



Advantages and Disadvantages of Long-term Proton Pump Inhibitor Use

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Proton pump inhibitors (PPIs) potently inhibit gastric acid secretion and are widely used for treatment of acid-related diseases including gastroesophageal reflux disease and secondary prevention of aspirin/NSAID-induced ulcers. Although clinically important adverse effects of PPIs can occur, just as with other drugs, those are not frequently observed during or after administration. Thus, PPIs are regarded as relatively safe and considered to be clinically beneficial. Recently, PPIs have become frequently administered to patients with functional gastrointestinal diseases or primary prevention of drug-related gastroduodenal damage, even though their beneficial effects for those conditions have not been fully confirmed. PPIs tend to be given for conditions in which the necessity of the drug has not been clarified, thus otherwise rare adverse effects are presented as clinically relevant. Although several PPI-related adverse effects have been reported, their clinical relevance is not yet clear, since the evidence reported in those studies is not at a high enough level, as the majority are based on retrospective observational studies and the reported hazard ratios are low. It is important to administer PPIs only for patients who will gain a substantial clinical benefit and to continue to investigate their adverse effects with high quality prospective studies.

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Key Words

Adverse effect; Allergic disease; Gastric acid; Gastroesophageal reflux; Ulcer

Introduction

The stomach is the only organ that secretes acidic fluid as low as pH 2. Such gastric secretion is important not only for sterilization of bacteria contained in ingested foods, but also for digestion and absorption of various nutritional factors, such as protein, iron, calcium, and vitamin B12. However, since 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 gas-

tric secretion-induced gastroesophageal damage. When those protective mechanisms are overcome by acid secretion, gastrointestinal mucosa can become damaged and irritated, resulting in unpleasant symptoms or even organic disease. Such pathological conditions are referred to as acid-related diseases and include gastroduodenal ulcers, gastroesophageal reflux disease (GERD), Barrett's esophagus, and functional dyspepsia.

For treatment of acid-related diseases, various inhibitors of gastric acid secretion and neutralizing agents have been developed. Initially, neutralizing drugs containing aluminum or magnesium, and anti-cholinergic agents were employed. However, the effects

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of those for acid inhibition are limited and their use frequently has adverse effects, including cardio-vascular events, diarrhea, and constipation. In addition, acid-neutralizing drugs are prone to interact with other drugs in the gastrointestinal tract and change the bio-availability of co-administered medication. Therefore, those originally used for acid-related diseases have been nearly completely replaced by histamine H₂ receptor antagonists (H₂RAs), which were developed in the late 1970s. An H₂RA cancels the acid secretory effects of histamine. Because of the stimulating effects of gastrin and acetylcholine, especially during the post-prandial period, an H₂RA most effectively inhibits gastric acid secretion during the nocturnal period.¹ Accordingly, H₂RAs are not potent enough for treatment of GERD with post-prandial reflux, though they are effective for gastroduodenal ulcers. Thereafter, along with the increase in prevalence of GERD from 1980 to 1990, proton pump inhibitors (PPIs) were developed for more potent acid inhibition during the daytime period and used as first-line treatment for acid-related diseases.²

Employment of PPIs steadily and remarkably increased after starting clinical use for treatment of acid-related diseases, and they are now some of the most frequently prescribed drugs throughout the world,³ with large numbers of affected patients provided ongoing treatment with PPI administration for several years. Along with their popularity, adverse events possibly related to long-term administration of PPIs have been reported, though the level of risk is not high. In this review, we describe the pharmacological characteristics of PPIs and compare them with those of H₂RAs. Furthermore, we present a balanced interpretation of reports concerning the advantages and disadvantages of PPI use.

Pharmacological Characteristics of Proton Pump Inhibitors

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.

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, rabeprazole and vonoprazan, P-CABs available throughout the world, are now used only in several countries including Korea and Japan, different from standard PPIs.

