Review Article

Chemistry, therapeutic benefit and new development on Proton Pump Inhibitors: A Review

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Abstract

Proton pump inhibitors irreversibly inhibit the enzyme hydrogen-potassium adenosine triphosphatase (H^+/K^+-ATPase), which suppresses acid production in the parietal cell of the stomach. Initiation and the continuous use of these drugs without correct indications will result in significant cost to the patient. **Omeprazole**, the prototype proton pump inhibitor, has proved to be very efficient. **Lansoprazole** is the second proton pump inhibitor available on the market. **Pantoprazole** is not yet available for general use in the United States. However, each of these drugs is slightly different from omeprazole, thus offering some possible clinical advantages. Compared with omeprazole, lansoprazole has a longer duration of action and improved activity against H. pylori, while pantoprazole has less interaction with the cytochrome P-450 system and more predictable bioavailability. All three agents have similarly high healing rates for acid peptic diseases and appear to be superior to H_2-receptor antagonists. However, newer agents are being designed to provide even more persuasive acid suppression and longer-acting proton pump inhibition, with the goal of further controlling gastric hyper secretion. PPIs are used to treat peptic ulcers (duodenal and gastric), erosive esophagitis, and drug-induced ulcers (e.g., non-steroidal anti-inflammatory drugs {NSAIDs}), symptoms of gastro esophageal reflux disease (GERD). The purpose of this review is to compares the benefits and harms of different PPIs.

Key words: PPI's, Omeprazole, Parietal cells, H^+/K^+-ATPase

Introduction

Inhibition of the Proton Pump in the parietal cells has been established as the major therapeutic category in the treatment of acid-related diseases, such as peptic ulcer and gastro-esophageal reflux. The effectiveness of PPIs has fueled a huge surge in their use since their release in the 1980s. Today they are available both over the counter and by prescription, and Nexium remains one of the most prescribed medications in the world. But some researchers have nonetheless suggested possible mechanisms by which long-term use of the drugs could trigger dementia or kidney problems (Weintraub, 2017). Proton pump inhibitors (PPIs) are widely used, and their use is associated with increased risk of adverse events. However, whether PPI use is associated with excess risk of death is unknown.

Chemistry of Proton pump (Roche, 2006)

The H^+, K^+/ ATPase proton pump is a large protein comprised of two subunits: The catalytic alpha subunit & glycosylated regulatory beta subunit.

The alpha subunit has 10 trans-membrane or membrane-inserted segments and contains a total of 28 cysteine (CYS) residues. CYS813 has been identified as the residue most critical to the inhibiting action of the PPIs. This CYS is located in the luminal vestibule of the ATPase and is accessible from the extra cytoplasmic area of the ATPase protein. CYS813 will interact with all activated PPI structures regardless of their chemical reactivity. PPIs that are more slowly activated also have time to react with CYS822.

Unlike H_2 antagonist compounds that interact competitively and reversibly with the H_2 receptor, PPIs form a covalent disulfide bond with the ATPase enzyme, leading to an irreversible inhibition of the pump. One sulfur atom in the disulfide bond will come from a CYS residue on the ATPase and the other will come from the PPI (Weintraub, 2017). Since the inactivation of the receptor site (the ATPase in this case) is irreversible and complete, the PPIs are very potent and long-acting therapeutic entities. The ATPase is not able to recover from its irreversible interaction with the inhibitor structure (the

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disulfide bond formed is non-reducible) and the body must synthesize new enzyme de novo which takes time. Until new protein is made, gastric acid secretion is halted. In addition to CYS813 and CYS822, an anionic GLU820 and a second anionic residue (GLU or ASP) at position 824 are believed to be important in holding the PPI structure to the enzyme and positioning the drug for irreversible interaction with the CYS residue (Tomina and Yabluchansky, 2014).

Classification of gastric acid secretion inhibitors (Buch, 2010**)**

H2 antihistamines: cimetidine, Rantidine, Famotidine, Roxatidine.

Novel drugs: Nizatidine, Lafutidine, Lavoltidine

Proton pump inhibitors: Omeprazole, esomeprazole, lansoprazole, Pantoprazole, S (-) Pantoprazole, Rabeprazole, Dexrabeprazole.

