expressing a requirement for better information and support.This all-encompassing strategy may result in better patient outcomes, reduced side effects, and more informed and engaged patients.

KEYWORD- Proton pump inhibitor, ulcer, gastroesophageal reflux disease, Helicobacter pylori

INTRODUCTION

BACKGROUND

Acid-labile promedicines with a weak basicity that decrease stomach acid output are known as proton- pump inhibitor (PPIs) [1]. Omeprazole, rabeprazole, and dexlansoprazole are among the medications of the PPI class. PPIs are the mainstay in the treatment of dyspepsia, GERD, ZE syndrome, Helicobacter pylori (H. pylori) eradication, gastric and duodenal ulcers, dyspepsia, and the management and avoidance of ulcers linked to non-steroidal anti-inflammatory drugs (NSAIDs) [2, 3]. Additionally, prophylaxis against gastritis linked to corticosteroids, anticoagulants, chemotherapy, and coronary heart disease is frequently used "off label" [4, 5].These Drug usage is common because of usefulness, safety profile, effectiveness, and tolerability. At a cost of GBP 82 million annually and with nearly 35 million prescriptions filled, omeprazole was the second most distributed item in England in 2020 [6]. With over 52 million prescriptions written, omeprazole was the ninth

most prescribed drug in the USA in 2019 [7]. PPIs cost the United States $19.99 billion in 2016–17 [8]. While PPIs are typically regarded as safe when taken for a short while, there is growing evidence that prolonged usage of PPIs can have substantial negative effects. These possible dangers include a higher chance of developing pneumonia, an intestinal infection, a bone fracture, malignancies of the digestive tract, and a decreased ability to absorb vitamins and minerals [2, 9].

DISCOVERY

Timoprazole was discovered in 1975 to suppress acid secretion regardless of external or intracellular stimulation. [10] Research on timoprazole showed atrophy of the thymus gland and expansion of the thyroid gland as a result of iodine absorption inhibition. A review of the literature revealed that some mercaptobenzimidazoles that had been substituted had no effect on the uptake of iodine. When these substituents were added to timoprazole, the harmful effects were eliminated without diminishing the antisecretory benefit. [11] Omeprazole, a timoprazole derivative, was the first of a new class of drugs known as proton pump inhibitors (PPIs) that regulate stomach acid secretion. It was discovered in 1979. The benzimidazole molecule of omeprazole was also modified by adding 5-methoxy-substitution, which significantly increased the compound's stability at neutral pH. [11] Omeprazole was introduced into Phase III human trials in 1982 following the filing of an Investigational New Drug (IND) application in 1980.[11]Omeprazole, which was first commercialized as Losec in Europe and Prilosec in the US in 1990, was a novel strategy to treating acid-related disorders. It was soon demonstrated to be therapeutically superior than histamine H2 receptor antagonists. More than 800 million by 2004 individuals had received treatment with Losec globally, making it the most successful medication ever sold in the world in 1996. About forty more companies joined the PPIs market in the 1980s, but merely a tiny percentage of them—Takeda with lansoprazole, Byk Gulden (now Nycomed) with pantoprazole, and Eisai with rabeprazole—achieved commercial success. [10]

DEVELOPMENT

The clinical pharmacology of omeprazole, lansoprazole, pantoprazole, and rabeprazole varies slightly while having similar structures and mechanisms of action. Modest but potentially significant variations in pyridine and benzimidazole substituents lead to differing physical and chemical characteristics. When pantoprazole sodium was directly compared to other anti-secretory medications, it was found to be either as effective as or superior to other clinically used PPIs, as well as far more effective than H2 receptor antagonists. [12]According to a different study, rabeprazole converts to the sulphenamide form more quickly than omeprazole, lansoprazole, and pantoprazole and experiences activation over a wider pH range. [13] Because of the medications' quick breakdown in the stomach's acidic environment, the most of oral PPI preparations are enteric-coated. Omeprazole, for instance, is much more stable at pH 7 (half-life of around 20 hours) than it is at pH 1-3, where it is unstable for 2 minutes. The secretory canaliculus's lumen is not penetrated by the acid protective layer, which stops the driving force in the stomach lumen from converting to it. The active principle will next act with any available sulfhydryl group in food.[10] PPIs possess a strong oral bioavailability rate: 89% for esomeprazole, 80–90% for lansoprazole, and 77% for pantoprazole. With the exception of tenatoprazole, all PPIs are quickly broken down in the liver by CYP enzymes, primarily CYP2C19 and CYP3A4. PPIs have distinct pharmacokinetic characteristics and are susceptible to CYP enzymes. Esomeprazole and tenatoprazole exhibit greater acid suppression and a longer duration of intragastric pH (pH > 4) in studies evaluating the effectiveness of PPIs.Development and discovery in clinical pharmacology Research examining tenatoprazole's impact on acid secretion in in vivo animal models, including rats with ligated stomach pylori and those with acute gastric fistulas, revealed a 2- to 4-fold increase in inhibitory action in comparison to omeprazole. Several types of induced gastric lesions also shown a more powerful inhibitory