PPIs are the most widely used medication for gastric acid inhibition in the world. All the PPIs available in Japan, including omeprazole, esomeprazole, lansoprazole, and rabeprazole, have a benzimidazole nucleus in their molecules along with various types of branch structures. These drugs covalently bind to SH residues of cysteine molecules in the alpha-subunit of proton pumps on the secretory canalicular membranes of gastric parietal cells and inhibit the acid secretory function of those pumps, resulting in inhibition of gastric acid secretion. Since all currently available PPIs share the same molecular structure, they also have similar pharmacological characteristics. A PPI is unstable in an acidic condition. Therefore, an enteric coating or co-administration with an acid-neutralizing agent such as sodium bicarbonate is necessary to obtain adequate per-oral bioavailability. Following absorption in the small intestine, a significant percentage of first-generation PPIs (omeprazole and lansoprazole) are degraded by hepatic enzymes including CYP2C19. In contrast, second-generation PPIs (esomeprazole and rabeprazole) are more stable and their plasma concentration is not strongly influenced by different CYP2C19 hepatic enzyme activities.^{14,15} Although their plasma half-life is only 2-3 hours, these drugs remain bind to proton pumps for an extended period and inhibit pump activity, until new pumps are finally synthesized and replace the old ones in parietal cells. According to a previous study, 25% of proton pumps in a parietal cell will be replaced by newly synthesized pumps within 1 day.^{16,17}

PPIs must be activated by highly concentrated hydrogen ions before binding to proton pumps. For that activation, the parietal cells must actively secrete hydrogen ions 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.¹⁸ PPIs are almost exclusively metabolized by the liver and not by the kidneys, thus their potency is not influenced by impaired renal function. Furthermore, their acid inhibitory effect does not decrease even after long-term continuous administration, which is different from H2RAs. Therefore, PPIs are effective for long-term acid inhibition, especially during the daytime period, because of their lack of tolerance phenomenon. PPIs are considered to be long-range marathon runners and not short-range track sprinters.

Advantages of Long-term Proton Pump Inhibitor Use

PPIs potently inhibit gastric acid secretion, especially during the daytime period following a daily single morning dose. Acid inhibition provided by per-oral administration gradually increases during the first 3-5 days after the start of administration. 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. These characteristics of PPIs may be considered to be advantageous for long-term control of gastric acid secretion.

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 For control of dyspepsia, which affects patients with functional dyspepsia (FD), acid inhibitors are intermittently administered or given on an on-demand basis, but not continuously. Therefore, GERD maintenance therapy and prevention of drug-related ulcer recurrence are 2 important conditions that necessitate long-term PPI administration. Patients with GERD mainly complain of reflux symptoms after meals, since gastroesophageal refluxes frequently occur during the postprandial period. Since the acid suppressing effect of a single morning dose of a PPI remains potent during the daytime

period, PPIs are reported to be effective to prevent recurrence of reflux symptoms and esophageal erosions/ulcers.¹⁹⁻²¹ With their continuous administration, recurrence of GERD during maintenance therapy for 1 year is reported to be less than 15%, while recurrence within 1 year without maintenance therapy is estimated to be greater than 50%.^{24,25} When the preventive effect of PPIs for GERD recurrence was compared with that of H2RAs, PPIs were found to be much more effective. Their long-term administration may also be effective for prevention of neoplastic transition of Barrett's esophagus to dysplastic Barrett's esophagus, such as an adenocarcinoma. It has not been completely established whether PPIs effectively prevent dysplastic changes of Barrett's esophagus. However, no report has indicated that these drugs aggravate dysplastic changes, though several have suggested that they effectively prevent dysplastic changes.²⁶ Thus, long-term maintenance therapy with a PPI is effective for preventing recurrence of GERD and may also prevent neoplastic progression of Barrett's esophagus.

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} Similarly, in cases administered with an NSAID, PPIs were reported to decrease the recurrence rate to one-tenth of that of a placebo group over a 6- to 12-month observation period.²² 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 Use

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 (Table).

Table. 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 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 Events Unrelated to Acid Inhibition

The relative importance of acid inhibition unrelated adverse events is shown in Figure 1.

Possible Allergic Reaction to Drug Chemicals

Anaphylaxis, pancytopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, acute liver damage, Lyell syndrome, Stevens-Johnson syndrome, interstitial nephritis, and rhabdomyolysis may occur in a small number of cases treated with a PPI, as well many other types of drugs.³⁰⁻³⁴ Since prediction of occurrence of these possibly life-threatening effects is difficult, it is important to correctly consider indications and administer PPIs only to patients who truly need potent acid suppression. In addition, patients should be instructed to report unexplained skin eruptions, fever, or general malaise appearing after starting a PPI administration to their attending physician without delay. Doctors also should check for possible adverse effects within the first few weeks after starting an administration by scheduling follow-up consultation sessions.