Anticholinergics: Pirenzepine, Propantheline, Oxyphenonium

Prostaglandin analogues: Misoprostol

Antacids (Gastric acid neutralizers)

Systemic: Sodium bicarbonate, Sodium citrate

Non-systemic: Magnesium hydroxide, Magnesium trisilicate, Aluminium hydroxide gel, Magaldrate, calcium carbonate.

Clinical investigation

The clinical indications of PPIs are mentioned in table 1.

Chemistry of proton pump inhibitors (Shin et al., 2008**;** Lau et al., 2015)

Because the H, K-ATPase is the final step of acid secretion, an inhibitor of this enzyme is more effective than receptor antagonists in suppressing gastric acid secretion. Timoprazole is a compound that inhibited acid secretion in vivo regardless of the nature of the stimulus, whether ligands acting via extracellular receptors such as histamine or acetylcholine or the intracellular second messenger, cyclic adenosine monophosphate (cAMP). This compound, a pyridylmethylsulfinyl benzimidazole, was synthesized in 1975. It was found that the compound was ineffective in the absence of acid transport by the ATPase. With acid transport in gastric ATPase vesicles, the drug inhibited acid production and ATPase activity. It was therefore an acid-activated prodrug. Omeprazole was subsequently synthesized, and in 1989 it became the first drug of this class to be introduced into clinical use. Omeprazole (Losec; AstraZeneca, Wilmington, DE) was followed by lansoprazole (Prevacid; TAP Pharmaceuticals, Lake Forest, IL), pantoprazole (Protonix; Wyeth Pharmaceuticals, Madison, NJ) or rabeprazole (Aciphex; Eisai Company, Woodcliff, NJ) and more recently by the S-enantiomer of omeprazole (Nexium, AstraZeneca).

PPIs are weak bases with a pK_a1 between 3.8 and 4.9. This weak base pK_a enables PPIs to accumulate selectively in the acidic space of the secretory canaliculus of the stimulated parietal cell, where the pH is about 1.0. This acid space–dependent concentration of PPIs is the first important property that determines their therapeutic index, giving a concentration at the luminal surface of the pump that is about 1000-fold higher than in the blood. The second step is acid-dependent conversion from the accumulated prodrug to the activated species, which is a highly reactive thiophillic reagent. A second protonation of these compounds is required for their activation to the compounds that form disulfides with luminally accessible cysteines of the H/K-ATPase. The actual inhibitory form of these prodrugs is a tetra cyclic sulfonamide or sulfenic acid. The order of acid stability is **tenatoprazole >**

Table 1. Clinical Indication for Proton Pump Inhibitors (Weintraub, 2017; Shin and Sachs, 2008**)**

Brand name	Drugs name	Indications
Prilosec, Prilosec OTC, Zegerid, Omesec,	**Omeprazole**	Treatment of gastric ulcer (GU), erosive esophagitis (EE), and gastro esophageal reflux disease (GERD) with or without esophageal lesion. Eradication of Helicobacter pylori in triple therapy with clarithromycin and amoxicillin or in double therapy with clarithromycin only.
Acilanz, Arlan, Cap Loc OD, Coslan, Domsin-LA, Dyzole, Elsaid.	**Lansoprazole**	Treatment of duodenal ulcer (DU), both H. pylori positive and negative, active benign GU, GERD, EE and pathological hyper secretory conditions, including Zollinger-Ellison syndrome (ZES). Maintenance therapy of DU and EE. Eradication of H. pylori in triple therapy with clarithromycin and amoxicillin, or in double therapy with amoxicillin only.
Abra, acera, acibitor, abizole, Aciless, aciraz.	**Rabeprazole**	Treatment of erosive or ulcerative GERD, DU and hyper secretory syndromes including ZES. Maintenance of erosive or ulceraive GERD.
Allpan, altopan, amcid-D, pancid-D, pancure-D, pandiff, panplus, pantop, pantop-D.	**Pantoprazole**	Treatment of EE (erosive esophagitis) associated with GERD (gastro esophageal reflux disease).
Ceso, Es-care, Esaktive, Esmonat, Es-Od, Esaktive-D.	**Esomeprazole**	In the treatment of GERD, healing of EE, maintenance of healing of EE, H. pylori Eradication to reduce the risk of duodenal ulcer recurrence in triple therapy with clarithromycin and amoxicillin.

pantoprazole > omeprazole > lansoprazole > rabeprazole (Shin et al., 2016).

