ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

Proton Pump Inhibitors, In terms of Pharmacology

Dr. Vaishali Lote[1]*, Dr. Shaktibala Dutta[2], Dr. Jyotsna Sharma[3]

[1] Assistant Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

[2] Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

[3] Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

ABSTRACT:

The H,K-ATPase that is found in the stomach is the key target for the treatment of disorders connected to acid. PPIs are weak bases that are made up of two different moieties: a substituted pyridine that has a primary pKa of about 4.0 and a benzimidazole that has a secondary pKa of about 1.0. This allows for selective accumulation in the secretory canaliculus of the parietal cell. Proton pump inhibitors (PPIs) are used to treat conditions such as peptic ulcer disease. PPIs are acid-activated prodrugs that, when exposed to an acidic environment, transform to sulfenic acids or sulfenamides, which then react covalently with one or more cysteines that are accessible from the luminal surface of the ATPase. Their inhibitory effects continue for a far longer period of time than their plasma half-life does because of the covalent binding. However, their efficacy in acid suppression is diminished, particularly throughout the night, due to the short half-life of the medication in the circulation as well as the requirement for acid activation. PPIs that have a longer half-life have the potential to provide better acid control. Every proton pump inhibitor (PPI) is capable of producing beneficial outcomes in patients with reflux esophagitis and peptic ulcer disease. When used in conjunction with antibiotics, PPIs are able to completely eradicate Helicobacter pylori.

Keywords*:* Suppression, Neurotransmitters, Luminal Surface, Acid, Enzyme Systems

INTRODUCTION:

From its resting condition to its stimulated state, the parietal cell goes through significant morphologic changes when it is activated by stimuli such as histamine and acetylcholine. These stimuli are examples of neurotransmitters. When the parietal cell is in its activated condition, the gastric H,K-ATPase that pumps stomach acid appears to be in the microvilli of the enlarged secretory canaliculus. When the parietal cell is in its resting state, it appears to be in the cytoplasmic tubular membranes of the parietal cell. This morphological alteration may have resulted from the fusion of cytoplasmic vesicles with the rudimentary microvilli to generate the elongated microvilli of the enlarged secretory canaliculus [1,2]. This hypothesis has been put forward. In the stimulated state, the gastric H,K-ATPase travels from the tubulovesicles to the apical membrane in the canaliculus. There, it is responsible for the

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

secretion of stomach acid by an electroneutral, ATP-dependent exchange of hydrogen and potassium [3]. The enzyme makes use of extracellular potassium in order to produce acid by exchanging cytoplasmic hydronium for extracellular potassium. This process is known as hydronium exchange. Through the insertion of K+ Cl– (KCNQ1, Clic6) channels into the microvillus membrane, the cation is able to make its way to the luminal surface of the ATPase.

PPIs, also known as proton pump inhibitors, work by decreasing stomach acid secretion by blocking the enzyme H,KATPase. Because of this effect, it is possible to repair peptic ulcers, gastroesophageal reflux disease (GERD), Barrett's oesophagus, and Zollinger-Ellison syndrome. Additionally, it is possible to eradicate Helicobacter pylori when used in combination with other treatments. In this article, the structure and function of the enzyme known as gastric H,K-ATPase, as well as the PPIs that block this enzyme, are discussed.

The Gastric H,K-ATPase

One of the ATPases that belongs to the P2 subfamily is the gastric ATPase. The phosphorylation of the catalytic subunit by MgATP, which is followed by the export of protons, is the first phase of the reaction. The second step of the reaction is the luminal potassium-dependent dephosphorylation, which is followed by the reabsorption of potassium. The end consequence is an exchange of cytoplasmic protons for exoplasmic potassium, which is an electroneutral process [3]. The H,K-ATPase in the stomach is made up of two different types of subunits: a catalytic subunit and a subunit. The fundamental structure of the gastric H,K-ATPase subunit was first determined in the rat [4], and subsequently it was determined in the hog [5], rabbit [6], dog [7], and finally in the human [8]. In every species, this catalytic subunit has 10 transmembrane segments and either 1033 or 1034 amino acids. Functional studies indicated that ATP catalysed an electroneutral exchange of H for K. The stoichiometry of this reaction was 2H/2K/ATP at pH 6.1, but it decreased to 1H/1K/ATP as the pH of the luminal environment dropped below 3.0 [9–11].

[12–14] The subunit is made up of 291 amino acids and has six or seven N-linked glycosylation sites in addition to a single transmembrane region. During the process of biosynthesis, the gastric H,K-ATPase is completely constructed in the endoplasmic reticulum. It is then transported as a heterodimeric oligomer to the apical membrane of the cell. It was found that the N-glycosylation of the subunit was the mechanism that was responsible for transporting molecules to the canalicular membrane. The steady state distribution of the H,K-ATPase subunit in polarised cells is dependent on the equilibrium between direct sorting from the trans-Golgi network, secondary associative sorting with a partner protein, and selective trafficking [15–17]. [Direct sorting from the trans-Golgi network] means that the H,K-ATPase subunit is taken directly from the trans-Golgi network.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

Chemistry and Biology of PPIs

An inhibitor of this enzyme is more efficient than receptor antagonists in decreasing gastric acid secretion [22]. This is due to the fact that the H,K-ATPase is the final stage in the acid secretion process.

