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Review article

Balancing therapeutic benefits and hidden risks of proton pump inhibitors in pediatric practice: a narrative review and update

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Proton pump inhibitors (PPIs) are drugs whose main effect is catalytic and long-lasting suppression of gastric acid secretion, with an anti-inflammatory effect. The main indications for PPIs use include the treatment of gastroesophageal reflux disease, peptic ulcer disease, functional dyspepsia, Barrett esophagus, eosinophilic esophagitis, and hypersecretory diseases such as gastrinoma and Zollinger-Ellison syndrome. Their contribution to eradication therapy for *Helicobacter pylori* is also important. However, the long-term use of PPIs has been associated with various adverse drug reactions and complications, such as the development of fundic gland polyposis, atrophic gastritis, gastric cancer, vitamin B_{12} deficiency, hypomagnesemia, osteoporosis/fractures, changes in the microbiome, increased risk of infection, necrotizing enterocolitis, renal injury, and other conditions. Thus, administration of PPIs should be based on scientific evidence of their efficacy and safety. Their long-term administration should be cautious, and continuation reassessed frequently. Caution should be exercised when administering PPIs to neonates and infants. This narrative review and update aims to summarize and critically evaluate the current evidence, based on the most recent clinical guidelines, regarding the use of PPIs in children, with a focus on their indications, efficacy, safety, and limitations.

Key words: Proton pump inhibitors, Gastroesophageal reflux disease, Indications in childhood, Adverse drug reactions, Side effects

Key message

Proton pump inhibitors (PPIs) effectively treat acid-related disorders, including gastroesophageal reflux disease, eosinophilic esophagitis, peptic ulcers, and Zollinger-Ellison syndrome. Long-term use, particularly in children, may lead to microbiome alterations, nutrient deficiencies, infections, renal injury, osteoporosis, fractures, and other gastrointestinal changes. PPI therapy should be guided by clear clinical indications, prescribed at the lowest effective dose for the shortest necessary duration, and regularly reassessed to minimize risks in young children.

Introduction

The first evidence of the existence of the proton pump (H^+/K^+ATPase) in the secretory membrane of gastric wall cells dates back to the late 1970s and emphasizes its importance in the secretion of acidic gastric juice.[1] The first evidence of proton pump inhibitors (PPIs) came in the 1980s with the widespread use of omeprazole.

PPIs are benzimidazole derivatives; that bind to and irreversibly inhibit the enzyme H^+K^+ATPase, pump located in the apical membrane of the parietal cells of the stomach that participate in the final phase of acid secretion. As weak bases, PPIs become concentrated in the areas of the parietal cells with the lowest pH, where they are converted into their active metabolites, thiophilic sulphonamides, owing to the catalytic action of the acid. The active substances of the PPI class differ from each other in terms of pKa (negative logarithm of the dissociation constant), bioavailability, maximum plasma concentration and metabolism and excretion routes.[2,3]

PPIs inhibit gastric acid secretions irreversibly binding to the H^+/K^+ ATPase pump (proton pump) within gastric wall cells.[4] Their half-life is estimated at 0.5–2 hours. They are most effective when taken after meals when parietal cells receive a palatable stimulus. The concentration of pump molecules increases after prolonged fasting; ideally, PPIs

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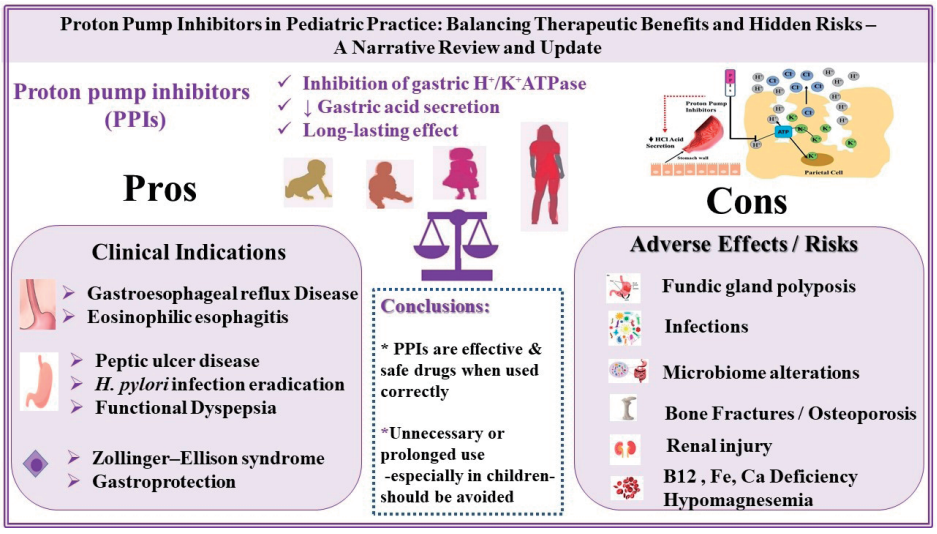

