Drugs in focus: proton pump inhibitors

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ABSTRACT

Proton pump inhibitors (PPIs) are amongst the most commonly prescribed drugs in infants and children with the last decades witnessing a dramatic rise in their utilization. Although PPIs are clearly effective when used appropriately and have been regarded as safe drugs, there is growing evidence regarding their potential adverse effects. Although, largely based on adult data it is clear that many of these are also relevant to pediatrics. PPI use potentially affects gastrointestinal microbiota composition and function, decreases defence against pathogens resulting in increased risk for infections, interferes with absorption of minerals and vitamins leading to specific deficiencies and increased risk for bone fractures as well as interferes with protein digestion resulting in increased risk of sensitization to allergens and development of allergic diseases and eosinophilic esophagitis. An association with gastric, liver and pancreatic cancer has also been inferred from adult data but is tenuous and causation is not proven. Overall, evidence for these adverse events is patchy and not always compelling. Overall, the use of PPIs, for selected indications with a good evidence base, has significant potential benefit but carries more caution in infants and children. Pediatricians should be aware of the concerns regarding the potential adverse events associated with their use.

Key Words: acid suppression, adverse effects, children, indications, proton pump inhibitors, safety

An infographic is available for this article at: *http://links.lww.com/MPG/C220*.

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Learning Points

- Proton pump inhibitors (PPIs) constitute a group of drugs that very effectively inhibit gastric acid production through irreversible binding to the gastric parietal cell H^+/K^+ ATPase pump (the ''proton pump'') and includes omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole.
- PPIs have specific, evidence based, indications for their use, including the treatment of gastroesophageal reflux disease, peptic ulcer disease and gastritis, hypersecretory states, *Helicobacter pylori* infection, eosinophilic esophagitis, pain-predominant functional dyspepsia, and cystic fibrosis.
- PPIs are among the most commonly prescribed drugs in infants and children with the last decades witnessing a dramatic rise in their utilization, including inappropriate use especially in infants.
- Although PPIs are clearly effective when used appropriately and have been regarded as safe drugs, there is growing evidence, albeit largely from adult studies, regarding their potential adverse effects. It is clear that many of these are also relevant to pediatrics.
- PPI use potentially affects gastrointestinal microbiota composition and function and decreases defense against pathogens resulting in an increased risk for infections. They may also interfere with absorption of minerals and vitamins as well as the digestion of

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proteins leading to specific deficiencies, and increased risks of developing bone fractures, allergic diseases and eosinophilic esophagitis. An association with gastric, liver, and pancreatic cancer has also been inferred from adult data but is tenuous and causation is not proven. Overall, evidence for these adverse events is patchy and not always compelling.
- The use of PPIs, for selected indications with a good evidence base, has significant potential benefit but carries more caution in infants and children. Pediatricians should be aware of the concerns regarding the potential adverse events associated with their use.

Proton pump inhibitors (PPIs) constitute one of the most commonly prescribed drugs in pediatric practice. They constitute a group of drugs that inhibit gastric acid production through irreversible binding to the gastric parietal cell H^+/K^+ ATPase pump (the ''proton pump'') (1), which includes omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole. The primary indication for their use, and clear evidence of success, has been in the treatment of peptic acid related diseases. The last 20 years or so, however, have seen a significant rise in their utilization, especially in infants, and across a number of conditions despite limited evidence for their use (2–4). This escalation in their use is paralleled by an increasing understanding and recognition of *potential* complications/adverse effects possibly related to their use. This has raised many questions regarding the correct indications, efficacy and safety of PPIs in pediatrics. The article aims to summarize and highlight these.