Collagenous Colitis

Diarrhea is frequently experienced by patients being treated with PPIs.³⁵ Some cases of PPI-related diarrhea may be complicated with collagenous colitis, which is characterized by diarrhea and histo-pathological identification of thick collagen bands beneath the

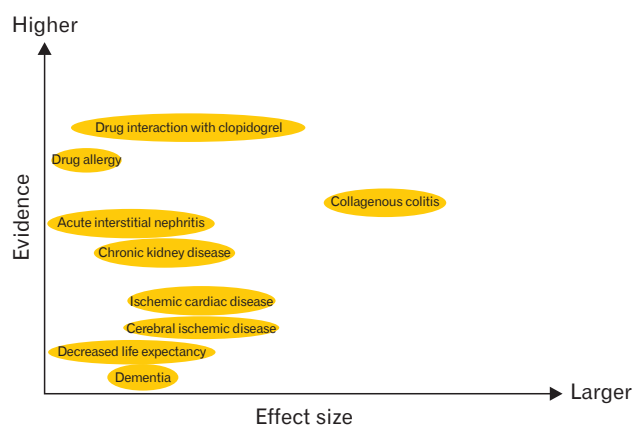


Figure 1. Acid-inhibition unrelated adverse events reported during proton pump inhibitor administration. Possible evidence level and effect size of each adverse effect is shown.

colonic epithelium. According to the case-control study, PPI use is associated with an increased risk for collagenous colitis (hazard ratio 4.5).³⁶ Although a variety of drugs, including all available PPIs, are reported to be possible pathogenetic factors of collagenous colitis, the PPI lansoprazole is most frequently reported as responsible.³⁷ Although the pathogenetic mechanism of PPI-related as well as that of non-drug-related collagenous colitis has yet to be clarified, PPI-induced augmentation of collagen gene expression in colonocytes may partially be responsible for it.³⁸ PPIs-related collagenous colitis usually resolves spontaneously after cessation of the drug.³⁹ Therefore, when patients complain of diarrhea after starting a PPI,

possible occurrence of collagenous colitis must be considered.

Acute Interstitial Nephritis and Chronic Kidney Disease

It has been reported that interstitial nephritis may occur in patients treated with a PPI, possibly because of an allergic reaction to the drug, though the precise mechanism is not clear.^{40,41} In biopsy-proven cases, 70% of acute interstitial nephritis was reported to be caused by the drugs and as high as 14% of them is caused by PPIs.⁴² In addition to an acute renal injury, it is reported by many investigators that long-term PPIs administration is associated with chronic kidney disease when the renal functions were evaluated by the serum creatinine levels or estimated glomerular filtration rate, though the hazard ratio is very modest (1.1-1.5) and the results are based only on observational studies.⁴³⁻⁴⁷ Thus, patients must be regularly checked while under prescription for the possible occurrence of renal dysfunction, although it is not clear whether acute interstitial nephritis and chronic kidney disease are causally related or not.⁴⁸

Drug Interaction During Activation and/or Degradation Phase in Liver

Many drugs including PPIs, diazepam, phenytoin, and warfarin are at least partially degraded by hepatic drug metabolizing enzyme CYP2C19. However, the capacity of that enzyme is not large sufficient, thus PPI administration may decrease the level of degradation of other drugs, augmenting their pharmacological effects. On the other hand, for activation of clopidogrel, CYP2C19 enzyme activity is necessary. Therefore, PPIs administration in patients treated with clopidogrel may decrease its anti-thrombotic activity and increase the risk of cardiovascular events.

Based on the pharmacodynamic studies, PPIs attenuate clopidogrel-induced inhibition of platelet aggregation. In these studies, ADP-induced platelet aggregation inhibition was measured by thromboelastography with and without PPIs administration in cases treated with clopidogrel. The results of the study and a systematic review clearly showed that clopidogrel-induced inhibition of platelet aggregation is weakened by the co-administration of PPIs, although some reports showed that rabeprazole, which is not mainly metabolized by CYP2C19, did not statistically significantly attenuate the anti-thrombotic effect of clopidogrel.⁴⁹⁻⁵²

This consistent pharmacodynamic study result, however, was not confirmed in clinical studies. Firstly performed epidemiological study supported this concept and suggested that PPIs interfered with clopidogrel activation and elevated cardiovascular risk.⁵³ How-

ever, some retrospective studies thereafter did not support this.^{54,55} A meta-analysis of retrospective studies suggested the possible risk of increased major cardiac events in association with PPI administration in cases chronically treated with clopidogrel, though not all such studies reached the same conclusion.^{56,57} The level of evidence presented by those retrospective studies was not adequate to make clinically relevant conclusions. Additionally, 3 prospective randomized controlled studies, including the famous (the Clopidogrel and the Optimization of Gastrointestinal Events Trial) COGENT study, suggested a lack of PPI-induced increase of major cardiac events, even when administered to patients treated with clopidogrel.⁵⁸⁻⁶⁰ Although further studies may be necessary to conclude whether PPIs and clopidogrel have clinically meaningful interactions, the available data in the literature considers to not prevent the use of PPIs in patients treated with clopidogrel, if they need PPI administration.