Graphical abstract

should be administered before the first meal of the day. One dose partially suppresses gastric secretion for ~36 hours, whereas the administration of a daily dose for 1×5 days suppressed gastric secretion by 66%.[5]

PPIs include omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole. These drugs are commonly used in the pediatric population to treat gastroesophageal reflux disease (GERD). However, except for esomeprazole the efficacy of PPIs for GERD in neonates and infants under 1 year of age has not been demonstrated despite their acid suppression effects.[6] Other indications for PPI administration include peptic ulcers, gastritis, hypersecretory disorders such as Zollinger-Ellison syndrome, *Helicobacter pylori* infection, functional digestive disorders, cystic fibrosis and eosinophilic esophagitis (EoE). This article presents the main indications for PPI administration in pediatric populations.

Mechanism of action of PPIs

PPIs work by irreversibly binding the proton pump (H^+/K^+ ATPase) of cells within the gastric wall. The proton pump is the final stage of gastric secretion, with the direct release of H^+ ions into the gastric lumen, making it an excellent target for inhibiting gastric secretion.

The mechanisms of action of PPIs in the gastric lumen are shown in Fig. 1.

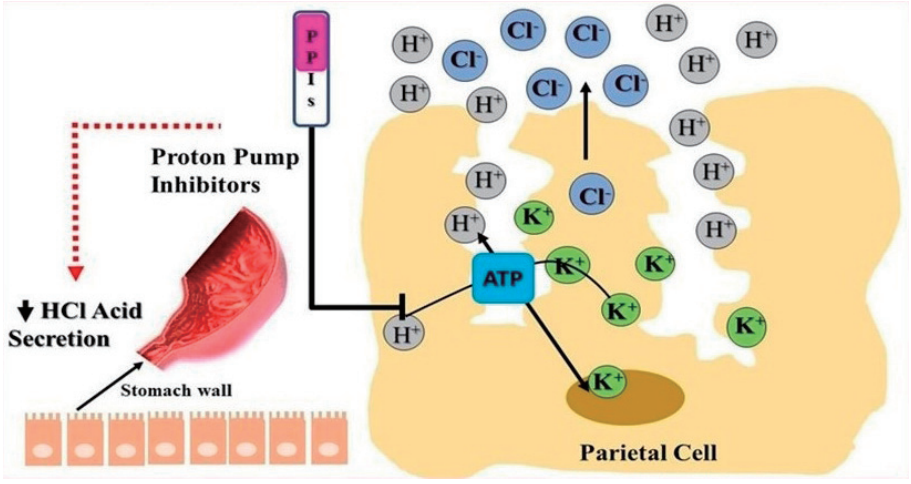

Fig. 1. The mechanism of antisecretory effect of proton pump inhibitors (PPIs) in gastric lumen. The gastric H^+/K^+-ATPase enzyme drives acid secretion by exchanging hydrogen ions for potassium ions at the surface of activated parietal cells. When stimulated, the enzyme moves from internal vesicles to the cell membrane of the secretory canaliculus, where it releases acid into the stomach through an ATP-dependent process supported by potassium and chloride channels. PPIs block this enzyme irreversibly, suppressing the final step of acid production and leading to a strong, sustained decrease in gastric acidity.

