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A REVIEW ON PROTON PUMP INHIBITORS

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ABSTRACT

Proton pump inhibitors (PPIs) were clinically introduced more than 25 years ago and have since proven to be invaluable, safe, and effective agents for the management of a variety of acid-related disorders. Although all members in this class act in a similar fashion, inhibiting active parietal cell acid secretion, there are slight differences among PPIs relating to their pharmacokinetic properties, metabolism, and Food and Drug Administration (FDA)-approved clinical indications. Nevertheless, each is effective in managing gastroesophageal reflux disease and uncomplicated or complicated peptic ulcer disease. Despite their overall efficacy, PPIs do have some limitations related to their short plasma half-lives and requirement for meal-associated dosing, which can lead to breakthrough symptoms in some individuals, especially at night. Longer acting PPIs and technology to prolong conventional PPI activity have been developed to specifically address these limitations and may improve clinical outcomes.

Keywords: Adverse effect, Allergic disease, Gastric acid, Gastroesophageal reflux, Ulcer.

INTRODUTION

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have steadily become the mainstay in treatment of acid-related disorders. When compared with earlier agents such as histamine2-receptor antagonists (H2RAs), synthetic prostaglandin analogues, and anticholinergics, PPIs have demonstrated consistent patient tolerance, excellent safety, and generally superior acid suppressing capability than prior agents. Adoption of PPI use has been widespread among primary care providers, and their presence is ubiquitous within the armamentarium of the modern gastroenterologist. [1] For most, this class of drugs represents the first choice for treatment of esophagitis, nonerosive reflux disease (NERD), peptic ulcer disease (PUD), prevention of nonsteroidal anti-inflammatory drugs (NSAID) associated ulcers, Zollinger-Ellison syndrome (ZES), and functional dyspepsia. In combination with antibiotics, PPIs are also an integral part of eradication therapy for Helicobacter pylori. PPIs has prompted several concerns about both their short- and long-term effects. This review will examine the pharmacokinetics and pharmacodynamics of these drugs and provide an update on both the clinical use of and remaining challenges with PPIs.[2]

Table 1. Commercially Available Proton Pump Inhibitors in the United States

Drug	Dosages, mg	IV	Liquid or suspension	Generic	Over the counter
Omeprazole	10, 20, 40	Yes	No	Yes	Yes
Esomeprazole	20, 40	Yes	Yes	Yes	Yes
Esomeprazole	15, 30	Yes	Yes	Yes	Yes
Dex lansoprazole	30, 60	No	No	No	No
Pantoprazole	20, 40	Yes	Yes	Yes	No
Rabeprazole	20	No	No	Yes	No

Chemistry and Biology of PPIs

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 pyridylmethyl sulfinyl 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 (Prev acid; 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). Typical structures of PPIs are shown in Figure 1.[3]

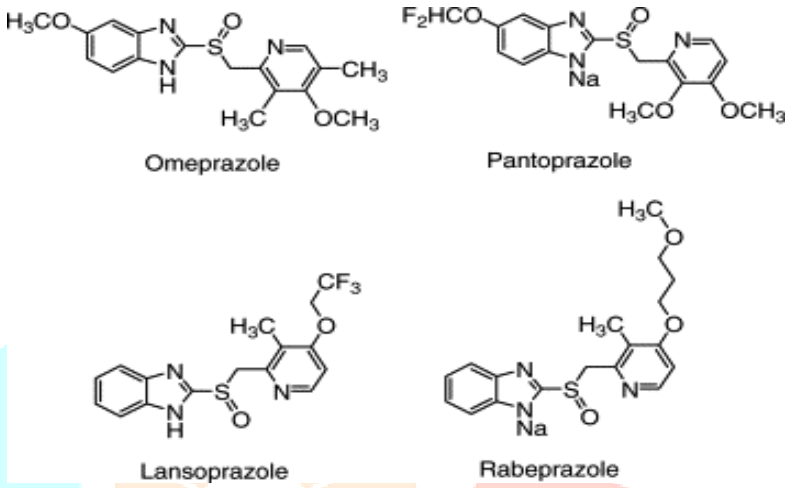

FIG:1- Proton pump inhibitors

TYPES OF PPIs

Data were provided on overall PPI and by specific PPI such as “Omeprazole,” “Esomeprazole,” “Pantoprazole,” “Lansoprazole,” and “Rabeprazole.” For less common PPIs such as Dex lansoprazole or other PPI combinations.