Dementia

Recently, a group of investigators reported 2 publications and suggested the increased risk of dementia in elderly persons treated with PPIs based on retrospective studies on a German database.^{61,62} Hazard ratios of these 2 studies were modest and were 1.38 and 1.44 respectively, though they claimed potentially enhanced amyloid beta peptide levels in the brain by direct inhibition of the enzymes beta- and gamma-secretase with PPIs as a possible causative mechanism.⁶³ Three following retrospective studies done in USA and in Europe, on the other hands, did not detect the statistically significant risk of dementia in patients treated with PPIs.⁶⁴⁻⁶⁶ In addition, recently reported prospective population-based study clearly indicated that PPIs use was not associated with the dementia risk, even for people with high cumulative exposure and suggested that PPI administration should not be avoided out of concern about dementia risk.⁶⁷

Others

Increased risks of cerebral ischemic diseases, ischemic cardiac diseases un-related to clopidogrel administration and even decreased life expectancy were recently reported in cases treated with long-term PPIs administration.⁶⁸⁻⁷¹ However, studies that presented findings suggesting those as risks were retrospectively performed using a database constructed for other purposes, and no prospective investigation has been done to determine the true risk of these pathological conditions developing from PPI use. The reliability of those retrospective studies is not high. Only a large risk over odds ratio (OR) greater than 2-3 is considered to be clinically relevant.

Since the reported OR values of these diseases are 1-2, they may not be clinically relevant. Furthermore, these studies did not fill the Hill criteria for Causation.^{72,73} Additional studies, possibly even prospective investigations, are needed in the future to establish the true risk of PPI administration in regard to these diseases.

Acid Inhibition Related Adverse Events

The relative importance of acid inhibition related adverse events is shown in Figure 2.

Pneumonia

Administration of PPIs decreases the bactericidal effect of gastric juice by increasing intra-gastric and lower esophageal intraluminal pH. In addition, PPIs may also decrease anti-bacterial immunity by decreasing lysosomal enzyme activity.⁷⁴ The increased risk of pneumonia in cases treated with PPIs was originally reported based on retrospective studies of a primary care based database.⁷⁵⁻⁷⁷ The majority of PPI-administered cases in the database were patients with GERD. Only during the period less than 30 days after starting administration was the risk of pneumonia shown to be elevated. On the other hand, long-term administration over 30 days was not associated with a risk of pneumonia.⁷⁸ The mechanism of this observed risk is difficult to understand. In addition, a study of cases administered PPIs for prevention of recurrent NSAIDs related ulcers did not show an increased risk of pneumonia after that administration.^{79,80} These results bring into question the reliability of the primary care diagnosis of GERD. Cough or laryngo-pharyngeal symptoms caused by a respiratory infection can be misdiagnosed as laryngo-pharyngeal symptoms related to GERD, with a PPI thus administered. The small risk of pneumonia observed only in the short term after starting PPI administration may not actually be a clinically relevant risk for long-term treatment of GERD. Additionally, different from retrospective studies, a meta-analysis of prospective randomized controlled studies did not show increased risk of pneumonia during the administration of various PPIs.⁸¹

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Increased Gastrointestinal Infection

Bacteria that may cause a gastrointestinal infection can be divided into acid-resistant and acid-labile. Acid-labile bacteria, including *Salmonella*, *Campylobacter*, and the vegetative form of *Clostridium difficile*, may have an increased chance to infect and grow in the gastrointestinal tract when gastric acid secretion is suppressed by a PPI.^{82,83} As for infection with *Salmonella* and *Campylobacter*, many retrospective studies have suggested increased infection rates during administration of PPIs, though some cohort studies have failed to show such increased infection in PPI-treated cases.^{84,85} Because of diverse study results, it is difficult to conclude whether PPIs increase the risk of *Salmonella* and/or *Campylobacter* infection.