All PPIs have the same basic chemical structure as the substituted benzimidols. The changes in substituted group type and position determines the individual differences in the pharmacokinetic and pharmacodynamic properties of the members of this drug group, while their mechanism of action remains the same.[2,3]

PPIs are administered in their inactive form as neutrally charged lipophilic molecules, which allows them to easily penetrate the cell membrane and enter the intracellular acidic environment of mural cells. PPIs are protonated in their active form and then irreversibly bind to the proton pump (the active cyclic sulfonamide irreversibly binds to the exposed thiol groups of cysteine H+/K+-ATPase, thereby inactivating it). To restore the enzymatic function of the proton pump, the gastric wall cells must synthesize new H^+/K^+-ATPase molecules.[3]

To prevent premature degradation of PPIs in the acidic environment of the stomach and ensure their transport into the duodenum, they should be administered as film-coated tablets that are rapidly absorbed in the duodenum and reach their maximum plasma concentration within 1–3 hours after ingestion.[7]

The absorption rates of omeprazole and lansoprazole decrease with the simultaneous intake of food. If treatment with these agents is indicated, they should be administered before breakfast to achieve better and more effective control of daily gastric secretions.[8]

PPI metabolism occurs mainly in the liver with the help of cytochrome P450 and its isoforms (CYP2C19 and CYP3A4) and secondarily by enterocytes of the intestinal barrier as the PPIs pass through it. Metabolic rate varies with age. Therefore, patient age should be considered when determining the optimal dose.

In addition to their antisecretory effect, PPIs have an anti-inflammatory effect that inhibits eotaxin-3 expression by esophageal epithelial cells following their stimulation by Th2 cytokines and activation of the transcriptional pathway (STAT6).[9-11]

PPIs as therapeutic allies

Increased gastric secretion is the main indications for PPIs use in the pediatric population. The main indications for PPIs use in children are shown in Fig. 2.[12]

1. Gastroesophageal reflux disease

PPIs are often prescribed to infants and children to treat of GERD.

Studies based on pH-metry/resistance measurements have shown that PPI administration can reduce the reflux of acidic gastric contents, but not the total number of reflux episodes percentage of time that gastric contents remain in the esophagus, or GERD.[13] Consequently, while PPIs appear to effectively treat of reflux esophagitis, they do not treat extraesophageal manifestations of GERD as effectively as they treat manifestations of the respiratory system.[14,15] Both clinical manifestations and mucosal damage recur in a significant number of patients after PPI discontinuation or dose reduction.[16]

According to the latest guidelines updated 2018 of the ESPGHAN/NASPGHAN (European and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition) for GERD, PPI use is restricted to children with typical clinical manifestations, but not those with extraesophageal manifestations (asthma, chronic cough,

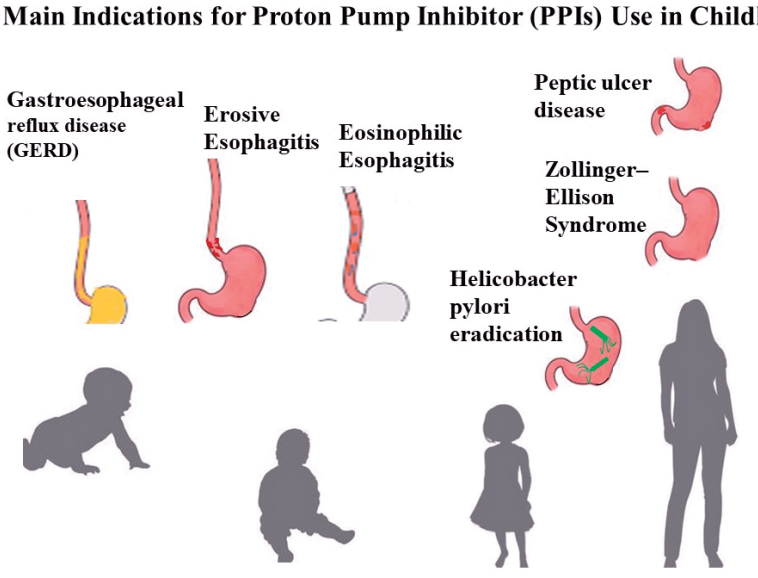

Fig. 2. Main indications for PPIs use in pediatric patients.

laryngitis, hoarseness, chronic pharyngitis, dental erosion and retrosternal pain of noncardiac etiology), except in the presence of typical GERD symptoms or in otherwise healthy infants with anxiety or visible reflux; however they are a first-line treatment for corrosive gastritis due to chronic exposure of the esophageal mucosa to acidic gastric fluids.[17]