Timoprazole is a compound that inhibited acid secretion in vivo regardless of the nature of the stimulus, whether it was ligands acting via extracellular receptors such as histamine or acetylcholine or the intracellular second messenger, cyclic adenosine monophosphate. Timoprazole inhibited acid secretion in vivo regardless of the nature of the stimulus (cAMP). The synthesis of this molecule, which is known as a pyridyl methylsulfinyl benzimidazole, took place in the year 1975. It was discovered that the chemical was ineffective when there was no acid transport provided by the ATPase enzyme. Acid generation and ATPase activity were both decreased by the medication when it was combined with acid transport in gastric ATPase vesicles. Therefore, it was a prodrug that needed to be activated by acid. Omeprazole was eventually manufactured, and in 1989 it was the first medicine of its class to be put into clinical use. Omeprazole was the first drug of its class to be put into clinical use. Omeprazole (Losec; AstraZeneca, Wilmington, DE) was later succeeded by lansoprazole (Prevacid; TAP Pharmaceuticals, Lake Forest, IL), pantoprazole (Protonix; Wyeth Pharmaceuticals, Madison, NJ), or rabeprazole (Aciphex; Eisai Company, Woodcliff, NJ), and most recently by the S-enantiomer of omeprazole (Nexium, AstraZeneca).

Efficacy of Inhibition of Acid Secretion

It is necessary to lengthen the plasma half-life of the PPI in order to achieve better acid inhibition. One strategy would be to switch out the benzimidazole for imidazopyridine, which would slow down the metabolism and increase the drug's half-life, similar to what was discovered with tenatoprazole [30]. The sluggish activation of this PPI reduces the benefit it provides for regulating acid secretion throughout the day, but it is more effective at preventing acid production during the night. An additional method would have been to create a slowly absorbed derivative of omeprazole. This would have resulted in an increase of the plasma half-life by around thrice and produced a median pH of approximately 5 in the early studies [23].

Clinical Pharmacology of PPIs

Except for tenatoprazole, all of the proton pump inhibitors (PPIs) are rapidly metabolised in the liver by CYP enzymes (mostly CYP2C19 and 3A4). As a result of the sensitivity of PPIs to CYP enzymes, the pharmacokinetic profiles of PPIs might vary greatly depending on the phenotypes of the individuals who metabolise the drug. Extensive metabolizers, also known as homEM, have been found in some communities, whereas individuals that possess both wild-type and mutant alleles have been found in other populations. These three phenotypes have been identified (hetEM). Only 3% of Caucasians and 15% to 20% of Asians are considered to have poor metabolic rates.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

Comparing the Effi cacy of PPIs

Acid-related disorders can be healed more quickly when the release of gastric acid is inhibited. When the intragastric pH is greater than 4 for 16 hours per day, good healing of reflux esophagitis can be achieved, and peptic ulcers can be healed to their full potential when the intragastric pH is greater than 3 for 16 hours per day. When evaluating PPIs against one another in vivo, the intragastric pH and total acid production are the appropriate measures to utilise as comparison points. It is not easy to compare the efficacy of different PPIs because they are administered in varying doses (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 40 mg, and tenatoprazole 40 mg, respectively). However, in general, all PPIs are effective at reducing the amount of acid produced by the stomach.

Comparisons of GERD healing rates have been made in a number of studies. There was no discernible difference in the endoscopic healing rates at 4 and 8 weeks between lansoprazole (30 mg) and omeprazole (20 mg) in the studies that compared the two medications. Again, when omeprazole (40 mg) and lansoprazole (30 mg) were examined, it was observed that there were no significant variations in the rates of healing or the treatment of symptoms. At 4 and 8 weeks, the healing rates and symptom relief afforded by rabeprazole and omeprazole, each at a dosage of 20 mg, were shown to be equal.

When compared with the effects of 20 mg of omeprazole, the effectiveness of 40 mg of esomeprazole in treating GERD patients at week 8 was much higher, ranging from 93.7% to 94.1% [58,59]. Both esomeprazole and pantoprazole, at a dose of 40 milligrammes, were found to have beneficial effects on the healing process.

PPIs have proven to be effective when taken in combination with clarithromycin and amoxicillin as part of triple-therapy regimens for the elimination of H. pylori. Different PPI-based regimens did not differ significantly from one another in any meaningful way.

CONCLUSIONS:

Prodrugs are what are known as PPIs. In order for these prodrugs to be transformed into the active sulfenamide or sulfenic acid that prevents gastric acid secretion, it is necessary for there to be gastric acid secretion. Every proton pump inhibitor (PPI), with the exception of tenatoprazole, has a half-life of less than an hour and is well absorbed orally. The majority of PPIs are metabolised by the CYP2C19 and 3A4 enzyme systems. An impaired liver, advanced age, and mutations in the CYP2C19 gene all contribute to a decreased clearance of PPIs.