C. difficile enteritis is an increasing problem especially in western countries, because of the growing population of strains resistant to antibiotics. Several studies have examined the risk of *C. difficile* enteritis in cases treated with PPIs, which found that long-term administration may be responsible for an increased risk, whereas short-term treatment may not increase that risk.^{84,86} The study results investigating whether PPI administration increases risk of recurrent *C. difficile* enterocolitis and/or severe-complicated diseases are not consistent.⁸⁷⁻⁹⁰ Thus, long-term administration of PPIs should be limited to patients who truly need medication, as that may increase the risk of *C. difficile* enteritis to an OR of 1.5-2.0.

Gastric Neuroendocrine Tumor

PPI administration increases plasma gastrin concentration by increasing intra-gastric pH. Since gastrin stimulates proliferation of gastric enterochromaffin like (ECL) cells with abundant gastrin receptors, PPIs have been consistently reported to increase the number of ECL cells in the gastric fundic mucosa.⁹¹ Patients with high grade chronic atrophic gastritis have an increased concentration of gastrin in plasma and occasionally show development of type 1 gastric neuroendocrine and carcinoid tumors, though hypergastrinemia is considered not to be a sufficient condition for the progression from hyperplasia to dysplasia of ECL cells.^{92,93} Gastric carcinoid tumors are divided into 3 types, type 1 with hypergas-

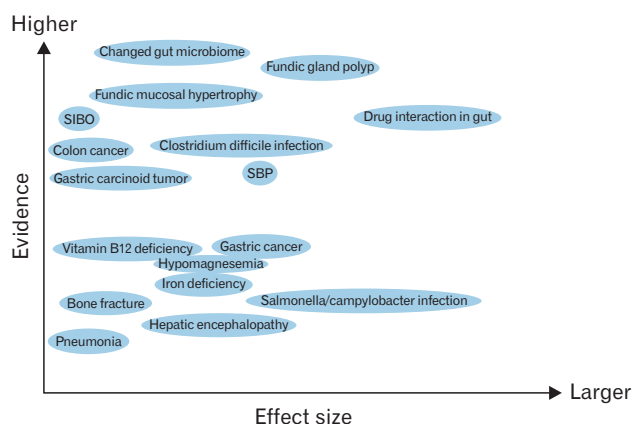


Figure 2. Acid-inhibition related adverse events reported during proton pump inhibitor administration. Possible evidence level and effect size of each adverse effect is shown. SIBO, small intestinal bacterial overgrowth; SBP, spontaneous bacterial peritonitis.

trinemia, type 2 with multiple endocrine adenomatosis, and type 3 without hypergastrinemia.⁹⁴ Type 1 gastric carcinoid tumors, which are most frequently found in the stomach in association with hypergastrinemia, are benign in their biological characteristics and rarely invade deeper into the gastric wall or metastasize to distant organs, while type 3 gastric carcinoid tumors without hypergastrinemia are malignant.^{95,96}

Based on a study done on experimental animals, long-term PPI-administration was found to develop gastric neuroendocrine tumors with accompanying hypergastrinemia at least in rodents. The result of the animal study temporally halted the clinical development of PPIs in the past.⁹⁷ After the start of worldwide clinical use of PPIs, only several case reports have noted cases of PPI administration-related gastric neuroendocrine tumors, though the reliability of those reports is not adequate. Some are too limited to be convincing of a pathogenic role of administered PPI and some cases were reported to have developed a carcinoid tumor soon after start of administration.^{98,99} In addition, the prognosis of patients with type 1 carcinoid tumors has recently been reported to be quite good even without treatment, though endoscopic resection is standard.⁹⁶ These reports suggest that the risk of gastric carcinoid tumor development during long-term PPI administration is not clinically relevant, though periodic endoscopic screening may be recommended during the period of administration.

Gastric Fundic Mucosal Hypertrophy

Hypergastrinemia increases proliferation of gastric mucosal stem cells located in the neck area of gastric fundic glands in addition to gastric ECL cells.^{100,101} Therefore, hypergastrinemia caused by PPIs increases gastric fundic mucosal thickness and gastric acid secretion when the administration is stopped.¹⁰² Such thickening of gastric fundic mucosa is reported to be especially prominent when these drugs are administered for a long period to patients not infected with *H. pylori*. Furthermore, similar thickening has been observed in cases of Zollinger-Ellison syndrome. An abrupt stop of PPI administration in patients with Zollinger-Ellison syndrome is accompanied by an abrupt rebound of acid hypersecretion, resulting in acid-induced complications such as higher grade reflux esophagitis.¹⁰³ Therefore, long-term PPI administration will lead to proliferation of gastric fundic mucosa, resulting in rebound acid hypersecretion once the administration is stopped. This phenomenon may make intermittent PPI use difficult, thus affected patients will likely be treated with the widely used long-term administration for maintenance of GERD.