action. Tenatoprazole showed a seven-fold longer half-life than the current H + /K + ATPase inhibitors in both Asian and Caucasian healthy volunteers. Therefore, a longer half-life is thought to cause a longer-lasting suppression of stomach acid output, particularly at night. There is just one clear correlation between the reported rate of recovery and symptom alleviation and the extent and and gastric acid duration inhibition, as determined by monitoring the stomach pH during a 24-hour period in pharmacodynamic trials. Tenatoprazole was determined to be substantially more potent than esomeprazole during the night, as shown by a clinical research that found the length of Acid breakthrough throughout the night was significantly shorter for 40 milligrammes of tenatoprazole compared to 40 mg of esomeprazole. However, more research is necessary to determine the therapeutic use of this pharmacological benefit.PPIs have been effectively employed in triple-therapy regimens containing amoxicillin and clarithromycin to eradicate Helicobacter pylori, with no discernible differences observed between PPI-based regimens. [13]

PHYSIOLOGY OF GASTRIC ACID SECRETION

Gastric acid secretion regulation

The highly acidic stomach lumen (pH <2), created by the gastric parietal cells' secretion of hydrochloric acid, kills germs derived from food, aids in food digestion, and enhances the absorption of minerals including phosphate, calcium, and iron. Increased acid output is another factor that could be detrimental to the stomach mucosa's integrity. The gastric mucosa must therefore preserve a balance between mucosal defense systems and acid secretion. The stomach's extrinsic and intrinsic neuroendocrine system maintains a safe range of acid output by balancing the consequences of agonists and antagonists. The knowledge currently available about how the stomach mucosa integrates the physiological balance between stimulatory and inhibitory pathways is highlighted here[14]

Proton Pump function in Acid Production

PPIs typically consist of substituted pyridylmethylsulfinyl benzimidazoles as their fundamental structure [15]. In vivo, the PPI timoprazole reduced the of acid in the stomach regardless of the agitation mechanism (aCh, histamine, or dibutyryl cAMP). Timoprazole could suppress acid secretion when acid transfer was present, but it was ineffective when H+-K+-ATPase was not involved in acid transport. The results of these early investigations revealed that the first PPI were triggered by acid, that was a crucial step in figuring out how PPIs interacted using the H+-K+-ATPase

[16].PPIs were an improvement over H2-receptor antagonists because the irreversible covalent binding of the H+-K+-ATPase pump resulting in a longer half-life of stomach acid suppression than for H2 receptor blockers. [14]. Following pyridine protonation, PPIs gather within the canaliculus secretory of parietal cells. Disulphide bonds are formed between PPIs and one or more accessible cysteines after they are activated following an additional protonation on the H+-K+-ATPase surface [17]

On the α-subunit of the stomach H+-K+-ATPase, cysteine 813 is reacted with by all PPIs. PPI-induced inhibition of H+-K+-ATPase within the E2 setup is caused by cysteine 813. In the extracytoplasmic region of the stomach H+-K+-ATPase α-subunit, several PPIs bind to additional locations, such as cysteine 892 for omeprazole and 822 cysteine for pantoprazole[18,19] The ability of omeprazole to reverse is probably partly because of the luminal exposure of cysteines of the H+-K+-ATPase, 813 and 892.Nevertheless, because of their intramembranous position and subsequent irreversibility, some PPIs become inaccessible to reducing