Acid suppression studies comparing omeprazole, lansoprazole, rabeprazole, and pantoprazole indicate equal effi cacy. When it comes to the treatment of reflux esophagitis or duodenal ulcers, the majority of trials that used normal doses did not find a significant difference between the four PPIs. Esomeprazole and tenatoprazole have a more potent acid suppression and maintain a higher intragastric pH for a longer period of time.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

REFERENCE:

1. Forte JG, Forte TM, Black JA, et al.: Correlation of parietal cell structure and function. J Clin Gastroenterol 1983, 5(Suppl 1):17–27.
2. Sawaguchi A, Aoyama F, Ide S, et al.: The cryofi xation of isolated rat gastric mucosa provides new insights into the functional transformation of gastric parietal cells: an in vitro experimental model study. Arch Histol Cytol 2005, 68:151–160.
3. Sachs G, Chang HH, Rabon E, et al.: A nonelectrogenic H+ pump in plasma membranes of hog stomach. J Biol Chem 1976, 251:7690–7698.
4. Shull GE, Lingrel JB: Molecular cloning of the rat stomach (H+ + K+)-ATPase. J Biol Chem 1986, 261:16788–16791.
5. Maeda M, Ishizaki J, Futai M: cDNA cloning and sequence determination of pig gastric (H+ + K+)-ATPase. Biochem Biophys Res Commun 1988, 157:203–209.
6. Bamberg K, Mercier F, Reuben MA, et al.: cDNA cloning and membrane topology of the rabbit gastric H+/K+-ATPase alpha-subunit. Biochim Biophys Acta 1992, 1131:69–77.
7. Song I, Mortell MP, Gantz I, et al.: Molecular cloning and structural analysis of canine gastric H+,K+-ATPase. Biochem Biophys Res Commun 1993, 196:1240–1247.
8. Maeda M, Oshiman K, Tamura S, et al.: Human gastric (H+ + K+)-ATPase gene. Similarity to (Na+ + K+)-ATPase genes in exon/intron organization but difference in control region. J Biol Chem 1990, 265:9027–9032.
9. Rabon EC, McFall TL, Sachs G: The gastric [H,K]ATPase: H+/ATP stoichiometry. J Biol Chem 1982, 257:6296–6299.
10. Munson K, Garcia R, Sachs G: Inhibitor and ion binding sites on the gastric H,K-ATPase. Biochemistry 2005, 44:5267–5284.
11. Morii M, Yamauchi M, Ichikawa T, et al.: Involvement of the H3O+-Lys-164 -Gln-161-Glu-345 charge transfer pathway in proton transport of gastric H+,K+-ATPase. J Biol Chem 2008, 283:16876–16884.
12. Reuben MA, Lasater LS, Sachs G: Characterization of a beta subunit of the gastric H+/K+-transporting ATPase. Proc Natl Acad Sci U S A 1990, 87:6767–6771.
13. Shull GE: cDNA cloning of the beta-subunit of the rat gastric H,K-ATPase. J Biol Chem 1990, 265:12123–12126.
14. Toh BH, Gleeson PA, Simpson RJ, et al.: The 60- to 90-kDa parietal cell autoantigen associated with autoimmune gastritis is a beta subunit of the gastric H+/K+-ATPase (proton pump). Proc Natl Acad Sci U S A 1990, 87:6418–6422.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022

15. Vagin O, Denevich S, Sachs G: Plasma membrane delivery of the gastric H,K-ATPase: the role of beta-subunit glycosylation. Am J Physiol Cell Physiol 2003, 285:C968–C976.

16. Vagin O, Turdikulova S, Sachs G: The H,K-ATPase beta subunit as a model to study the role of N-glycosylation in membrane traffi cking and apical sorting. J Biol Chem 2004, 279:39026–39034.

17. Vagin O, Turdikulova S, Yakubov I, et al.: Use of the H,KATPase beta subunit to identify multiple sorting pathways for plasma membrane delivery in polarized cells. J Biol Chem 2005, 280:14741–14754.

18. Munson K, Law RJ, Sachs G: Analysis of the gastric H,K ATPase for ion pathways and inhibitor binding sites. Biochemistry 2007, 46:5398–5417.

19. Shin JM, Sachs G: Differences in binding properties of two proton pump inhibitors on the gastric H+,K+-ATPase in vivo. Biochem Pharmacol 2004, 68:2117–2127.

20. Besancon M, Shin JM, Mercier F, et al.: Membrane topology and omeprazole labeling of the gastric H+,K+-adenosinetriphosphatase. Biochemistry 1993, 32:2345–2355.

21. Shin JM, Sachs G: Restoration of acid secretion following treatment with proton pump inhibitors. Gastroenterology 2002, 123:1588–1597.

22. Gedda K, Scott D, Besancon M, et al.: Turnover of the gastric H+,K+-adenosine triphosphatase alpha subunit and its effect on inhibition of rat gastric acid secretion. Gastroenterology 1995, 109:1134–1141.

23. Hunt RH, Armstrong D, Yaghoobi M, et al.: Predictable prolonged suppression of gastric acidity with a novel proton pump inhibitor, AGN 201904-Z. Aliment Pharmacol Ther 2008, 28:187–199.