2. Peptic ulcer and gastritis

The term "peptic ulcer" refers to an erosion site on the inner wall of the stomach (gastric ulcer) or the first portion of the small intestine (duodenal ulcer). Helicobacter pylori infection, the ingestion of pharmaceutical preparations such as nonsteroidal, anti-inflammatory drugs, various systemic diseases, and stressful situations (multiorgan failure, burns, shock and major surgery) are predisposing conditions that pathogenetically influence the occurrence of a peptic ulcers. However, in many cases the primary cause of the ulcer development remains unknown.18) Clinical experience has shown that the administration of even low doses of PPIs (0.3–0.7 mg/kg/day) can contribute to ulcer healing.[18]

3. Hypersecretory states

Zollinger-Ellison syndrome and G-cell hyperplasia of the gastric cavity are extremely rare disorders in the pediatric population characterized by the hypersecretion of gastric acid leading to the formation of gastroduodenal ulcers, which often recur. To control gastric acid secretion and its complications, the administration of PPI at high doses (≥ 80 mg/24 hours) is recommended.[18]

4. *Helicobacter pylori* infection

PPIs are part of the treatment to eradicate *Helicobacter pylori* according to 2024 ESPGHAN guidelines.[19] The goal of treatment is to achieve 90% eradication. However, this is not always possible due to the development of antibiotic resistance in these strains, as well as limited patient compliance.

5. Functional dyspepsia

PPIs can be administered to treat pain in functional digestive disorders.[20] They are reportedly to be more effective than H2 blockers at relieving pain.[21]

6. Drug-induced dyspepsia in children

PPIs are sometimes prescribed to children to manage drug-induced dyspepsia, particularly when epigastric pain or reflux symptoms are prominent. However, their routine prophylactic use is not supported by strong evidence; thus, PPIs should generally be reserved for children at higher risk, such as those with a history of ulcer disease or significant comorbidities. The shortest effective duration, should be employed because PPIs can alter the gut microbiota and potentially worsen complications when combined with nonsteroidal anti-inflammatory drugs or corticosteroids.[22]

7. Eosinophilic esophagitis

EoE is a chronic, local, immune-mediated disease characterized by dense eosinophilic infiltration of the esophageal mucosa with symptoms of esophageal dysfunction. Its prevalence and frequency have increased significantly in recent decades. EoE is the most common cause of dysphagia and lumpiness in children and significantly impairs their quality of life.[2] PPIs are used to achieve clinical response and histological remission in patients with EoE, [23] especially those with signs of increased gastric acid secretion.

The recent 2024 update of the 2014[24] ESPGHAN guidelines on EoE recommend the use of PPIs for the induction of remission of EoE as one of 3 treatment strategies (PPIs, elimination diet or topical steroids) and not as a diagnostic criterion.[22] In patients who respond to PPIs, long-term treatment with these therapeutic agents is recommended, as symptoms and esophageal eosinophilia usually recur within 3–6 months after discontinuation of treatment.[22] However, PPI duration and dose for maintenance therapy have not yet been established. In the absence of new data in literature, it seems reasonable to gradually reduce the administered dose to the lowest possible required to maintain remission.[22]

The recommended treatment regimens for PPI dosage and duration of administration are listed in Table 1.

PPIs as potential hidden adversaries

1. Interactions with other drugs

PPIs are metabolized by the hepatic cytochrome P450 enzyme system, with the isoenzymes CYP2C19, CYP3A4, and CYP1A playing an essential role. These enzymes play important roles in the metabolism of other substances and drugs such as warfarin, diazepam, clopidogrel, theophylline, phenytoin, and methotrexate. This common metabolic pathway may lead to drug interactions and alter their pharmacokinetics and pharmacodynamics; therefore, special care must be taken when administering these drugs simultaneously.[25]

2. PPIs uses by children younger than 1 year of age

Evidence is limited for the use of PPIs by preterm infants with GERD. Small trials indicated that PPIs reduce gastric acid but do not clearly improve symptoms or cardiores-

Table 1. Indicated dose/duration per condition of most commonly used PPIs in children