MECHANISMS OF ACTION

All PPIs have the same basic chemical structure of substituted benzimidazoles, with variation in the type and position of the substituted group, accounting for the differences in pharmacokinetic and pharmacodynamics properties of individual drugs; however, the basic mechanism of action is essentially the same (1). PPIs can be regarded as prodrugs, which are converted into active forms when the nitrogen on the pyridine group is protonated, resulting in the formation of a permanent cation called cyclic sulfenamide. Being weakly basic compounds with a p*K*a value around 4, PPIs are minimally protonated at neutral pH, and maximally protonated in the greatly acidic environment of the intracellular canaliculi of actively secreting parietal cells in the stomach. The active cyclic sulfenamide irreversibly binds to exposed cysteine thiol groups of the H^+/K^+ ATPase enzyme on the luminal surface of parietal cells. Once covalently bound, the H^+/K^+ ATPase enzyme becomes nonfunctional and activity only returns by parietal cell synthesis of new H^+/K^+ ATPase molecules (Fig. 1).

For oral administration, PPIs should be enteric-coated to prevent premature protonation in the acidic environment in the stomach cavity in order to enable delivery of the intact drug into the duodenum. There they are rapidly absorbed, and their plasma concentration reaches a maximum 1–3 hours after ingestion (5).

PPIs are metabolized to inactive metabolites in the liver by cytochrome P450, mainly by its isoforms CYP2C19 and CYP3A4. The degree of metabolism by CYP2C19 compared with CYP3A4 varies among PPIs. They are also partially metabolized in the enterocyte on their passage across the intestinal barrier. The activity of these enzymes is affected by maturational changes (6). Results of clinical pharmacokinetic studies using either oral or intravenous administration of PPIs in neonates, infants, and older children confirm that metabolic clearance of PPIs is slower in neonates, faster in infants and young children and comparable with adults in the older child (7–10). These data suggest that the patient's age should be taken into account when considering optimal dosing and interval between PPI doses. In addition, CYP2C19 gene allele variations result in different phenotypes: poor metabolizers, extensive metabolizers, and ultrarapid metabolizers (11). Both genetic and age-related variations in metabolism result in a great interindividual variability of the dose of PPI required to achieve an adequate antisecretory effect. For example, omeprazole doses in the range from 0.7 to 3.5 mg kg^{-1} day^{-1} in one study were needed to achieve an intragastric pH >4 for 94% of a 24-hour period (7).

In addition to their well-known anti-secretory effect, PPIs also have a direct anti-inflammatory mechanism of action. They inhibit eotaxin-3 expression by esophageal epithelial cells stimulated by T_H2 cytokines by blocking activation of the transcription (STAT6) pathway (12,13). Although this mechanism of PPIs is probably more important in treatment of eosinophilic esophagitis (EoE), the effect is observed not only in epithelial cultures taken from patients with EoE but also in those taken from gastroesophageal reflux disease (GERD) patients (13).

INDICATIONS AND EFFICACY

The primary indication for PPI use is the treatment of peptic acid related diseases, such as GERD, peptic ulcer disease, hypersecretory states (Zollinger-Ellison syndrome), and for treatment of EoE and *Helicobacter pylori* infection (14,15).