Depending on the difference of the substituents on the pyridine or benzimidazole, PPIs bind to different cysteines. Omeprazole binds at cysteine 813 and cysteine 892. Lansoprazole binds at cysteine 813 and cysteine 321. Pantoprazole and tenatoprazole bind at cysteine 813 and cysteine 822. With acid transport by the ATPase, the second proton is added and then the compound converts to the sulfenic acid. If this occurs rapidly, as for omeprazole or lansoprazole, reaction with cysteine 813 and/or cysteine 321 takes place, and no drug can access cysteine 822. However, if the activation is delayed, the drug can access cysteine 822 before activation to the sulfenic acid. Then, when activated, both cysteine 813 and 822 are derivatized, as found for pantoprazole or tenatoprazole (Shin et al., 1993; Shin et al., 2004).

Differences of PPI binding sites modify biologic activity. When the PPI-bound enzyme was treated with glutathione, an endogenous reducing agent with a concentration of about 3 mM in the parietal cell, omeprazole and pantoprazole differed in loss of PPI binding. Pantoprazole binding resists glutathione reduction. These observations suggest that removal of binding of the drug to cysteine 813 accounts for the fast phase of recovery of acid secretion; the slow recovery occurs because of a delay in removal of the drug from cysteine 822. Both residues, cysteine 813 and 822, are equally labeled by pantoprazole in vivo. The small amount of cysteine 822 bound by omeprazole in vivo is not seen in vitro, presumably because acidification in isolated gastric vesicles is less than occurs in vivo. In vivo, it is likely that a minor fraction of the omeprazole remains protonated at both the pyridine and benzimidazole nitrogen and is slowly activated, allowing some access to cysteine 822.

The activation of PPIs (Weintraub, 2017; Arthur et al., 2015**)**

Proton pump inhibitors (also called PPIs) reduce the production of acid by the stomach. They do this by irreversibly blocking the actions of an enzyme responsible for acid production, H+/K+ ATPase that is located in the parietal cells in the stomach wall. This allows any ulcers present in the esophagus, stomach, and duodenum to heal and helps prevent new ulcers from forming. PPIs are also used to treat other gastrointestinal disorders characterized by excessive acid secretion.

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine tri-phosphatase enzyme system (the H+/K+ ATPase, or, more commonly, the gastric proton pump) of the gastric parietal cells. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion. Targeting the