Indication	Omeprazole	Esomeprazole	Lansoprazole	Duration	Reference
GERD/erosive esophagitis	1–4 mg/kg/day once daily (max 40 mg)	0.5–1 mg/kg/day once daily (max 40 mg)	1–2 mg/kg/day once daily (max 30 mg)	4–8 Wk	17)
Eosinophilic esophagitis	1–2 mg/kg/day divided BID (max 80 mg)	1 mg/kg/day divided BID (max 60–80 mg)	1–2 mg/kg/day divided BID (max 60 mg)	8–12 Wk[a)]	23)
Peptic ulcer disease	1–2 mg/kg/day (max 80 mg)	1–2 mg/kg/day (max 80 mg)	1–2 mg/kg/day (max 60 mg)	4–8 Wk	25)
H. pylori eradication	Weight-based BID: 15–24 kg → 20 mg, 25–34 kg → 30 mg, 35–49 kg → 40 mg, ≥50 kg → 40 mg	Weight-based BID: Same as omeprazole	Weight-based BID: 15–24 kg → 15 mg, 25–34 kg → 30 mg, 35–49 kg → 30 mg, ≥50 kg → 30 mg	14 Days	19)

PPIs, proton pump inhibitors; GERD, gastroesophageal reflux disease; BID, twice a day; *H. pylori, Helicobacter pylori.*
[a)]Lower maintenance dose after remission for at least 1 year.

Table 2. Most common side effects of (prolonged) PPI use

System/category	Potential side effects	Comments/evidence in children
Infectious	Increased risk of gastrointestinal infections (e.g., *Clostridioides difficile*), respiratory tract infections	Most consistently reported association, especially in infants and young children; likely related to reduced gastric acidity
Gastrointestinal	Diarrhea, constipation, abdominal pain, nausea	Generally mild and transient; among the most common short-term adverse effects
Nutritional/metabolic	Reduced absorption of iron, magnesium, calcium, vitamin B_{12}	Clinical significance in children remains uncertain; concern mainly with long-term use
Bone health	Possible increased fracture risk	Evidence largely from observational studies; data in children are limited and conflicting
Immune/microbiome	Altered gut microbiota; potential immune modulation	Particularly relevant in early life; long-term consequences not fully understood
Allergic/atopic disease	Possible association with food allergy, asthma, eczema	Associations reported in some cohort studies; causality not established
Renal	Acute interstitial nephritis (rare)	Very rare in pediatric patients; mostly extrapolated from adult data
Neurologic	Headache, dizziness	Uncommon and usually mild

PPI, proton pump inhibitor

piratory events, and no studies have compared PPIs with nonpharmacologic measures such as positioning or dietary changes; safety data are also insufficient, so routine use is not supported.[6)] An observational analysis of 464 adverse events reported to the U.S. Food and Drug Administration that occurred in reports in neonates and infants receiving PPI monotherapy found that 69.6% of the events were serious—including vomiting, diarrhea, hypertrichosis, choking, and erythema—with vomiting being the most frequent (reporting odds ratio, 2.88); 3.2% were temporally related to mortality, and 10.8% involved medication errors, highlighting substantial safety concerns and the need for improved neonatal pharmacovigilance.[26)] A multicountry observational study of infants in Denmark, Norway, and Sweden (2007–2020) reported a more than fourfold increase in PPI dispensing despite guideline recommendations against their routine use in infancy; in 2020, the dispensing rates were 46.4, 23.4, and 18.9 per 1,000 infants per year in Denmark, Norway, and Sweden, respectively, suggesting widespread and likely unnecessary PPI use with significant variation across countries.[27)]

3. More and less common side effects of PPIs

The most common side effects of (prolonged) PPI use are shown in Table 2.

PPIs are among the most commonly prescribed medications in infants and children, and their use has increased in recent decades despite limited evidence of their efficacy.[28)] Their long-term use has been associated with disorders that we explore below. Common side effects, occurring in 1%–3% of patients, include: headache, nausea, rash, dizziness, diarrhea or constipation, flatulence and epigastric discomfort. However, in addition to the usual immediate side effects, prolonged use of these drugs is also of concern, as the prolonged inhibition of gastric acid production is associated with persistent hypergastrinemia and hyperplasia of enterochromaffin-like (ECL) cells, leading to the development of gastric polyps, atrophic gastritis, cancer, vitamin B_{12} deficiency, hypomagnesemia, osteoporosis and bone fractures; disruption of the gastrointestinal microbiome; and an increased risk of infection, necrotizing enterocolitis, kidney damage, and other conditions.[29,30)] The potential side effects of PPIs are shown in Fig. 3.[30)]