Proton-pump inhibitors (PPIs) represent a class of drugs most prominently known for their use in acid-related disorders. Omeprazole, a drug belonging to this class, is among the top 10 most prescribed drugs in the United States. PPIs are derivatives of the heterocyclic organic molecule benzimidazole. They are often the first-line agents amongst gastroenterologists for the following

1. Esophagitis
2. Non-erosive reflux disease
3. Peptic ulcer disease
4. Prevention of nonsteroidal anti-inflammatory drug-induced ulcers
5. Zollinger-Ellison Syndrome
6. Part of the triple therapy regimen for Helicobacter pylori infections

The FDA has approved the following PPIs as of 2015:

1. Omeprazole
2. Esomeprazole
3. Lansoprazole
4. Dex lansoprazole
5. Pantoprazole
6. Rabeprazole

PPIs also have utility in treating paediatric diseases. Currently, these drugs are FDA approved to treat symptomatic GERD in the short term and for healing eosinophilic esophagitis in the paediatric population.

As for non-FDA-approved uses, PPIs have been used as an add-on therapy for patients on antiplatelet therapy before or after endoscopic procedures with a high risk of bleeding sequelae, functional dyspepsia, and eosinophilic esophagitis. Touched on above, PPIs may also be useful in conditions that may result in heavy NSAID use, such as acute coronary syndrome or chronic pain, as a preventative measure against NSAID-induced ulcers. Furthermore, new research is exploring the potential anti-tumour effects of PPIs in the treatment of melanomas, multiple myeloma, colorectal cancer, lymphomas, metastatic breast cancer, and other cancer pathologies. [4]

MECHANISAM OF ACTION

Ultimately, PPIs function to decrease acid secretion in the stomach. The proximal small bowel absorbs these drugs, and once in circulation, affect the parietal cells of the stomach. The parietal cells contain the H+/K+ ATPase enzyme, the proton pump, that PPIs block. This enzyme serves as the final step of acid secretion into the stomach. Interestingly, PPIs are prodrugs activated only after undergoing an acid-catalysed cleavage in the acidic secretory canaliculi of the parietal cells. Hepatic P450 enzymes degrade PPIs. While there are slight variations in the exact P450 enzymes that are dominant in the degradation of the variety of PPIs, most dominantly degrade by the action of CYP2C19. Understanding the metabolism of PPIs allows us to understand why some PPIs work better for some individuals than others. For example, those of Asian ethnicity tend to have increased bioavailability of PPIs and thus should be managed initially with lower dosages. Furthermore, as we age, the bioavailability of PPIs increases, and thus dosages in the elderly should also be closely monitored and adjusted accordingly. While other drugs can reduce acid secretion in the stomach, PPIs represent the most potent drugs for acid reduction [5].