Changes in Gut Microbiome and Small Intestinal Bacterial Overgrowth

PPIs have been reported to change the gut microbiome and increase the number of *Streptococcus* organisms, which densely colonize the oral cavity.¹⁰⁴⁻¹⁰⁶ In addition, PPI administration increases bacterial density in the duodenum and jejunum. The presence of 100 000 bacterial colonies/mL in small intestinal contents is called small intestinal bacterial overgrowth (SIBO). PPI administration is considered to be a risk factor of SIBO.¹⁰⁷ These results suggest that PPIs decrease gastric acid secretion and the bactericidal effect of the gastric juice, with a resulting increase in microbial density in the small intestine and in *Streptococcus* even in the gut microbiome. In addition, the possible lability of PPIs administered to patients with trans-oral infection of other pathogenetic bacteria has been suggested, though the clinical relevance of that has not been clarified. At present, the clinical importance of a changed microbiome in PPI-treated patients is not clear.

Hypomagnesemia

Magnesium, important for regulation of neuromuscular and various enzyme activities, is absorbed from the small intestine and excreted in urine. Therefore, chronic diarrhea is a risk factor for hypomagnesemia and affected patients may experience convulsions, muscle cramps, seizures, or anorexia. Chronic PPI administration has been reported to cause hypomagnesemia, possibly through decreased absorption of magnesium in the small intestine.^{108,109} Other reports, on the other hand, did not confirm the association between PPI administration and hypomagnesemia.¹¹⁰ A reported systematic review and meta-analysis of observational studies suggested the statistically significant association between PPI administration and hypomagnesemia, although the hazard ratio is modest (1.43) and the causation relationship is not clear.¹¹¹ One of the reported possible mechanism is that the PPIs-induced alteration in the gut microenvironment especially intra-luminal pH, may change the activity of gut magnesium transporters including transient receptor potential melastin 6 and 7.^{108,112} Based on this hypothesis, hypomagnesemia may be classified as an acid inhibition related adverse event. Although the number of reported cases with clinically meaningful hypomagnesemia that developed during chronic PPI administration is not high, periodic measurement of serum magnesium concentrations may be necessary to detect the possible subclinical hypomagnesemia.

Decreased Absorption of Other Nutrients

Some nutrients require gastric acid for effective absorption, including iron, calcium, and vitamin B12. Long-term PPI administration may decrease gastric acid secretion, especially during the daytime postprandial period, thus decreasing levels of iron, calcium, and vitamin B12 absorption, and possibly causing a pathological condition associated with lack of those nutrients.

Iron usually requires acid-induced solubilization from foods before being absorbed. However, the duodenal mucosal iron absorption system has a potent regulatory power for iron absorption and up-regulates that even without gastric acid when storage of iron in the body is decreased. Because of this regulating power of the iron absorption system, iron shortage rarely occurs, even in patients treated long-term with a PPI.^{113,114} However, in cases with a deficient regulatory mechanism including hereditary hemochromatosis, decreased iron absorption may occur during long-term administration.^{115,116}

For absorption of calcium, gastric acid may have important roles. Decreased absorption of insoluble calcium such as calcium carbonate during potent acid suppression has been reported, though that caused by diet during acid suppression has not been clearly shown.¹¹⁷ Such decreased absorption from the diet, if caused by PPI administration, may cause calcium deficiency, leading to osteoporosis and increased risk of bone fracture, although a study did not support the concept that PPI administration decreases calcium absorption.¹¹⁸ Several observational studies have suggested elevated femoral neck fracture risk in patients treated with PPIs.¹¹⁹⁻¹²¹ Surprisingly, no positive correlation between the length of PPI administration and increased risk of fracture has yet been shown.¹¹⁹ Some prospective observational studies failed to show decreased bone mineral density during long-term administration of PPIs, and other studies have shown that their administration did not increase fracture risk in cases without additional clear risk factors related to osteoporosis and bone fracture.¹²²⁻¹²⁵ Thus, the results of many studies suggest that PPI use does not increase the risk of osteoporosis or bone fracture.

