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Editorial

Pros and cons of long-term use of PPI — an editorial

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The parietal cells of stomach secrete hydrochloric acid which is important not only for sterilization of bacteria contained in ingested foods, but also essential for digestion and absorption of various nutritients, such as iron, calcium, vitamin B12, and protein,. Gastric acid secretion is a multifactorial and complex process regulated by at least three different pathways upon the parietal cell. These pathways include the paracrine secretion of gastrin and histamine, as well as the actions of postganglionic muscarinic acetylcholine. As the secreted acid may damage the gastrointestinal tract, various types of protective mechanisms, including mucosal mucous/bicarbonate secretion and sphincter contraction of the gastroesophageal junction, are present to prevent gastric acid-induced gastroesophageal damage. When these protective mechanisms are overcome by acid secretion, gastrointestinal mucosa can become irritated and damaged, resulting in unpleasant symptoms or even organic diseases i.e. acid-related diseases. Acid-related diseases include gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), Barrett's esophagus, Zollinger-Ellison syndrome and functional dyspepsia. Neutralizing agents and various inhibitors of gastric acid secretion have been developed for treatment of acid-related diseases. There is a long history of development of various drugs for acid-related diseases; initially, neutralizing drugs containing aluminum or magnesium, were developed, then anti-cholinergic agents. Then, Histamine2-receptor antagonists (H2RAs) were introduced for treatment. Proton pump inhibitor (PPI)-omeprazole was first introduced in 1989, and have steadily become the main drug for treatment of acid-related disorders. Six PPIs are approved by the United States Food and Drug Administration (FDA) in 2015 [1].

These six PPIs are

- Omeprazole
- Esomeprazole
- Lansoprazole
- Dexlansoprazole
- Pantoprazole
- Rabeprazole

PPI inhibits the final common pathway of acid secretion (H/K ATPase) and is the most potent inhibitor of acid secretion [2, 3]. PPIs have demonstrated excellent safety, consistent patient tolerance, and generally superior acid suppressing ability than other agents [2,4]. PPI represents the first choice of drugs for treatment of gastroesophageal reflux disease (GERD), 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 [5-7]. In combination with antibiotics, PPIs are also an integral part of Helicobacter pylori eradication therapy [8]. The beneficial therapeutic effects of PPIs for the treatment of GERD, gastroduodenal ulcers, and H. pylori eradication are well established, while their effects for symptomatic improvement in patients with functional dyspepsia are limited [9]. PPI is recommended for 4 weeks in patients with dyspepsia or peptic ulcer and 8 weeks in patients with reflux symptoms. In a clinical context, when PPI is used for more than 8 weeks in patients with reflux symptoms and more than 4 weeks in patients with dyspepsia or peptic ulcer might be a reasonable definition of long-term use. Long-term suppression of acid secretion is essential for GERD maintenance therapy and prevention of occurrence of peptic ulcers during administration of aspirin or NSAIDs [10-14]. In other indications, PPIs are administered intermittently or on an on-demand basis, but not continuously. Therefore, GERD maintenance therapy and prevention of drug-related ulcer recurrence are considered 2 important conditions that necessitate long-term PPI administration. 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 aspirin-induced ulcers in these patients group. Thus, PPI is the first-line drug used for the prevention of aspirin/NSAID-related ulcer recurrence, and its continuous use is effective and potent for the prevention of recurrence as well as maintenance therapy of GERD. All currently available PPIs have both beneficial and adverse effects like other drugs. The majority of adverse effects related to PPI administration are reported to occur after chronic use. Since the basic chemical structure of available PPIs is similar, the adverse effects of the drugs are also similar and can be of 2 types, those related and unrelated to acid inhibition shown in Table 1.

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Table – I: Adverse Events of 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 tumor
• Chronic kidney disease	• Gastric fundic mucosal hypertrophy
• Drug interaction	• Changes in gut microbiome
• Dementia	• Small intestinal bacterial overgrowth
• Cerebral ischemic diseases	• Iron deficiency
• Ischemic cardiac diseases	• Bone fracture
	• Vitamin B12 deficiency
	• Hypomagnesemia
	• Gastric fundic gland polyps
	• Gastric cancer
	• Colon cancer
	• Spontaneous bacterial peritonitis
	• Hepatic encephalopathy
	• Drug interaction

Adverse effects unrelated to acid inhibition are observed in patients with both long-term and short-term use while the majority of acid inhibition-related adverse effects occurred during long-term treatment with a PPI. Though the list is long, practically the incidence and prevalence are not high, whereas because of diverse study results, it is difficult to conclude. Some examples are given below-

1. A retrospective study observed a small risk of pneumonia only in the short term after starting PPI administration, but a meta-analysis of prospective randomized controlled studies did not show increased risk of pneumonia during the administration of various PPIs [15].
2. Acid-labile bacteria such as Salmonella, Campylobacter, and the vegetative form of Clostridium difficile, may have an increased risk of infection and grow in the gastrointestinal tract when gastric acid secretion is suppressed by a PPI [16,17]. Because of inconsistent study results, it is difficult to conclude whether PPI increases the risk of Salmonella and/or Campylobacter infection. Several studies have assessed the risk of C. difficile enteritis in cases treated with PPIs, which found that long-term use may be responsible for an increased risk, whereas short term treatment may not increase that risk [18,19]. Other prospective study results did not support this claim [20-23].
3. In 2006, a nested, case-controlled series including more than 13,000 patients from the UK suggested that the risk of hip fracture was increased with PPI use that exceeded 1 year (OR, 1.44) and was especially increased in those patients who had received high-dose PPIs (OR, 2.65) [24]. A later study which did not include patients who had major risk factors for hip fracture showed no association with PPI use and postulated that the earlier findings may have been due to confounding [25].
4. All PPIs are, to some extent, metabolized by the cytochrome P450 isozyme 2C19 and have enzyme inhibition property. Specifically, the fact about PPI induced enzyme inhibition to prevent the activation of clopidogrel was first observed during in vitro studies which found that that simultaneous administration of omeprazole diminished the effect of clopidogrel on platelet inhibition, but have no in vivo data which has conclusively connected the use of omeprazole and clopidogrel with adverse clinical outcomes. In 2009, the FDA recommended avoiding the use of both drugs simultaneously [26]. Never the less given our knowledge of the pharmacodynamics, we should avoid omeprazole (and its stereoisomer, esomeprazole) in patients taking clopidogrel and use alternatives such as lansoprazole, dexlansoprazole, or pantoprazole.

There are multiple studies about adverse effects but results are not consistent.

PPIs have several adverse effects although the clinical impacts of these adverse effects are not so serious. However, balancing beneficial and adverse effects as well as selecting appropriate patients who will get larger benefits by the PPIs use are critically important.

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