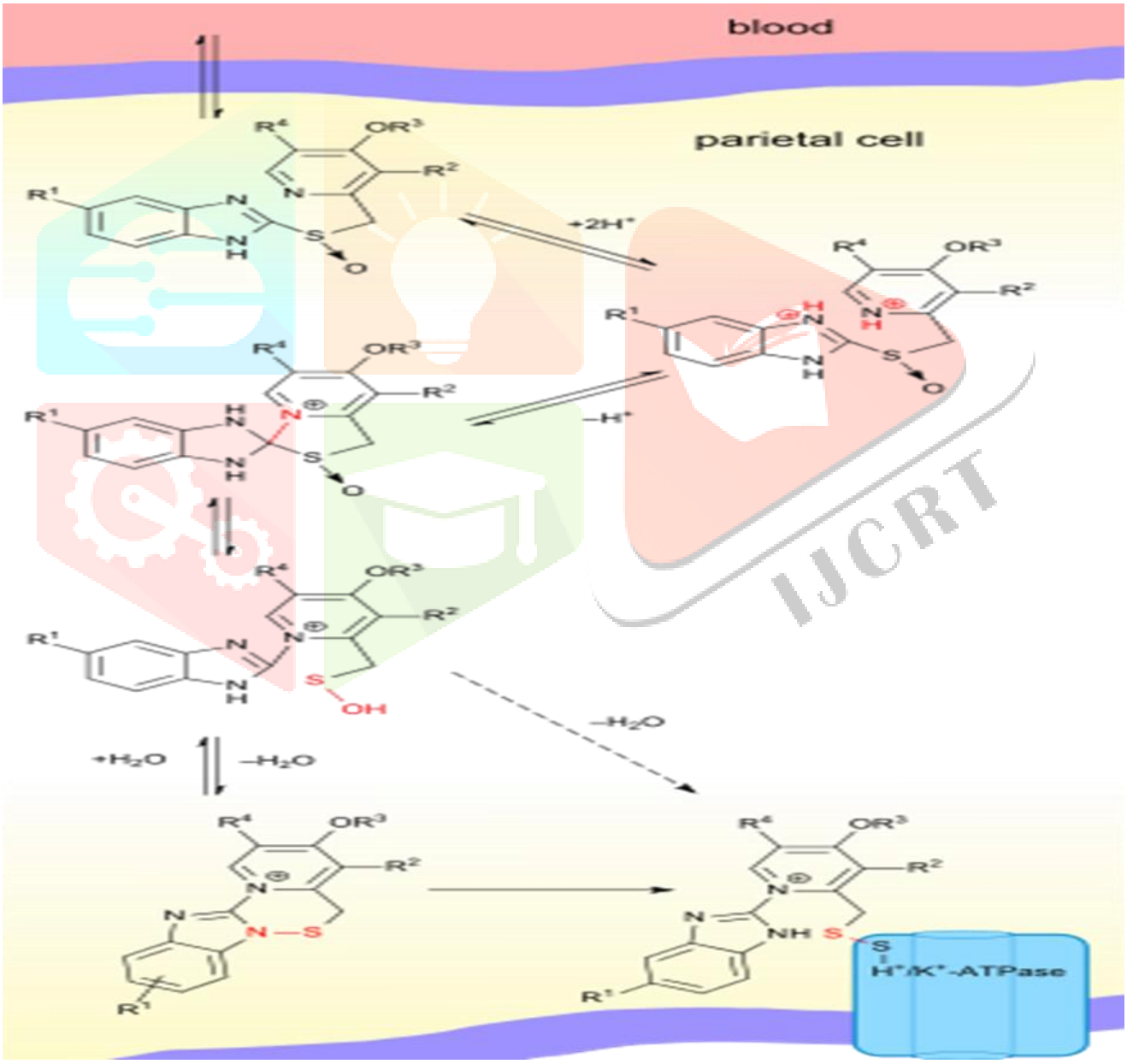

FIG -2: Mechanism of action of PPIs

Potential Mechanisms of PPIs Induced Fracture Risk:

PPIs, histamine antagonists, and other antiacid medications have improved the quality of life of patients affected by many gastrointestinal disorders. It has been demonstrated that a chronic use of PPIs is associated with potential adverse drug events, such as hypomagnesaemia, interstitial nephritis, and iron and vitamin B12 malabsorption. During the past 10 years, the relationship between PPIs and bone health has received attention from many investigators. In particular, PPIs seem to be associated with an increased risk of osteoporotic fractures, with a primary potential mechanism involving the physiological effects of chronic acid suppression on calcium, magnesium, and parathyroid hormone (PTH) metabolism. effect of PPI on bone cells has not been widely described, and available findings are limited and sometimes controversial. In general, PPI may cause dose-dependent inhibitory effects on osteoclastic and osteoblastic human cells leading to a kind of low bone turnover syndrome). Therefore, PPI-related bone fragility might be determined by the impairment of the repair mechanisms for bone microfractures that occur daily. However, PPIs use does not appear to determine significant bone quality impairment [6].