Vitamin B12 contained in food binds to dietary protein. For its absorption, vitamin B12 must be released from protein by digestion with acid and pepsin, and then binds with an intrinsic factor produced by parietal cells in the stomach. Only intrinsic factor-bound vitamin B12 can be absorbed from the terminal ileum. PPIs may decrease vitamin B12 absorption by decreasing protein digestion in the stomach. However, the results of several studies that measured changes of serum vitamin B12 during long-term PPI administration were diverse and suggested little clinically relevant adverse ef-

fect of the drugs on absorption of vitamin B12.¹²⁶⁻¹²⁹

Gastric Fundic Gland Polyp

Gastric fundic gland polyps are small and benign growths found in the gastric fundic gland area in cases without *H. pylori* infection, which consist of hyperplastic and often cystic fundic glands. When PPIs are continuously administered to *H. pylori*-negative patients, multiple fundic gland polyps are reported to develop in fundic gland mucosa.¹³⁰⁻¹³² Though beta-catenin mutations have been reported to be found in some fundic gland polyps found during PPI administration, these polyps show regression and finally disappear when PPI administration is stopped.^{133,134} Therefore, those polyps formed during chronic PPI administration are considered to be not clinically important, although follow-up endoscopy is still necessary for detection of possible neoplastic changes.

Gastric Cancers

In patients infected with *H. pylori*, the administration of PPIs has been repeatedly reported to augment mucosal inflammation and accelerate mucosal atrophy, which may increase the risk of gastric cancer, although some diversities in study results are found.^{91,135,136} Furthermore, some observational studies have suggested that PPIs increase gastric cancer risk in patients infected with *H. pylori*, whereas others have presented contrasting findings.^{132,137-139} A recent study reported that PPI administration even after successful eradication of *H. pylori* augmented the risk of gastric cancer up to a hazard ratio value of 4.29.¹⁴⁰ The level of risk reported by different investigators is not homogenous, thus it is difficult to reach a conclusion based on current findings. Additional studies will be necessary to determine whether PPIs increase gastric cancer risk in patients with *H. pylori* infection, as well as those who have successfully undergone eradication.

Colon Cancers

Some colon cancer cells have been reported to have gastrin receptors, which were found to be linked to cell proliferation.^{141,142} Therefore, hypergastrinemia caused by PPI administration may stimulate neoplastic colonic cells and increase the risk of colon cancer. Based on an observational study, the long-term use of PPI did not influence the frequency, growth or histology of colonic adenomatous polyps.¹⁴³ Two large independent observational studies investigated the risk of colon cancer during chronic administration of PPIs, and both found no evidence of increased risk.^{144,145} Therefore, PPIs are considered not to increase the risk of colon cancer despite their association with elevated plasma gastrin levels.

Spontaneous Bacterial Peritonitis and Hepatic Encephalopathy

Spontaneous bacterial peritonitis is a bacterial infection of the abdominal cavity observed in cases with ascites caused by liver cirrhosis. Because of the increased permeability of the intestinal mucosa in cases with cirrhosis, gut bacteria may penetrate the intestinal wall and proliferate in the ascites fluid without macroscopic intestinal damage. PPIs administration has been repeatedly reported to increase the risk of spontaneous bacterial peritonitis from a hazard ratio of 1.4 to 5.0 by many investigators, although there are some inconsistencies in the study results.¹⁴⁶⁻¹⁵⁰

Recently, in addition, PPI administration is also reported to be associated with hepatic encephalopathy in patients with cirrhosis.^{70,148} The PPI-induced gut microbial changes or PPI-induced hypomagnesemia and vitamin B12 deficiency are considered to be possible links between hepatic encephalopathy and PPI administration, though the precise mechanism is not yet clarified.

The risk of PPI use in cases with cirrhosis, thus, need to be considered, though these study results are just an association and do not show the causal relationship. PPI administration is necessary in some cases with cirrhosis, since PPI decreases the risk of esophageal varix rupture and the occurrence of peptic ulcers.^{151,152} Balancing the benefit and risk of PPI administration should always be considered when doctors prescribe PPIs to cases with liver cirrhosis.

Drug Interactions in the Gastrointestinal Tract

Absorption of several different drugs is under the strong influence of gastric acid secretion, such as digitalis, which is degraded by gastric acid in the stomach. Therefore, the pharmacological effect of digitalis and others may be augmented during PPI administration. On the other hand, effective absorption of several drugs including itraconazole and atazanavir becomes difficult when PPIs are administered, since their solubility is low at neutral pH. Drugs that are not absorbed and remain functioning in the gastrointestinal tract, such as polycarbophil calcium, may partially lose their potency with PPIs, since acid-induced activation of those drugs is incomplete in an acid neutral environment. Although all drugs that inhibit gastric acid secretion may cause drug interactions in the gastrointestinal tract, the interaction with PPIs may be strong because of their potent acid suppression.