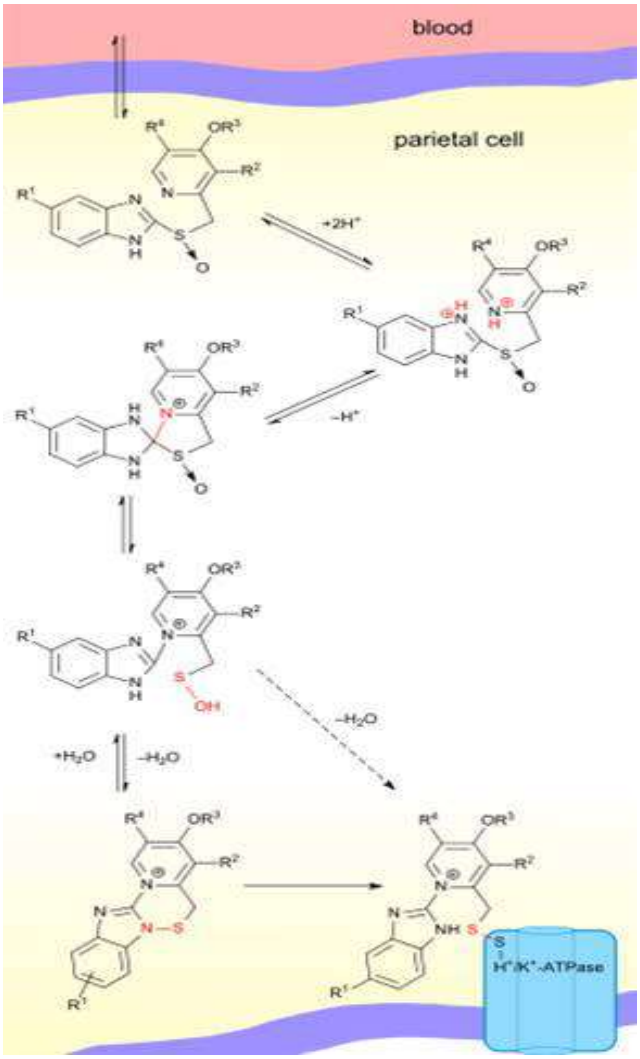

Figure 1. Drug is covalently and irreversibly binds to active form of gastric proton pump

terminal step in acid production, as well as the irreversible nature of the inhibition, results in a class of drugs that are significantly more effective than H2 antagonists and reduce gastric acid secretion by up to 99%. Decreasing the acid in the stomach can aid the healing of duodenal ulcers and reduce the pain from indigestion and heartburn. However, stomach acids are needed to digest proteins, vitamin B12, calcium, and other nutrients, and too little stomach acid causes the condition hypochlorhydria. The PPIs are given in an inactive form, which is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) with acidic environments. In an acid environment, the inactive drug is protonated and rearranges into its active form. As described above, the active form will covalently and irreversibly bind to the gastric proton pump, deactivating it.

Relationship of PPI in total human body (Kresser et al.,

2016)

Most of the current evidence suggests that chronic PPI use does not have a significant negative correlation with BMD changes assessed by dual-energy X-ray absorptiometry (DXA). The risk of sustaining a fracture after minimal trauma can be attributed to an increased risk of falls, but also from low BMD values (which signifies low bone quantity), and poor structural bone quality. A case control study conducted using the Korean Health Interview Review and Assessment Service database found that the adjusted odds ratio of sustaining a hip fracture was 1.71 (95% CI 1.31–2.23) in PPI users treated concurrently with a bisphosphonate.

However, the adjusted odds ratio of sustaining a hip fracture in PPI users who were not taking a bisphosphonate was 1.30 (95% CI 1.19–1.42).

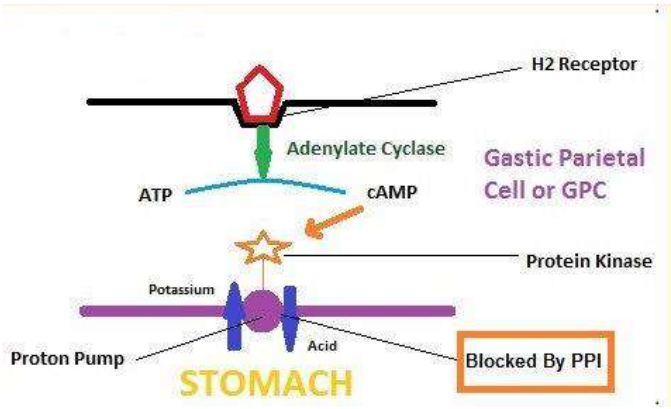

Figure 2. Mechanism of PPI in stomach

A key protein for acid secretion is the H^+/K^+-ATPase (or proton pump). This protein, which is expressed on the apical membrane of parietal cells, uses the energy derived from ATP hydrolysis to pump hydrogen ions into the lumen in exchange for potassium ions. Proton pumps, specifically the proton/potassium pump of parietal cells in the stomach. Parietal cells in the stomach secrete roughly two liters of acid a day in the form of hydrochloric acid. Acid in the stomach functions to kill bacteria, and to aid digestion by solubilizing food. The acid is also important to establish the optimal pH (between1.8-3.5) for the function of the digestive enzyme pepsin.