Acid Inhibition by Proton Pump Inhibitors

Proton pump inhibitors are used for the treatment of erosive gastroesophageal reflux disease (GERD). It is possible that gender may influence the degree of gastric acid inhibition afforded by PPIs. In a study conducted to determine the effect of two PPIs on stimulated gastric acid secretion, a sub analysis examined the influence of gender on proton pump inhibition of Penta gastrin-stimulated GAO. The results demonstrated that proton pump inhibition of Penta gastrin-stimulated GAO was significantly more effective in females compared to males in decreasing both volume and GAO. The inhibition of GAO in women was reflective of a significant decrease in gastric volume and H + secretion. Therefore, gender differences may exist in the inhibition of gastric acid secretion induced by PPIs.

Table:2 Proton Pump Inhibition of Penta Gastrin-Stimulated Gastric Acid Output

Empty Cell	N	Age	cumulative 24 hr GAO (mEq)	% change	cumulative 24 hr volume (ml)	$[H^+]$ (mEq/L)
Female	10	20-42	122 ± 35	65%	1766 ± 297*	61± 10*
Male	21	19–46	269 ± 35	22%	2917 ± 227	84± 7

Placebo (n = 3 females, 1 male; age 20–38), cumulative (24 hr) Penta gastrin-stimulated GAO was 344 ± 28 mEq; cumulative volume was 3100 ± 349 ml; and $[H^+]$ was 109 ± 10 mEq/L. Mean ± SEM;

*

= p < 0.05; % change = % decrease from placebo. Data collection after administration of a single dose of PPI.

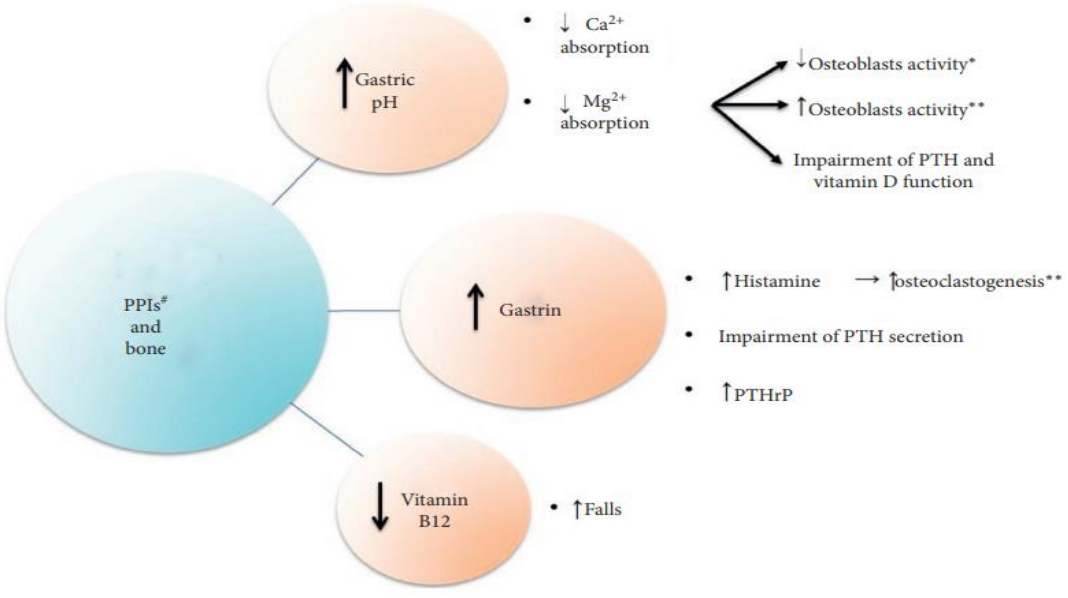

Figure-3 Potential mechanisms of PPIs induced fracture risk.