agents consequent to their covalent binding with cysteine 822, which is existence within the pump's transport domain close to ion binding sites[18,19] Poor bases are PPIs. PPIs' weak base pKa makes it is simpler for them to accumulate on the outside the H+-K+-ATPase pump's surface or when the acidity is high region seen within the activated parietal cells' secretory canaliculi. Among the causes.PPIs work so well is because of this feature. PPI concentrations where binding to occurs, in the secretory canaliculus H+-K+-ATPase takes place, are far greater than those of blood levels.In PPIs, compound benzimidazole undergoes protonation after the pyridines first. Because it enables close proximity to the H+-K+-ATPase facilitates the transformation of the prodrug into the active form rather than within the abdomen lumen, the necessity of a second PPI protonation boosts their medicinal effectiveness. Through disulfide bonds, PPIs bind irreversiblyin reaction to the protonation that occurs, to accessible cysteines of the H+-K+-ATPase controls PPI activation.[20]

Acid-Related Disorders

Acid reflux disorder (GERD) is a broad category of disorders affecting the stomach, duodenum, and esophagus. In US, GERD accounts for over part of the illness burden, with a frequency of long-term acid-related illnesses of about 2.3%. 44.9% or more of patients may have a single or more upper gastrointestinal symptoms, according to other reports. Over 60 million people in the US have GERD, making it Among the most prevalent GI ailments. As much as 20% of people experience at least twice a week in symptoms [21].

Gastroesophageal reflux disease

The esophagus mucosa is exposed to acidic stomach contents, pepsin, and bile acids, which causes illness caused by reflux of the stomach. The stomach's anatomical and functional relationships, lower esophageal sphincter, gastroesophageal junction, and neurological system are the reason behind reflux. Changes in reflux result in modifications to the esophageal protection and clearance processes. The esophagus mucosa may be damaged by GERD, a chronic condition that typically manifests as erosive esophagitis. Nonetheless, it is thought that between 50 and 70 percent of those with GERD never experience esophagitis; these individuals are known as having NERD. The typical symptoms of individuals with GERD are regurgitation both acidic and heartburn. 90% of the time, a clinical When these two are present, a diagnosis can be made .[22]

Peptic ulcer disease

The cornerstone providing care for people who have PUD is antisecretory therapy. In fact, there acted as a significant improvement in rates of recovery and cure since PPIs were introduced. Eliminating the When H. pylori is present,completely changed the way PUD is treated and is currently the cornerstone of care. This has caused a decrease in the frequency of ulcers and a high rate of ulcer healing, especially in those who have with duodenal ulcers. It was discovered that H. pylori removal combined with antisecretory therapy was optimal than antisecretory medication alone in 34 studies combined into a meta-analysis involving individuals with duodenal ulcers, with a 14-person treatment requirement.[23]

Duodenal ulcers

FDA-approved therapies often involve an amalgamation of already available PPIs and either metronidazole or clarithromycin-amoxicillin. The three that are authorized for a 10-to 14-day regimen are omeprazole, lansoprazole, and esomeprazole. according to trial data showing similar results in comparison with control regimens utilizing omeprazole for 10 days, rabeprazole can be utilized in a 7-day regimen. According to European research, H. pylori can be successfully eradicated with PPI-based triple therapy in as little as 4-5 days. These brief eradication regimens also improve patient compliance and lower the likelihood of medication side effects [24]

Gastric ulcers & NSAID-induced mucosal injury

Numerous tactics have been created to stop NSAID-induced gastropathy, moreover, a few of them are frequently used in medical settings. These tactics include co-administration of H2RAs, PPIs, gastroprotective drugs, and COX-2-specific inhibitors (coxibs). It's interesting noting that those who are afflicted with gastric ulcers typically show usual or reduced both induced and basal acid production [21]. NSAID-induced ulcers arise in the stomach more often because of abnormalities during mucosal defences.Since most gastric ulcers heal following eight weeks of therapy when the stomach pH is kept over 3 for 18 to 20 hours a day, suppressing acid continues being the cornerstone therapy for this illness [25].

Helicobacter pylori & NSAID use

There is disagreement about the best course of action for treating NSAID users who have H. pylori infection, and it is unclear how exactly the infection contributes to ulcerogenesis and complications in NSAID users. While the significance of The PPIs inside the context NSAID usage is well documented, the significance of eliminating H. pylori in GI prevention disease when using NSAIDs is not comfortable understood. However, potential for developing an ulcer is considerably decreased in individuals those who will shortly start NSAID medication therapy if they undergo screening for and H. pylori eradication. Nevertheless, it remains unclear to what extent eradication is advantageous for those who are already receiving long-term NSAID medication [26].