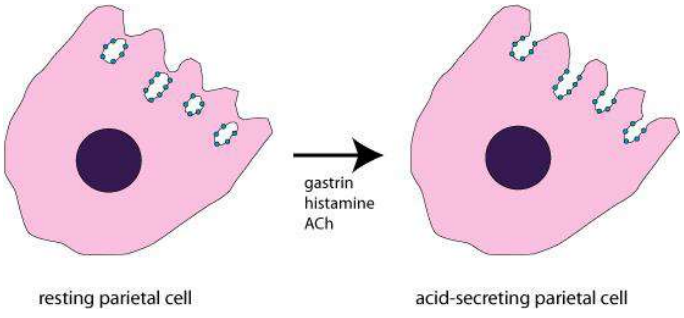

Figure 3. Resting position (Vs) Active position of parietal cell

When the cell is resting (not stimulated), H^+/K^+-ATPases are located in vesicles inside the cell. When the cell is stimulated, these vesicles fuse with the plasma membrane, thereby increasing the surface area of the plasma membrane and the number of proton pumps in the membrane. The theory is that heartburn is caused by excess production of stomach acid by these cells, so inhibiting this proton pump will reduce the acidity of the stomach and prevent the burning sensation of acid reflux or the formation of peptic ulcers by using PPIs (Panchumarthy Ravisankar et al., 2016).

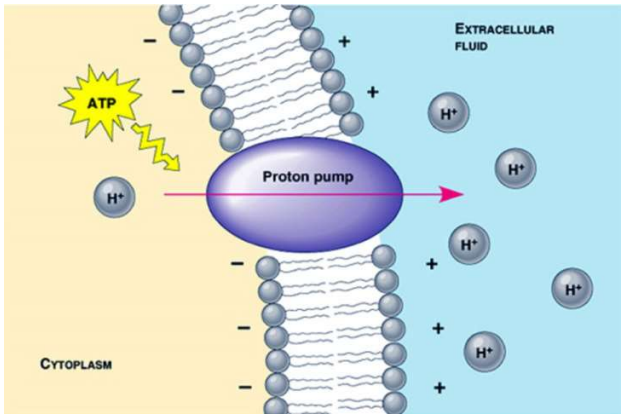

Figure 4. Regular mechanism of proton pump

Proton pumps aren't limited to the stomach; they are present in just about every cell in your body and these are also important in the transport of various substances in the body. All of your cells, with the exception of red blood cells, have mitochondria that allow your body to metabolize carbohydrates and fat to produce energy. They do this by pumping protons across the membrane to generate a source of electric potential that can be harnessed to form ATP, the body's main storage form of energy.

Without an efficient proton-pumping system, the body must rely on anaerobic systems for energy production, leading to rapid fatigue.

Mechanism of PPIs (Shin et al., 1993**)**

The PPIs function as prodrugs that share a common structural motif, a substituted pyridylmethylsulfinyl benzimidazole, but vary in terms of their substitutions, which yield slightly different pKa values. The prodrug is a weak protonatable pyridine that traverses the parietal cell membrane. As the prodrug accumulates in the highly acidic secretory canaliculus, it undergoes an acid catalyzed conversion to a reactive species, the thiophillic sulfonamide. This active moiety then covalently binds to a specific cysteine residue (Cys-813) on the H^+/K^+ ATPase (via disulfide bond formation) and inactivates it, thus

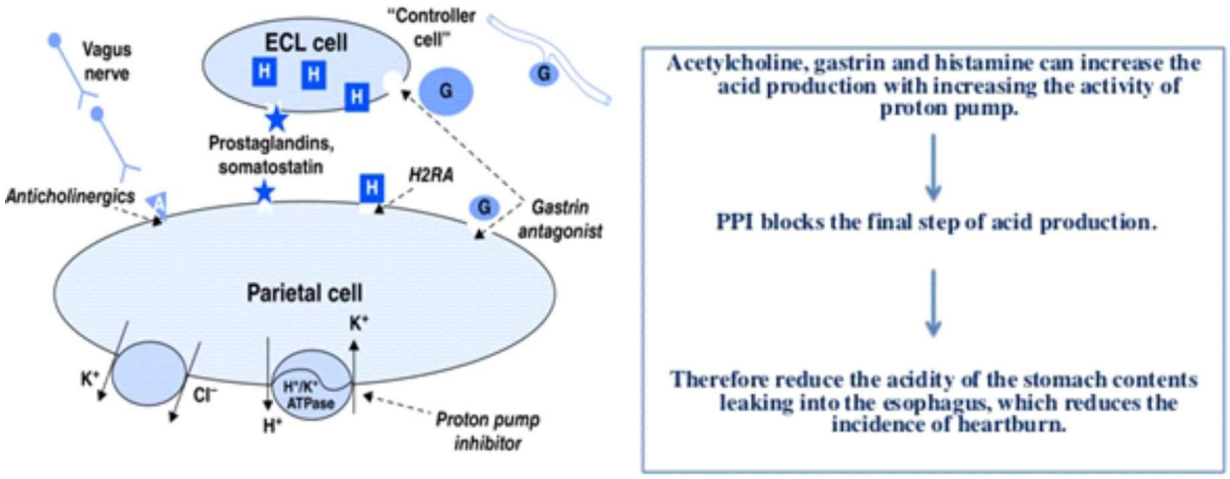

Figure 5. Functions of various drugs on Parietal cell

suppressing basal and stimulated gastric acid secretion.

The rate of conversion to the active form varies among the PPIs, as activation occurs when the regional pH decreases below the pKa of the specific PPI (Shin et al., 2013). Thus, some PPIs may have a slightly faster onset of action, with rabeprazole having the most rapid onset (pKa 5.0), followed by omeprazole, lansoprazole, esomeprazole (pKa 4.0), and finally pantoprazole (pKa 3.9). These pharmacokinetic differences have not proven to be clinically significant.

The PPIs are the most potent inhibitors of gastric acid secretion available when administered correctly, based on their pharmacodynamics. Because acid secretion must be stimulated for maximum efficacy, PPIs should be taken before the first meal of the day. PPIs are most effective when administered after a prolonged fast, when the greatest number of H^+/K^+ ATPase molecules is present in parietal cells, which is in the morning for most patients. In addition, administration of PPIs should be followed by food ingestion, when the gastric parietal cells are stimulated to secrete acid in response to a meal. Moreover, these drugs should not be used in conjunction with H2RAs, prostaglandins, somatostatin analogs, or other anti secretory agents. Animal studies have demonstrated that the concomitant administration of PPIs and other anti secretory agents markedly reduces the acid inhibitory effects of PPIs. In most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition. A second dose, if required, should be administered before the evening meal. Importantly, meals should include protein or another stimulant of gastric acid secretion (e.g., coffee). In addition, based on the pharmacokinetics of PPIs, the most effective response occurs with consistent (i.e., daily) dosing, rather than sporadic (i.e., as needed) dosing.

The oral bioavailability of PPIs ranges from 45% (omeprazole) to 85% (lansoprazole). Although PPIs have a circulating $T_{½}$ of only 1–1.5 hours, the biological $T_{½}$ of the inhibited complex is ~ 24 hours, due to its mechanism of action. Because all the PPIs require accumulation and acid activation, their onset of inhibition is delayed, and after the initial dose, acid secretion continues, but at a reduced level. Subsequently, H^+/K^+ ATPase enzymes that are recruited to the secretory canaliculus in the parietal cell are then inhibited by additional doses of PPI, further reducing acid secretion. Steady state acid inhibitory properties occur by ~ 5 days and inhibit maximal acid output by 66%.

Metabolism (Skrzydlo-Radomanska et al., 2015**)**

PPIs are principally metabolized by CYP2C19, a member of the hepatic cytochrome P450 family of enzymes, with the exception of lansoprazole, which is mainly metabolized by CYP3A4. It is possible that PPIs may affect the metabolism of other drugs that are metabolized by this family of enzymes, including warfarin, diazepam, phenytoin, digoxin, carbamazepine, and theophylline. Asian populations and the elderly commonly harbor polymorphisms in the CYP2C19 gene, which affects PPI metabolism and has been shown to increase the drugs' acid inhibitory properties. PPIs are mainly excreted in urine, with the exception of lansoprazole, which is mainly excreted in feces.

New drug development on proton pump inhibitors (Roche et al., 2006; Blanton et al., 2016; Maradey-Romero et al., 2014**)**

AGN201904-Z (Alevium)

AGN201904-Z (Alevium) is a prodrug of omeprazole. It is acid-stable and therefore requires no enteric coating. This drug has a long plasma half-life due to slow absorption throughout the small intestine. After absorption, the drug is rapidly hydrolyzed in the systemic circulation to omeprazole. A comparison of Alevium (600 mg once daily)

with esomeprazole (40 mg once daily) in 24 healthy subjects resulted in significantly greater and more prolonged acid suppression during both daytime and nighttime. Alevium once daily showed a 1.9 fold increase in serum half-life as compared with esomeprazole. After 5 days of treatment, Alevium demonstrated significantly higher mean 24-hour intragastric pH, nocturnal median pH, and percentage of time intragastric pH > 4 was as compared with esomeprazole ($P = 0.0001$)

Ilaprazole

Ilaprazole is a benzimidazole compound that is extensively metabolized to the major metabolite ilaprazole sulfone. The drug's antisecretory activity, half-life, and safety profile have all been shown to be superior to omeprazole. In one randomized study conducted in 235 subjects who had been diagnosed with a duodenal ulcer, ilaprazole at a lower dose (10 mg/day) was better tolerated, safe, and more efficacious than omeprazole. Another trial investigated ilaprazole at three different doses (5, 10 and 20 mg) as compared with omeprazole (20 mg once daily) in 12 healthy subjects. This study demonstrated that 20 mg ilaprazole resulted in a significantly higher mean 24-hour intragastric pH on day 5 as compared with standard dose of omeprazole ($P < 0.05$). A phase II clinical trial was conducted to evaluate the safety and efficacy of different doses of ilaprazole (5, 20 and 40 mg) as compared with lansoprazole (30 mg) on healing of EE. Thus far the results of the study remain unavailable.

Esomeprazole stronium delayed-release (Esomezol)

Esomeprazole stronium delayed-release (Esomezol) is an incrementally modified drug (IMD) manufactured by a pharmaceutical company from South Korea. Strontium salt was used instead of magnesium salt to develop a generic esomeprazole. No clinical data are currently available in relation to this drug; however, this product has recently received tentative approval from the FDA but has yet to be released into the market.

Tenatoprazole

It is a proton pump inhibitor drug candidate that was undergoing clinical testing as a potential treatment for reflux oesophagitis and peptic ulcer as far back as 2003. The compound was invented by Mitsubishi Tanabe Pharma and was licensed to Negma Laboratories (part of Wockhardt as of 2007. Mitsubishi reported that tenatoprazole was still in Phase I clinical trials in 2007 and again in 2012. Tenatoprazole has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors, and has a half-life about seven times longer than other PPIs.

Proton pump inhibitor combinations

Dexlansoprazole

It is modified release (MR) is an R-enantiomer of lansoprazole and a new-generation proton pump inhibitor exhibiting high efficacy in the treatment of symptoms and lesions associated with erosive oesophagitis caused by gastroesophageal reflux disease (GERD). The dual release of the active ingredient-in the duodenum and the small intestine – makes it possible to achieve two peak concentrations at various times, within two and five hours of administration. Dexlansoprazole can be taken regardless of meal times. It has a good safety profile and carries a low risk of adverse interactions with other drugs. Dexlansoprazole is intensively metabolized in the liver by oxidation and reduction followed by conjugation with sulphates, glucuronate and glutathione to inactive metabolites. Metabolites of oxidation arise through the activity of the cytochrome P450 (CYP) enzymatic system via hydroxylation, mainly by CYP2C19, and oxidation to sulphone by CYP3A4. In patients with moderate and intensive CYP2C19 metabolism the main plasma metabolite is 5-hydroxy dexlansoprazole and its glucuronate, and in patients with weak CYP2C19 metabolism the main plasma metabolite is the sulphonic metabolite (Kerner et al., 2016).

Proton pump inhibitor-VB101 (Vecam)

PPI-VB101 (Vecam) is the co-administration of a PPI with a ligand that activates proton pumps in the parietal cells. The rationale behind this combined therapy is to increase the efficacy of the PPI by maximizing activation of proton pumps. In addition, it may allow administration of PPI without regard to food. Vecam is a combination of omeprazole and succinic acid, which has a pentagastrin-like activity that potentiates activation of proton pumps. In an open-label study, 36 healthy subjects were randomized to receive once daily Vecam (20 or 40 mg) at bedtime or omeprazole (20 mg) before breakfast. The effect of the different therapeutic arms on intragastric acidity was compared over a 24-hour period. Vecam (40 mg) was significantly better at providing greater nighttime intragastric pH > 4 as compared with Vecam (20 mg) and omeprazole ($P < 0.0001$). Similarly Vecam (20 mg) showed significantly better control of intragastric pH as compared with omeprazole (20 mg) ($P = 0.0069$).

OX17

OX17 is an oral tablet containing a combination of omeprazole and famotidine (doses are unclear).This combination has shown a 60% increase in total time intragastric pH > 4 as compared with omeprazole alone. A combination of tenatoprazole and H2RA has been recently patented. However, we are still awaiting studies

demonstrating the clinical value of this novel compound as compared with PPI alone.

NMI-826

NMI-826 is a nitric-oxide (NO)-enhanced PPI. The drug has been shown to be more effective than a PPI alone in healing gastric ulcers.

Secretol

Secretol is a novel pharmacological compound that combines omeprazole with lansoprazole. Currently, secretol is undergoing a phase II trial that compares its healing rates and symptom control with esomeprazole in subjects with severe EE. The combined compounds are likely to be niched in certain areas of unmet needs in GERD rather than competing with the currently available PPIs.

Adverse effects (Daniel Kerner et al., 2016; Ami Kapadia et al., 2015; Centre for medicine and medicare services (CMS)-2013; Hunfeld et al., 2010**)**

Emerging evidence indicates that PPI therapy, particularly with long-term and/or high-dose administration, is associated with several potential adverse effects, including enteric infections (*Eg: Clostridium difficile*), community-acquired pneumonia, and hip fracture, nutritional deficiencies, chronic kidney disease, and dementia.

Food Allergies

PPIs may also play a role in promoting increased allergic reactivity in patients on acid suppressive therapy. Rising food allergen formation possibly associated with PPIs may result in escalating rates of severe allergic reactions such as anaphylaxis and lead to significant restrictions in diet.

Community Acquired Pneumonia

H_2RAs and PPIs create a hypochlorhydric to achlorhydric environment in the gut, thereby facilitating survival of certain ingested pathogens that would otherwise be killed by unaltered pH gastric juices. Regurgitation of ingested bacteria into the oropharynx can precipitate respiratory infections.

Vitamin B12 Deficiency

Another proposed adverse effect of long term PPI use is cobalamin mal-absorption. Several mechanisms have been proposed by which PPI use may lead to cobalamin mal-absorption. First, a more basic gastric environment may slow the release of cobalamin from dietary food sources.

In March 2011, the FDA published a Drug Safety Communication to inform consumers and health professionals that long-term use of PPIs can cause hypomagnesaemia.

Is it safe to use a proton pump inhibitor with clopidogrel ***?***

Omeprazole reduces the efficacy and ability of clopidogrel's antiplatelet effect, which may increase the risk of a heart attack. Patients at risk for heart attacks or strokes who are given clopidogrel to prevent blood clots may not get the full protective anti-clotting effect if they also take omeprazole.

Rebound acid hyper secretion raising a subject's intragastric pH is the primary goal in acid-related diseases. However, there are speculations that this may lead to an overstimulation of acid production after the drug is stopped, as is shown for H_2-receptor antagonists (especially ranitidine). This process is called rebound acid hyper secretion (RAHS). If RAHS would occur after cessation of PPIs, it might have consequences for patients because of aggravation of complaints. It has been suggested that the introduction of stronger acting PPIs, like esomeprazole, would more rapidly induce RAHS. In literature, there are few clinical data about the occurrence of RAHS after stopping the intake of PPIs. Its existence and occurrence need further investigation.

Conclusion

PPIs represent an essential part of the modern gastroenterologist's protection for combating everyday clinical problems. In general they are highly efficacious in the treatment of acid-related disorders. Despite of this, the ubiquitous presence and indiscriminant use of PPIs has led to increased oversight among insures and appropriate concern about the risk of indefinite hypochlorhydria and drug interaction. Careful consideration by the prescriber of appropriate indication, Patient cofactors and the expected dose and duration of treatment is a necessary part of responsible use of any drug including PPIs.

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