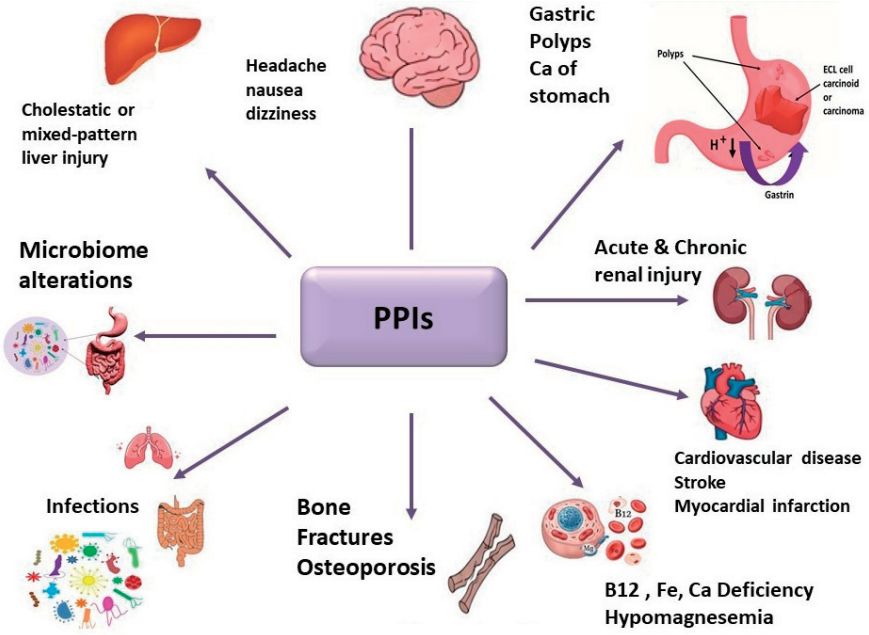

Fig. 3. Possible side effects of proton pump inhibitors (PPIs).

4. PPIs and gastric polyps

Due to the antisecretory effect of PPIs, changes in physiological balance with their use lead to gastrin hypersecretion. Gastrin stimulates cell proliferation. In addition, increased levels of chromatographin A lead to chronic stimulation of ECL cells.[31] In recent years, an increase in adenoid polyps of the gastric fundus has been observed after long-term PPI use.[32] These polyps are usually benign, multiple and located in the mucosa of the gastric vault and body; however, dysplastic disorders have also been described in some cases.[33]

5. PPIs and gastric cancer

There is some evidence that long-term PPI use in adults may be associated with an increased risk of developing precancerous lesions such as polyps, mucosal atrophy, metaplasia and gastric cancer.[33,34] Gastrin is a hormone produced by G cells in the pyloric antrum of the stomach. Gastrin induces gastric acid secretion by binding to cholecystokinin 2 receptors on the enterochromaffin cells of the dome and body and simultaneously releasing histamine, which in turn stimulates the parietal cells of the stomach to secrete hydrogen ions. Moreover, gastrin regulates processes such as cellular proliferation, apoptosis, infiltration and angiogenesis and is suspected to play a role in gastric cancer developement.[35] Long-term PPI use is associated with gastrin hypersecretion; therefore, prolonged use should be evidence-based and regularly reassessed, especially in children and adolescents.[36]

6. PPIs and vitamin B_{12} deficiency

Vitamin B_{12} is involved in the metabolism of all human cell types. It is particularly important to normal functioning of the nervous system because of its role in the myelin synthesis and red blood cell maturation in the bone marrow. Vitamin B_{12} deficiency is usually caused by insufficient intake but can also be caused by malabsorption, intestinal diseases, low binding protein levels and the use of certain medications. PPIs inhibit the production of hydrochloric acid by the parietal cells of the stomach, which converts pepsinogen to pepsin. Pepsin aids the release of B_{12} from food. The absence or deficiency of gastric acid reduces pepsin levels, resulting in reduced B_{12} release and reduced availability for its absorption in the ileum.[20] Reduced B_{12} administration was observed in empirical studies following PPI use. Other studies have shown that, after several months of PPI use in adults, significantly reduced absorption of protein-bound vitamin B12 but unaffected absorption of unbound B_{12}.[37]