Therapeutics:

Proton pump inhibitors are prescribed for the treatment of acid related gastrointestinal diseases including gastric and duodenal (peptic) ulcers, reflux esophagitis, and Zollinger-Ellison syndrome. The beneficial acid-reducing properties of PPIs are due to formation of active sulphonamide metabolites. PPIs have also been shown to be effective in combination with antibiotics for the eradication of Helicobacter pylori. Administered orally in the form of enteric-coated "slow release" tablets, PPIs are normally taken before food, with the dose and duration of treatment depending on the PPI prescribed. Not recommended for children. For further information refer to parent pro-drugs including esomeprazole magnesium, lansoprazole omeprazole, pantoprazole (sodium sesquihydrate), and rabeprazole sodium (sodium salt)[7].

ADVERSE EFFECTS

As the usage of PPIs continues to rise, it becomes extremely important to understand the extent of their adverse effects. As the use of these medications is common, potential adverse effects have received significant media attention; however, it is essential to note that most of these associations have as their basis on low-grade evidence and observational associations rather than clear causation. The following is a description of the variety of adverse effects described in the literature.

Hypomagnesemia

Albeit a rare side-effect, PPIs may lower magnesium to a level not easily replenished by supplementation and only corrected with removal of PPI. Hypomagnesemia is a serious complication that predisposes the patient to tetany, seizure, muscle weakness, delirium, and cardiac arrhythmias. It is not yet entirely clear what causes this adverse effect, but one hypothesis suggests that it may be due to decreased active intestinal absorption of magnesium by the transient receptor protein channels (TRPM 6/7) that are stimulated by extracellular protons.

Infection

While the acidic environment of the stomach serves as an environment in which proteins become activated to perform certain functions, so too does it serve as a chemical barrier against bacterial infection. PPIs have correlations with an increased amount of *Clostridium difficile* infections, other enteric foodborne infections, and potentially increased risk of community-acquired pneumonia. While it is still unclear as to the exact mechanism for this increased infection risk, one hypothesis proposed that the decreased acidic environment of the stomach leads to bacterial overgrowth and increased risk of bacterial aspiration [8].

Rebound Acid Secretion

PPIs can increase the levels of gastrin, which in turn leads to increased proliferation of ECL cells. ECL cells produce histamine, which under normal circumstances, stimulates parietal cells to activate their H+/K+ ATPase and produce acid into the stomach. Because PPIs act a step further than histamine, this side-effect does not negate the effect of PPIs. However, the problem lies in the discontinuation of PPIs after prolonged use, which has been shown in some cases to result in acid levels higher than before the initiation of PPIs. This effect has been referred to as rebound acid secretion.

Vitamin Deficiency

When vitamin B12 enters the stomach, it is bound to a protein molecule, R-factor. For vitamin B12 to release from R-factor, proteases need to be activated by an acidic environment. Once activated, the peptidases release R-factor from vitamin B12 so that it may bind another molecule, intrinsic factor, for absorption at the level of the terminal ileum. Disruption of the stomach's acidic environment by PPIs may lead to a vitamin B12 deficiency, although this appears to be clinically rare. Additionally, iron deficiency has also been reported with prolonged PPI use, although the exact mechanism remains elusive. There is also slight malabsorption of insoluble calcium separate from food, which many believe to be subclinical in most cases.

Other Potential Associations

Due to the frequency of PPI administration, numerous other potential associations have been reported and have received significant attention. Conflicting data have linked PPI use with osteoporosis and bone fracture; proposed mechanisms include calcium malabsorption, increased gastrin, decreased vitamin B12, and potential proton pumps in the bone. However, the data are not consistent, and while there may be an association, there is not a clearly established ethology at present. Likewise, isolated retrospective analyses have suggested a potential link between PPI use and dementia, kidney disease, and heart disease. However, these associations have not occurred to date in prospective studies, and there have been significant concerns raised with the retrospective analyses given potential confounding. Moreover, for dementia and heart disease, in particular, the findings, even in retrospective analyses, have been inconsistent [9].