PPI therapy for ulcers

When high-dose omeprazole is administered to individuals with bleeding peptic ulcers and recent bleeding symptoms, the likelihood of more bleeding and the need for surgery are reduced According to this method, the sustained effective acid suppression of oral formulations may help prevent rebleeding when high-dose oral PPIs are used twice daily.But when it comes to treating acute ulcer bleeding or ulcers with high-risk stigmata for bleeding, the standard practice now is to administer intravenous formulations of PPIs at doses that include an initial bolus of 80 mg followed by a continuous infusion of 8 mg/h of omeprazole or pantoprazole.[27]

Conclusion

In conclusion, understanding and appropriately using proton pump inhibitors (PPIs) is crucial for effective management of conditions like gastroesophageal reflux disease and peptic ulcers. While PPIs offer significant benefits in reducing stomach acid, their long-term use should be carefully monitored due to potential side effects and risks. Healthcare providers must assess the necessity and duration of PPI therapy, considering alternative treatments and lifestyle modifications. Educating patients about the benefits and risks of PPIs will empower them to make informed decisions about their treatment, ultimately enhancing their health outcomes.

References

Howden CW, Ballard ED, Koch FK, Gautille TC, Bagin RG (2009) Control of 24-hour intragastric acidity with morning dosing of immediate-release and delayed-release proton pump inhibitors in patients with GERD. J Clin Gastroenterol 43(4):323–326

New Zealand Formulary (NZF) (2021) New Zealand Formulary (NZF), NZF v[114]. Available from: www.n zf. org. nz. Accessed 1 Dec 2021

National Institute for Health and Care Excellence (NICE) (2019) Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management Clinical guideline (CG184). Available from: https:// www. nice. org. uk/ guida nce/ cg184/ chapt er/ Appen dix- A- Dosage- infor mation- on- proton- pump- inhib itors. Accessed on 1 Dec 2021

National Institute for Health and Care Excellence (NICE) (2019) Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management Clinical guideline (CG184). Available from: https:// www. nice. org. uk/ guida nce/ cg184/ chapt er/ Appen dix- A- Dosage- infor mation- on- proton- pump- inhib itors. Accessed on 1 Dec 2021

Ntaios G, Chatzinikolaou A, Kaiafa G, Savopoulos C, Hatzitolios A, Karamitsos D (2009) Evaluation of use of proton pump inhibitors in Greece. Eur J Intern Med 20(2):171–173

National Health Service (NHS Digital). Prescription cost analysis -England (2020/2021) 2020. Available from: https:// www. stati sta. com/ stati stics/ 378445/ presc ripti on- cost- analy sis- top- twenty- chemicals- by- items- in- engla nd/ Accessed 27 Sept 2021

ClinCalc.com. Omeprazole. Drug usage statistics, United States 2013-2019. Available from: https:// clinc alc. com/ DrugS tats/ Drugs/ Omepr azole. Accessed 9 Jun 2022

Mishuk AU, Chen L, Gaillard P, Westrick S, Hansen RA, Qian J(2020) National trends in prescription proton pump inhibitor use and expenditure in the United States in 2002–2017. J Am Pharm Assoc (2003)

National Institute for Health and Care Excellence (NICE). Guidance for safe and effective use of proton pump inhibitors (PPIs). 2020. Available from: https:// www. barns leyccg. nhs. uk/ CCG/ 20Dow nloads/ Membe rs/ Medic ines/2 0mana gemen t/ Area/2 0pre scribi ng/2 0com mittee/ 201803- 04/ 20-/ 20APC/ 20Memo/ 20Enc losure/ 20-/ 20Gui dance/20for/ 20Safe/ 20and/ 20Eff ective/ 20use/ 20of/ 20Pro ton/ 20Pump/20Inh ibito rs/ 20-/ 20Mar ch- April/ 202018. pdf. Accessed on 26 Apr2022

Sachs, George; Shin, Jai Moo; Vagin, Olga; Lambrecht, Nils; Yakubov, Iskandar; Munson, Keith (2007-7). "The gastric H,K ATPase as a drug target: past, present, and future". Journal of Clinical Gastroenterology 41 Suppl 2: S226–242. doi:10.1097/MCG.0b013e31803233b7. ISSN 0192-0790. PMID 17575528. PMC 2860960. https://www.ncbi.nlm.nih.gov/pubmed/17575528.