7. PPIs and trace element deficiencies

Recent studies reported that PPI use may be an independent risk factor for osteoporosis and bone fractures.[38] The presence of hypochlorhydria, which occurs with PPI use, can reduce calcium solubility, resulting in reduced intestinal absorption and a negative calcium balance. Data from different studies are contradictory, as some have shown that PPI use is associated with reduced calcium absorption, while others have not.[39]

Long-term PPI use is associated with the occurrence of hypomagnesemia. Mg absorption occurs via a passive and active transport mechanism involving 2 proteins (transient receptor potential melastatin 6 and 7), in the apical membrane of enterocytes, which have a high

affinity for Mg absorption and ensure its balance during times of its reduced intake. The activity of these proteins is influenced by their intraluminal acid–base state. An acidic environment increases their activity, whereas PPI ingestion decreases it, leading to reduced Mg absorption and hypomagnesemia, as shown in several studies and case reports. A recent meta-analysis[40] showed that the long-term use of PPIs, especially when administered at high doses, is associated with an increased risk of hypomagnesemia. The authors concluded that Mg levels should be monitored in patients taking high doses of or long-term of PPIs.

8. PPIs and osteoporosis/fractures

The risk of fractures in the general population taking PPIs has been investigated in several studies[41] and meta-analyses,[42] and an increased risk of fractures has been reported in patients taking PPIs, independent of other complicating factors. One study,[38] of children aged 4–17 years followed up over a 5-year period reported, a positive association between PPIs and an increased risk of fracture.

However, in a recent retrospective cohort study[43] involving 851,631 children, 97,286 (11%) of them were prescribed acid-suppressive therapy in their first year of life: 7,998 (0.9%) received PPIs, 71,578 (8%) H2RAs and 17,710 (2%) a combination of PPIs and H2RAs. Children with other medical conditions associated with an increased risk of fractures were excluded from the study. The authors reported that children who received acid-suppressive therapy in infancy suffered fractures earlier in life (3.9 years vs. 4.5 years). They also found that an increased risk of fracture was associated with the use of PPIs (21%) or combined PPIs and H2RAs (30%), but not when H2RAs were used alone. Longer treatment duration and earlier age at treatment initiation were associated with an increased risk of fracture. Hypergastrinemia and decreased acid secretion are possible mechanisms underlying the association between PPIs and occurrence. As mentioned above, long-term PPI use increases gastrin levels. Elevated gastrin levels appear to cause secondary hyperparathyroidism, which negatively affects bone remodeling. Moreover, hypergastrinemia causes enterochromaffin cells hyperplasia and histamine hypersecretion. Increased histamine secretion may increase the differentiation of osteoclast precursors, although its effect on the bone is not entirely clear. The reduced acid secretion observed with PPI use leads to reduced absorption of trace elements such as Ca and Mg, which are involved in bone metabolism. The reduced vitamin B12 content and a vitamin B_6 and folic acid deficiencies observed with long-term PPI use lead to hyperhomocysteinaemia, which negatively affects bone and collagen quality. Vitamin B deficiency can lead to neurological disorders and muscle weakness, which also contribute to the occurrence of bone fractures.[41]

9. PPIs and the microbiome

Almost all parts of the human body have their own microbiome. Microbiome composition is determined by environmental and intramicrobial factors.[44] PPIs are used to suppress gastric acid. However, their long-term use has been associated with changes in the acidity of gastric juices, potentially affecting the microbiome of the stomach and intestine an individual's overall health. Studies have shown that PPI use is associated with dysbiosis, microbial overgrowth in the small intestine and changes in the microbiota composition,[45,46] in terms microorganism types and diversity.[44] In patients taking PPIs, significant increases in Streptococcaceae and Enterococcaceae and decreased Faecalibacterium loads were noted,[45] in other studies,[44] PPI use led to species diversification and increased species in the microbiota of the upper respiratory tract and oral cavity. PPIs can alter the normal microbiota throughout the gastrointestinal tract. In the esophagus, they modify the physiological environment, leading to reduced exposure of the lower esophagus to gram-negative bacteria, which may reduce an individual's risk of developing Barrett esophagus. In the stomach, they alter microbial population and species such as *H. pylori* that have implications for peptic ulcers and stomach cancer. They also cause microbial overgrowth in the small intestine, which is associated with the occurrence of coeliac disease. In the large intestine, PPI use has been associated with *Clostridium difficile* infection, possibly through changes in the anaerobic microbiota in the large intestine.[47]