USES

Doctors prescribe PPIs to treat stomach acid-related symptoms, such as heartburn and acid reflux. Sometimes, these symptoms will occur due to an underlying condition. Common underlying causes of chronic heartburn and acid reflux include:

- stomach ulcers, or a helicobacter pylori infection
- GERD and hiatal hernias
- lower oesophageal sphincter dysfunction
- Anxiety, smoking, and frequent alcohol consumption can also trigger heartburn and acid reflux in some people.

USAGE ISSUES

Although significant overlap exists between EE and nonerosive reflux disease (NERD), it is estimated that 40% to 50% of patients with typical reflux symptoms have non-EE. It is believed that patients with true EE and treated with PPIs may develop healed EE, therefore being misclassified as having NERD. It has therefore been suggested that patients with reflux-like symptoms have upper endoscopy while off PPI for accurate endoscopic diagnosis. This distinction is important because lower and slower response rates to PPIs have been noted in NERD as compared with EE. This is possibly related to underlying H pylori infection in patients with NERD, as noted in a 2009 meta-analysis. Therefore, a test-and-treat strategy may be used in which a trial of PPI may be initiated,

and if symptoms are refractory to treatment, then testing and treating H pylori may be undertaken.In patients who fail PPI once-daily treatment for both healing EE and symptom relief of GERD, two strategies are often used. Switching to another PPI is one strategy and doubling PPI dose is the more common strategy. Although the latter is the strategy recommended by the 2008 American Gastroenterological Association guidelines for GERD, there is no PPI dose-response relationship for EE or NERD. If double-dose therapy is to be considered, PPI should be taken before eating breakfast and before eating dinner on the basis of studies showing improved control of gastric pH when PPI is taken twice per day as opposed to taking two pills before breakfast. Patients should be advised regarding the increased risk of adverse effects before initiating twice-daily therapy [10].

PHARMACOKINETIS

The rate of omeprazole absorption is decreased by concomitant food intake. In addition, the absorption of lansoprazole and esomeprazole is decreased and delayed by food. It has been reported, however, that these pharmacokinetics effects have no significant impact on efficacy. In healthy humans, the half-life of PPIs is about 1 hour (9 hours for tenatoprazole), but the duration of acid inhibition is 48 hours because of irreversible binding to the H, K-ATPase. All the PPIs except tenatoprazole are rapidly metabolized in the liver by CYP enzymes (mostly by CYP2C19 and 3A4). Dissociation of the inhibitory complex is probably due to the effect of the endogenous antioxidant glutathione which leads to the release of omeprazole sulphide and reactivation of the enzyme.

Table:3 Pharmacokinetic Properties of Proton Pump Inhibitors

	Omeprazole	Esomeprazole	Lansoprazole	Dex lansoprazole	Pantoprazole	Rabeprazole
Bioavailability, %	30–40	64-90	80-85	-	77	52
Time to peak plasma level (t_{max}, 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 CYP3A4	CYP2C19 CYP3A4	CYP2C19

H2RAs competitively bind to histamine H2 receptors on the basolateral plasma membrane of parietal cells and inhibit binding of histamine to these receptors, resulting in inhibition of gastric acid secretion mainly during the nocturnal period, since histamine-stimulated acid secretion is important at that time.[1,4] H2RAs do not effectively inhibit gastrin- or acetylcholine-induced stimulation of gastric acid secretion, which is important in regard to post-prandial acid secretion. The acid suppressing effect of an H2RA quickly appears when its concentration in plasma increases after the first dose.[5] However, as with many types of receptor antagonists, H2RAs show gradually weakened acid suppression, a tolerance phenomenon, following repetitive administration of only approximately 2 weeks.[1,4] Thus, H2RAs are considered to be short-distance track sprinters and not long-distance marathon runners.

Pharmacological action

Potassium competitive acid blockers (P-CABs) inhibit acid secretion by binding to the potassium binding site of alpha-subunit of proton pumps with iron bonds.[6,7] Although P-CABs show a very quick acid suppressing effect with oral administration, their superior clinical benefits as compared to conventional PPIs are not confirmed, except for *Helicobacter pylori* eradication therapy and for PPI-resistant GERD.[8–11] Various P-CABs have indeed been found to have therapeutic effects similar to those of standard PPIs when used for treatment of uncomplicated GERD.[12,13] In fact, revaprazan and vonoprazan, P-CABs available throughout the world, are now used only in several countries including Korea and Japan, different from standard PPIs.

PPIs must be activated by highly concentrated hydrogen irons before binding to proton pumps. For that activation, the parietal cells must actively secrete hydrogen irons into the secretory canaliculi when the PPI reaches that network. When gastric acid secretion has been inhibited by a pathological condition or medication, even partially, complete activation of the PPI may be prevented and its acid suppressing effect weakened. Only after acid-induced activation has occurred, PPIs bind to SH residues of proton pump cysteines.[17] Since only a part of the proton pump is in an active acid secreting state when a PPI is administered, repeated administrations of the drug are necessary for adequate and complete inhibition of proton pumps. Even during the period of stable acid inhibition following several initial oral doses, acid inhibition during the nocturnal period is weaker with a once daily morning dose, since approximately 25% of proton pumps are replaced by newly synthesized ones within 24 hours and the newly synthesized pumps after the morning PPI administration will begin to secrete acid during the nocturnal period[11].

Advantages of long-term proton pump inhibitors use

1. PPIs potently inhibit gastric acid secretion, especially during the daytime period following a daily single morning dose.
2. Acid inhibition provided by per-oral administration gradually increases during the first 3–5 days after the start of administration.
3. PPIs do not show tolerance phenomenon, even after long-term treatment. Since nocturnal acid inhibition is not so strong and intra-gastric pH during the nocturnal period remains at around 2.0 in the majority of administered cases, the pre-breakfast plasma gastrin concentration measured in the early morning does not show a remarkable elevation.
4. These characteristics of PPIs may be considered to be advantageous for long-term control of gastric acid secretion.
5. Long-term inhibition of gastric acid secretion is necessary for GERD maintenance therapy and prevention of occurrence of gastroduodenal ulcers during administration of aspirin or NSAIDs.[19–23]
6. Long-term PPI administration is also helpful for preventing recurrence of aspirin-induced gastroduodenal ulcers and is more effective than H2RAs, with a decrease in recurrence to approximately one-tenth of that seen in placebo-treated groups.[23,27–29]
7. Since many patients with cerebrovascular or cardiovascular diseases are treated with aspirin as an anti-thrombotic drug, prevention of aspirin-induced ulcers is critically important for prevention of NSAID-induced ulcers. Thus, PPIs are first-line drugs used for the prevention of aspirin/NSAID-related ulcer recurrence, and their continuous administration is effective and potent for the prevention of recurrence as well as maintenance therapy of GERD.

Disadvantages of long-term proton pump inhibitors:

All clinical drugs have both therapeutic and adverse effects, including PPIs. Since the basic chemical structure of available PPIs is similar, the adverse effects of the drugs are also similar and can be divided into 2 types, those related and unrelated to acid inhibition. The majority of acid inhibition-related adverse effects are observed during long-term treatment with a PPI, while those unrelated to acid inhibition are observed in patients with long-term as well as those with short-term treatment [12].

Table :4 Adverse events reported in patients treated with proton pump inhibitors

Adverse events unrelated to acid Inhibition	adverse events related to acid Inhibition
Allergic reaction to drug chemicals	pneumonia
Collagenous colitis	gastrointestinal infection
Acute interstitial nephritis	gastric carcinoid tumour
Chronic kidney disease	gastric fundic mucosal hypertrophy
Drug interaction	changes in gut microbiome

CONCLUSION

Absolute indications for PPI use include PUD, chronic NSAID use, treatment of H pylori infection, and EE. Further studies are needed to establish treatment duration after H pylori clearance for bleeding PUD and for chemoprophylaxis in Barrett oesophagus. PPIs are not without significant adverse effects; therefore, their long-term use must be reevaluated periodically and discontinued when appropriate. This specifically applies to patients with NERD or PUD and patients taking double-dose PPI, from which questionable benefit is obtained. After 20 years of experience with these drugs, many caveats apply to their use.

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