Balancing Advantages and Disadvantages of Proton Pump Inhibitors

All PPIs currently available show both beneficial and adverse effects. Therefore, of course, the appropriate indications of PPIs therapy should be confirmed as a first step when we decide the potential administration of PPIs.^{153,154} When deciding when to administer any medicine, it is important to re-confirm that the beneficial effects will outweigh any potential adverse events. The beneficial therapeutic effects of PPIs for the treatment of GERD, gastroduodenal ulcers, and *H. pylori* eradication are quite clear, while their effects for symptomatic improvement in patients with functional dyspepsia and for patients with esophageal hypersensitivity are limited.¹⁵⁵ PPIs are not effective for symptom improvement in functional heartburn cases. Therefore, when administered to patients with functional dyspepsia, esophageal hypersensitivity, or functional heartburn, attention must be given to potential adverse effects, even if the risk is reported to be low. To gain only a small therapeutic benefit, a low risk of adverse effects should be avoided. On the other hand, when the expected therapeutic effect is large enough, a low risk of adverse effects can be accepted. Thus, expected therapeutic effects must always be balanced with possible adverse events (Fig. 3).

The majority of adverse effects related to PPI administration

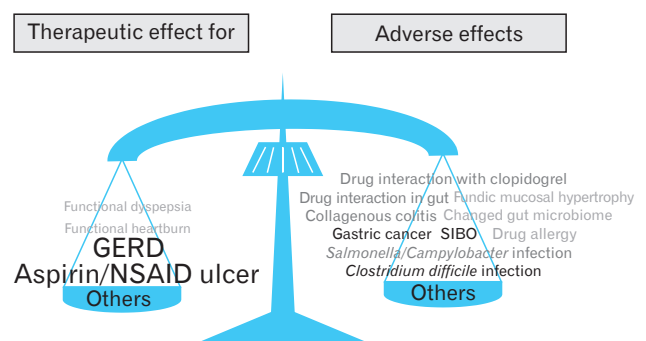


Figure 3. Beneficial effects and possible adverse effects need to be balanced, when proton pump inhibitors (PPIs) are administered as many other drugs. Beneficial effects of PPIs for the long-term treatment of gastroesophageal reflux disease (GERD) and prevention of aspirin/non-steroidal anti-inflammatory drug (NSAID)-induced ulcers are strong enough when PPIs are administered only to appropriate patients. PPIs also have several acid-inhibition related and unrelated adverse effects although the clinical impacts of these adverse events are not so serious. However, balancing beneficial and adverse effects as well as selecting appropriate patients who will get larger benefits by the PPIs administration are critically important. SIBO, small intestinal bacterial overgrowth.

are reported to occur after long-term administration has been given. For symptom control in patients with low grade reflux esophagitis, intermittent or on-demand administration may be effective enough. Low grade reflux esophagitis, such as Los Angeles grade A or B, has repeatedly been reported not to progress to high grade reflux esophagitis or develop clinically relevant complications, including bleeding and esophageal stricture, even without intensive treatment. Therefore, long-term PPI administration may be necessary for maintenance treatment mainly in patients with high grade reflux esophagitis, Los Angeles grade C or D. Patients with high grade reflux esophagitis are reported to comprise only 5-10% of all cases of reflux esophagitis. For treatment of low grade reflux esophagitis and non-erosive GERD, long-term PPI administration should be avoided, if possible.

Long-term PPIs are also frequently given for prevention of NSAID- or aspirin-related ulcers. High dose NSAID/aspirin administration, elderly age, past history of ulcers, and bleeding ulcers are well known to increase the risk for ulcer recurrence. Therefore, for risky cases, PPI administration for prevention of recurrence is considered to be a reasonable option. However, for patients without such risks, long-term PPI use should be avoided.

Majority of reported adverse effects of PPIs are conflicting and their clinical impacts are not large enough. Since most of the studies concerning the adverse events of PPIs are retrospective and observational, the inclusion risks of potential bias are not negligible. In these conditions, only the study results showing the large clinical impact can be reliable and clinically important. Therefore, the presence of clinically meaningful risk of long-term PPIs administration is considered to be not fully established. However, even under these conditions, specialists in gastroenterology must always be careful to balance the merits and demerits of long-term PPI administration in daily medical practice.

In conclusion, known risks of long-term PPI administration must be considered in clinical practice, though the majority of evidence presented in regard to such risks is not consistent or adequate to make firm conclusions.

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