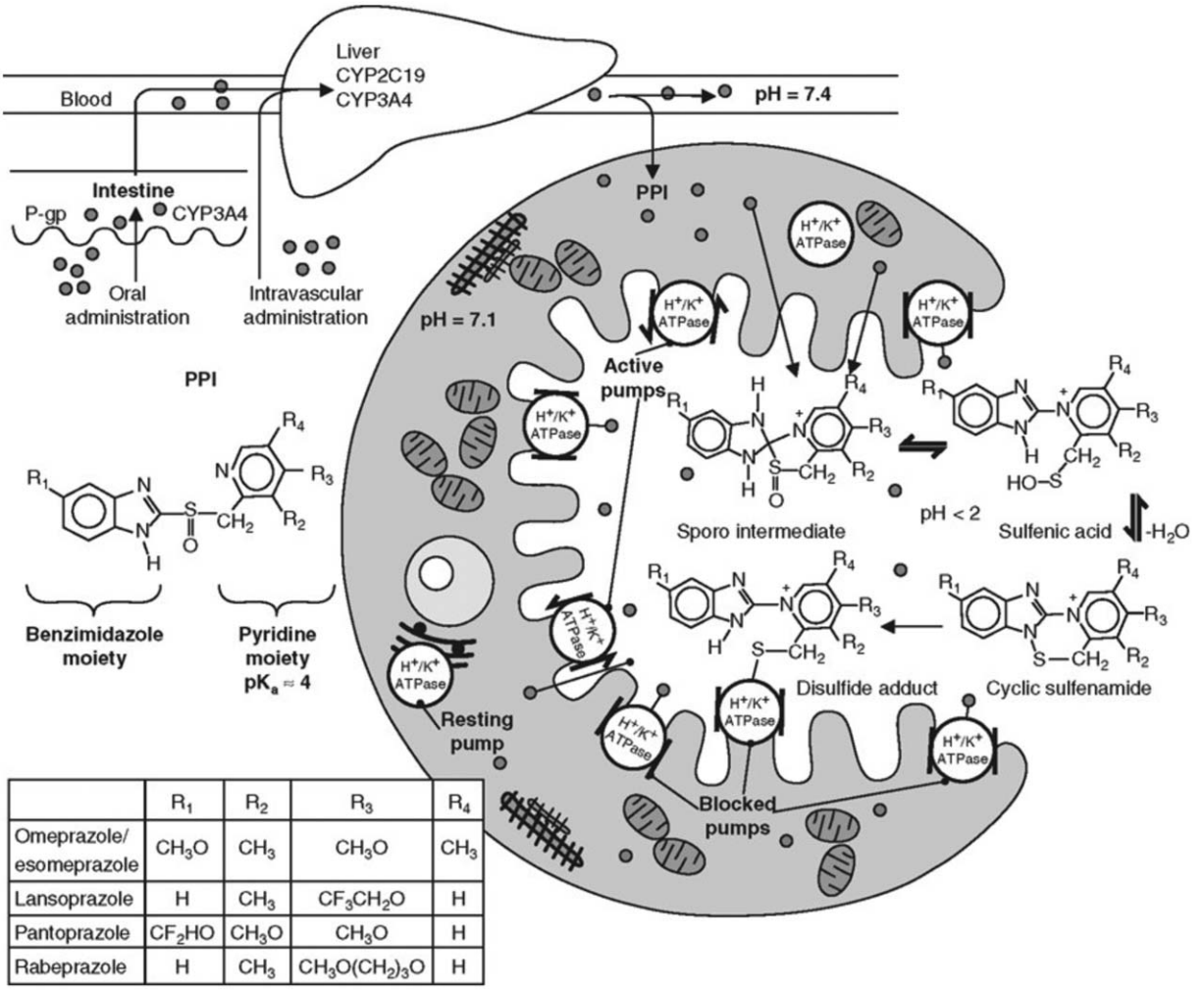
GASTROESOPHAGEAL REFLUX DISEASE

Most objective data on the efficacy of PPIs in infants and children are derived from randomized controlled trials (RCTs) of treatment for GERD and a number of systematic reviews covering this topic have been published in recent years (11,14,16,17). The majority of these reviews concluded that PPIs were effective in control of GERD symptoms in children older than 1 year and adolescents but the evidence of efficacy in infants was weak, with some studies in this age group revealing either no effect or that comparable to placebo. It is likely that these infant studies were ''under-powered,'' used heterogeneous populations and may have used inadequate doses accepting a higher potential metabolism of the prodrugs in this age group.

Although there is evidence that PPIs as a class improve the reflux index and other pH-metric parameters, the correlation between pH-monitoring results and symptomatic benefit is less clear, particularly in infants (16), where studies are likely to have been underpowered and used heterogeneous populations. Therefore, accepting there is a need for larger, better designed studies utilizing a range of doses in infants, the existing evidence does not support PPI use in infants with ''spitting,'' crying and irritability without objectively proven GERD.

PPIs are more effective in acid secretion control when compared with H2-receptor antagonists (17). PPIs are very effective in healing erosive esophagitis, but both symptoms and esophagitis may relapse in a substantial proportion of patients after stopping or even lowering PPI therapy (18). