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Review Article

Proton pump inhibitors: An incisive review

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ABSTRACT

Proton pump inhibitors (PPIs) were clinically introduced a few years ago and have since become an important, safe, and successful treatment for a variety of corrosive-related issues. To specifically overcome these limitations, longer-acting PPIs and innovation to draw out ordinary PPI action have been created, which may improve clinical outcomes. PPIs are identified by their pharmacokinetic properties, digestion, and clinical indications that have been approved by the Food and Drug Administration (FDA).

1. Introduction

Proton-pump inhibitors (PPIs) are a class of drugs that reduce gastric acid development significantly and for a long time. They are the most powerful acid secretion inhibitors currently available. This class of drugs preceded and eventually replaced H2-receptor antagonists & synthetic prostaglandin analogs, as well as anticholinergic, which had similar effects but a different mode of action. PPIs have shown consistent patient tolerance, excellent protection, and generally superior acid suppressing capability than previous agents. PPIs are among the most commonly prescribed medications in the world, with the first, omeprazole, being on the WHO's List of Essential Medicines. [1,2]

2. Mechanism of Action

Proton pump inhibitors work by irreversibly inhibiting the gastric parietal cells' hydrogen/potassium adenosine triphosphatase enzyme mechanism (the H+/K+ ATPase, or, more colloquially, the gastric proton pump). Because the proton pump is directly responsible for secreting H+ ions into the gastric lumen at the end of acid secretion, it is an ideal target for acid secretion inhibition.

Since the inhibition is permanent, targeting the terminal stage in acid production results in a class of drugs that are significantly more effective than H2 antagonists and reduce gastric acid secretion by up to 99 percent. The term "irreversibility" refers to the effect on a single copy of the proton pump; the effect on the whole human digestive system is reversible since the proton pump protein is rendered redundant and can be replaced by new copies. [3]

Reduced stomach acid aids in the healing of duodenal ulcers and alleviates the discomfort of indigestion and heartburn, both of which can be caused by stomach acid. Low stomach acid, also known as hypochlorhydria, is a lack of adequate hydrochloric acid, which is needed for protein digestion and nutrient absorption, especially vitamin B12 and calcium. PPIs are given in an inactive state that is neutrally charged (lipophilic) and easily crosses cell membranes into acidic intracellular compartments (such as the parietal cell canaliculus). In an acidic state, the inert drug is protonated and rearranges into its active form. The inactive drug is protonated and rearranges into its active form in an acidic state. As previously mentioned, the active form will bind to the gastric proton pump covalently and

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Table 1: Commercially available proton pump inhibitors [5]

Drug	Dosages, mg	IV	Liquid or suspension	Generic	Over-the-counter
OM	10,20,40	Yes	No	Yes	Yes
ES	20,40	Yes	Yes	Yes	Yes
LA	15,30	Yes	Yes	Yes	Yes
DE	30,60	No	No	No	No
PZ	20,40	Yes	Yes	Yes	No
RZ	20	No	No	Yes	No

Table 2: Pharmacokinetic properties of proton pump inhibitors [6,7]

P'cokinetic parameters	OM	ES	LA	DE	PZ	RZ
Bioavailability, %	30-40	64-90	80-85	-	77	52
Time to peak plasma level (tmax, hr)	0.5-3.5	1.5	1.7	1-2,4-5	2-3	2-5
Protein binding, %	95	97	97	96	98	96.3
Half-life, hr	0.5-1	1-1.5	1.6	1-2	1-1.9	1-2
Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19	CYP2C19	CYP2C19

irreversibly, deactivating it. [4]

3. Pharmacological uses

These medications are used to treat a variety of disorders, including:

1. Dyspepsia
2. Peptic ulcer condition, even after endoscopic hemorrhage therapy.
3. As part of Helicobacter pylori eradication therapy.
4. Gastro-esophageal reflux disease (GERD or GORD) including symptomatic endoscopy-negative reflux diseaseand associated laryngo pharyngeal reflux causing laryngitis and chronic cough. [8]
5. Barrett's esophagus.
6. Eosinophilic esophagitis.
7. In emergency care, stress gastritis and ulcer prevention. [9]
8. Gastrinomas and other conditions that cause hyper secretion of acid including Zollinger–Ellison syndrome (often 2–3x the regular dose is required. [10,11]

When used to treat gastroesophageal reflux disease on a long-term basis, specialist specialist associations advise people to use the lowest possible PPI dosage to achieve the best clinical outcome. In the United States, the Food and Drug Administration recommends that no more than three 14-day rehab courses be used in a calendar year. [10]

Despite their common use, the evidence for their use in any of these conditions is mixed. PPIs have never been shown to be effective in any case. For example, while they reduce the risk of esophageal adenocarcinoma in Barrett's esophagus, they have little impact on the esophageal length. [11]

4. Advantages of Long-term Proton Pump Inhibitor Use

During the first 3–5 days after starting administration, the acid inhibition produced by per-oral administration gradually increases. Even after long-term therapy, PPIs do not cause tolerance. Since nocturnal acid inhibition is weak and intra-gastric pH during the nocturnal period remains about 2.0 in the majority of administered cases, the pre-breakfast plasma gastrin concentration measured in the early morning does not show a significant elevation. Long-term inhibition of gastric acid secretion is needed for GERD maintenance therapy and the prevention of gastritis. [12]

Long-term administration of these medications can also be beneficial in preventing the neoplastic transformation of Barrett's esophagus to dysplastic Barrett's esophagus, such as adenocarcinoma. It is not clear whether PPIs effectively avoid dysplastic changes in the esophagus caused by Barrett's esophagus. However, no evidence has been found that these medications aggravate dysplastic changes, despite the fact that some studies have suggested that they effectively prevent dysplastic changes. [13] Long-term PPI administration is also beneficial in preventing the recurrence of aspirin-induced gastro duodenal ulcers and is more successful than H2RAs, with a recurrence rate that is one-tenth of that seen in placebo-treated classes. [12]

5. Disadvantages of Long-term Proton Pump Inhibitors use

The majority of acid inhibition-related side effects occur during long-term PPI therapy, while those unrelated to acid inhibition occur in both long-term and short-term PPI patients. [14] They are discussed are Adverse reactions that

aren't linked to acid inhibition and Acid inhibition-related side effects.

5.1. Adverse reactions that aren't linked to acid inhibition

1. Chronic kidney disease
2. Collagenous colitis is a form of colitis
3. Acute interstitial nephritis
4. Chronic kidney disease is a disease that affects the kidneys
5. Interaction between drugs

5.2. Acid inhibition-related side effects

1. Pneumonia is an infection of the lungs.
2. Infection of the gastrointestinal tract
3. Carcinoid tumor of the stomach
4. Hypertrophy of the fundic mucosa of the stomach
5. Microbiome changes in the gut
6. Bacterial overgrowth in the small intestine
7. A lack of iron
8. Fracture of the bones
9. Deficiency in vitamin B12
10. Gastric cancer
11. Colon cancer

6. Nutritional

Gastric acid is essential for the breakdown of food and the release of micronutrients, but some studies have shown that it can interfere with iron, calcium, magnesium, and vitamin B12 absorption. The evidence for iron and vitamin B12 is limited, and several confounding factors have been identified. People taking PPIs have low magnesium levels, which can be corrected by switching to H2-receptor antagonists. PPI use at high doses and/or over long periods of time has been linked to an increased risk of bone fractures not seen with short-term, low-dose use; the FDA included a note about this on PPI drug labels in 2010.[15]

7. Gastrointestinal

The use of PPIs has been linked to Clostridium difficult infections in some studies. Despite the conflicting and disputed evidence, the FDA was concerned enough to include a notice about this side effect on the label of PPI products. Concerns have also been raised regarding small intestinal bacterial overgrowth and spontaneous bacterial peritonitis in older people taking PPIs and people with irritable bowel syndrome taking PPIs; both forms of infections occur in these populations as a result of underlying conditions, and it is unclear if this is a PPI class impact.

Long-term use of PPIs is linked to the production of benign fundic gland polyps (which are not the same as fundic gland polyposis); these polyps do not cause cancer and disappear when PPIs are stopped. There is no connection between the use of PPIs and cancer or pre-cancer. PPI use has been linked to the masking of gastric cancers and other severe gastric issues, and physicians should be mindful of this possibility. The use of proton pump inhibitors has also been linked to the development of microscopic colitis.[16,17]

8. Cardiovascular

PPI use and cardiovascular events have also been researched extensively, but no firm conclusions have been reached because these relative risks are masked by other factors. When aspirin is given for its antiplatelet effects, PPIs are widely used in cardiovascular patients for gastric defense. There is an established relationship between PPIs and the platelet inhibitor clopidogrel's metabolism, and this drug is often used in patients with heart disease. PPIs bind to and inhibit dimethyl argininase, the enzyme that degrades asymmetric dimethyl arginine (ADMA), resulting in higher ADMA levels and a decrease in bioavailable nitric oxide (NO).[18]

9. Side Effects of PPI

PPI side effects are uncommon. A headache, diarrhea, constipation, nausea, or scratching are all possible symptoms. Inquire with your doctor about the risks of long-term use, such as infections and bone fractures. Before taking these medications, consult the doctor if you are breastfeeding or pregnant. If you're taking some other medications, let your doctor know. Certain products, such as anti-seizure medications and blood thinners like warfarin or clopidogrel, can be affected by PPIs (Plavix). Headaches, nausea, diarrhea, stomach pain, weakness, and dizziness are all common side effects. Rash, itch, flatulence, constipation, anxiety, and depression are some of the less common side effects. PPI usage has also been linked to the development of myopathies, including the severe reaction rhabdomyolysis.[19]

10. Adverse effect of PPI

Proton pump inhibitors are generally well tolerated and have a low occurrence of short-term side effects. Long-term PPI usage has received less research than short-term use, making it difficult to make definitive claims. The severity and frequency of adverse effects are comparable for all PPIs, though omeprazole has been documented more frequently. This may be attributed to the fact that it has been available for a longer time and therefore has more clinical experience.[20] Some others Adverse Effects PPI use has been linked to an increased risk of pneumonia, particularly in the first 30 days after starting therapy, when it was found to be 50% higher in group users.

Table 3: Marketed used Proton Pump Inhibitors [21,22]

Generic Name	Brand Name	Manufactures
Omeprazole	Prilosec, Zegerid, ocid, Lomac, Omepral, Zolppi, Omez, Omepep, GastroGard	Astra Zeneca, Santarus, San Diego, CA
Dexlansoprazole	Kapidex, Dexilant	Janssen Cilag
Lansoprazole	Prevacid, Zoton, Monolitum, Lupizole	Takeda Pharma, Lake Forest, IL
Esomeprazole	Nexium, Esotrex, esso	Astra Zeneca, Wilmington
Pantoprazole	Protonix, Somac, Pantoloc, Pantozol, Pantozol, Pantomed,	Wyeth Pharma, Madison
Rabeprazole	AcipHex, Pariet, Erraz, Zechin, Rabecid, Nzole-D	Eisai, Teaneck, NJ

11. Advances in PPI Technology [23]

A number of efforts have been made to overcome the inherent pharmacologic limitations of currently available PPIs, in particular their short plasma half-life (and therefore short duration of effect) and the need for preprandial dosing.

1. Tenatoprazole, the first imidazopyridine PPI.
2. Rabeprazole-ER is a 50 mg capsule.
3. Dual-release dexlansoprazole is formulated to release drug in two separate pH controlled phases.

12. Conclusion

PPIs are a critical component of the advanced gastroenterologist's lethal toolkit for dealing with common clinical issues. Overall, they are extremely effective in treating acid-related problems. Prodrugs are what PPIs are. These prodrugs necessitate the conversion of gastric corrosive emission to the dynamic sulfenamide or sulfenic corrosive, which squares gastric corrosive discharge. Except for tenatoprazole, all PPIs have short half-lives (around 60 minutes) and high oral bioavailability.

13. Source of Funding

None.

14. Conflict of Interest

There are no conflicts of interest.

References

1. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: A double-blind, randomized clinical trial. *Am J Gastroenterol*. 2000;95(8):1894–9. doi:10.1111/j.1572-0241.2000.02233.x.
2. Huang JQ, Hunt RH. pH, healing rate and symptom relief in acid related diseases. *Yale J Biol Med*. 1996;69(2):159–74.
3. U.S. Food and Drug Administration. FDA drug safety communication: low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs) [Internet]. Silver Spring: U.S. Food and Drug Administration; 2011.
4. Bamberg K, Mercier F, Reuben MA, Kobayashi Y, Munson KB, Sachs G. cDNA cloning and membrane topology of the rabbit gastric H+/K+-ATPase α-subunit. *Biochim Biophys Acta (BBA)*. 1992;1131(1):69–77. doi:10.1016/0167-4781(92)90100-e.
5. Roche VF. The Chemically Elegant Proton Pump Inhibitors. *Am J Pharm Educ*. 2006;70(5):101. doi:10.5688/aj7005101.
6. Langtry HD, Wilde MI. Lansoprazole: an update of its pharmacological properties and clinical efficacy in the management of acid related disorders. *Drugs*. 1997;54:473–500.
7. Prakash A, Faulds D. Rabeprazole. *Drugs*. 1998;55(2):261–7. doi:10.2165/00003495-199855020-00009.
8. Sakurai Y, Nishimura A, Kennedy G, Hibberd M, Jenkins R, Okamoto H, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Rising TAK-438 (Vonoprazan) Doses in Healthy Male Japanese/non-Japanese Subjects. *Clin Transl Gastroenterol*. 2015;6(6):e94. doi:10.1038/ctg.2015.18.
9. Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects - a randomised open-label cross-over study. *Alimentary Pharmacol Ther*. 2015;42(6):719–30. doi:10.1111/apt.13325.
10. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. *Gut Liver*. 2017;11(1):27–37. doi:10.5009/gnl15502.
11. Chey WD, Inadomi JM, Booher AM, Sharma VK, Fendrick AM, Howden CW. Primary-Care Physicians' Perceptions and Practices on the Management of GERD: Results of a National Survey. *Am J Gastroenterol*. 2005;100(6):1237–42. doi:10.1111/j.1572-0241.2005.41364.x.
12. Sugano K, Kinoshita Y, Miwa H, and TT. Randomised clinical trial: esomeprazole for the prevention of nonsteroidal anti-inflammatory drug-related peptic ulcers in Japanese patients. *Alimentary Pharmacol Ther*. 2012;36(2):115–25. doi:10.1111/j.1365-2036.2012.05133.x.
13. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut*. 2014;63(8):1229–37. doi:10.1136/gutjnl-2013-305997.
14. Goh KL, Choi MG, Hsu PI. Pharmacological and safety profile of dexlansoprazole: a new proton pump inhibitor-implications for treatment of gastroesophageal reflux disease in the Asia Pacific region. *J Neurogastroenterol Motil*. 2016;22:355–66.
15. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Ther Adva Drug Saf*. 2013;4:125–33. doi:10.1177/2042098613482484.
16. Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. *World J Gastroenterol*. 2017;23(35):6500–15. doi:10.3748/wjg.v23.i35.6500.
17. Patil R, Blankenship L. Proton Pump Inhibitors and Clostridium Difficile Infection: Are We Propagating an Already Rapidly Growing Healthcare Problem? *Gastroenterol Res*. 2013;6(5):171–3.
18. Sukhovershin RA, Cooke JP. How May Proton Pump Inhibitors Impair Cardiovascular Health? *Am J Cardiovasc Drugs*. 2016;16(3):153–61. doi:10.1007/s40256-016-0160-9.
19. Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-Proton Pump Inhibitor Drug-Drug Interaction and Risk of Adverse Clinical Outcomes Among PCI-Treated ACS Patients: A Meta-analysis. *J Manag Care Spec Pharm*. 2016;22(8):939–47. doi:10.18553/jmcp.2016.22.8.939.

20. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301(9):937–44.
21. Available from: https://www.transparencymarketresearch.com/proton-pump-inhibitors-arket.html.
22. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. *Gut Liver*. 2017;11(1):27–37. doi:10.5009/gnl15502.
23. Peura A, Berardi RR, Gonzalez J, Brunetti L. The value of branded proton pump inhibitors: formulary considerations. *P T*. 2011;36(7):434–45.

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