Shin, Jai Moo; Munson, Keith; Vagin, Olga; Sachs, George (2009-1). "The gastric HKATPase: structure, function, and inhibition". Pflugers Archiv: European Journal of Physiology 457 (3): 609–622. doi:10.1007/s00424-008-0495-4. ISSN 0031-6768. PMID 18536934. PMC 3079481. https://www.ncbi.nlm.nih.gov/pubmed/18536934

. Lindberg, Per; Carlsson, Enar (2006-06-21). Fischer, János. ed. Analogue-based Drug Discovery. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA. pp. 81–113. doi:10.1002/3527608001.ch5. ISBN 9783527608003. http://doi.wiley.com/10.1002/3527608001.ch5.

Arif Fadlan[i], Sarmoko,Discovery and development of proton pump inhibitors,WikiJournal of Medicine,2019 page no.3-4

Quigley EM, Turnberg LA. pH of the microclimate lining human gastric and duodenal mucosa in vivo. Studies in control subjects and in duodenal ulcer patients. *Gastroenterology* 92: 1876–1884, 1987. doi: 10.1016/0016-5085(87)90619-6. [PubMed] [CrossRef] [Google Scholar]

Fellenius E, Berglindh T, Sachs G, Olbe L, Elander B, Sjöstrand SE, Wallmark B. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H+ + K+)ATPase. *Nature* 290: 159–161, 1981. doi: 10.1038/290159a0. [PubMed] [CrossRef] [Google Scholar]

Wallmark B, Sachs G, Mardh S, Fellenius E. Inhibition of gastric (H+ + K+)-ATPase by the substituted benzimidazole, picoprazole. *Biochim Biophys Acta* 728: 31–38, 1983. doi: 10.1016/0005-2736(83)90433-9. [PubMed] [CrossRef] [Google Scholar]

Shin JM, Cho YM, Sachs G. Chemistry of covalent inhibition of the gastric (H+, K+)-ATPase by proton pump inhibitors. *J Am Chem Soc* 126: 7800–7811, 2004. doi: 10.1021/ja049607w. [PubMed] [CrossRef] [Google Scholar]

Besancon M, Shin JM, Mercier F, Munson K, Miller M, Hersey S, Sachs G. Membrane topology and omeprazole labeling of the gastric hydrogen ion-potassium-adenosinetriphosphatase. *Biochemistry* 32: 2345–2355, 1993. doi: 10.1021/bi00060a028. [PubMed] [CrossRef] [Google Scholar]

Sachs G, Shin JM, Besancon M, Prinz C. The continuing development of gastric acid pump inhibitors. *Aliment Pharmacol Ther* 7, Suppl 1: 4–12, 1993. doi: 10.1111/j.1365-2036.1993.tb00582.x. [PubMed] [CrossRef] [Google Scholar]

Shin JM, Sachs G. Restoration of acid secretion following treatment with proton pump inhibitors. *Gastroenterology* 123: 1588–1597, 2002. doi: 10.1053/gast.2002.36593. [PubMed] [CrossRef] [Google Scholar

Laine L, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology.* 2008;135:41–60. [PubMed] [Google Scholar]

Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet.* 1990;335:205–208. [PubMed] [Google Scholar]

Ables AZ, Simon I, Melton ER. Update on *Helicobacter pylori* treatment. *Am Fam Physician.* 2007;1:351–358. [PubMed] [Google Scholar]

Vakil N, Lanza F, Schwartz H, Barth J. Seven-day therapy for *Helicobacter pylori* in the United States. *Aliment Pharmacol Ther.* 2004;20:99–107. [PubMed] [Google Scholar]

Huang JQ, Hunt RH. pH, healing rate and symptom relief in acid-related diseases. *Yale J Biol Med.* 1996;69:159–174. [PMC free article] [PubMed] [Google Scholar]

. Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of Helicobacter pylori eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Helicobacter Eradication for Lesion Prevention. *Lancet.* 1998;352:1016–1021. [PubMed] [Google Scholar]

Katz PO, Scheiman JM, Barkun AN. Review article: acid-related disease – what are the unmet clinical needs? *Aliment Pharmacol Ther.* 2006;23(Suppl 2):9–22. [PubMed] [Google Scholar]