10. PPIs and infections

A nationwide French cohort study of over 1.2 million children found that PPI use in early childhood was associated with an increased risk of serious infections. Children exposed to PPIs had a higher risk of infections overall (adjusted hazard ratio, 1.34) as well as at specific sites, including the digestive tract, respiratory tract, ear/nose/throat, urinary tract, and nervous system. Bacterial and viral infections were also more frequent among PPI users. These findings suggest that PPIs may compromise immune defenses or alter the microbiota, highlighting the need for their cautious use in young children.[48]

11. PPIs and *C. difficile* infection

Over the last 2 decades, *C. difficile* infection rates have increased worldwide, both frequency and severity. A meta-analysis,[49] of 46 studies (40 case-control studies, 16

cohort studies) with 356,863 patients showed that, despite the limitation that these were observational studies and a causal relationship could not be proven, PPI use increases the likelihood of *C. difficile* infection by almost twofold. Another recent meta-analysis,[50] which also included pediatric patients, found a strong association between PPI use and the occurrence and recurrence of *C. difficile* infection.

12. PPIs and gastroenteritis and community-acquired pneumonia

PPI use has also been associated with the occurrence of microbial gastroenteritis in pediatric patients.[51] PPI induced gastric acid suppression leads to the loss of their antimicrobial properties against microbes, i.e. pathogens that cause gastroenteritis.

Studies in adults have shown an increased association between PPIs and community-acquired pneumonia. In a multicenter study,[51] in Italy, children with GERD aged 4–36 months were treated with PPIs and H2 agonists and developed community-acquired pneumonia more frequently than the healthy controls. Another study showed that PPI treatment was associated with more frequent lower respiratory tract infections in infants aged 1–12 months.[52]

13. PPIs and necrotizing enterocolitis

The use of gastric acid-inhibiting drugs such as PPIs and H2RA in patients within the neonatal intensive care unit is associated with a higher incidence of necrotizing enterocolitis and more frequent episodes of microbiome/alterations and sepsis.[53] Particular caution should be exercised, when administering these drugs to preterm or term infants.[53]

14. PPIs and renal injury

PPI use has also been reported to be associated with renal injury such as acute renal failure, acute interstitial nephritis, chronic renal impairment and chronic renal failure, although there are currently no studies in pediatric patients.[54] Acute kidney injury is considered immune-mediated, and affects interstitial tissue and renal tubules. The epithelial cells of the tubules are damaged first, followed by lymphocytic inflammatory infiltration. This can lead to renal scarring and decreased renal function.[54] In a cohort study, chronic PPI use was associated with an increased risk of chronic kidney damage. Similar results were found in another large cohort study in which PPI use was associated with an increased risk of renal dysfunction and chronic renal failure.[54,55]

15. PPIs and cardiovascular risk

Long-term PPI use in adults may be associated with an increased risk of cardiovascular disease, stroke, and myocardial infarction.[56] Several mechanisms have been hypothesized, such as deficiency of the trace elements Mg and Ca, of vitamins, their effect on enzymatic metabolic pathways, and interactions with drugs, such as clopidogrel, whose antiplatelet effect is reduced by PPIs. It has been suggested that their long-term intake may reduce nitric oxide synthase activity, leading to the dysregulation of vascular homeostasis. They have also been shown to impair endothelial lysosomal acidification *in vitro*, disrupt the protease system and accelerate vascular aging.[56] Therefore, their limited use is recommended with consideration of all possible risks, and the duration of administration should be regularly re-evaluated.[56]

16. PPIs and hirsutism

There have been reports of children developing hirsutism after taking omeprazole.[57] Omeprazole significantly increases prostaglandin E2 synthesis in the duodenum. Prostaglandins appear to be involved in the regulaion of hair growth; E2 and F2α, stimulate it, whereas D2, inhibits it.

Conclusions

PPIs are a group of drugs whose main effects include strong and long-lasting reduction in gastric acid secretion and an anti-inflammatory effect. PPIs are considered safe, have rare adverse effects, and are among the most commonly prescribed medications worldwide for all age groups. They effectively treat digestive diseases. However, their use is often not evidence based or unjustifiably prolonged.

Prolonged or inappropriate PPI use, by young patients, is associated with adverse side effects and complications. Therefore, care and critical considerations are required regarding when and for how long PPI should be administered.

Footnotes

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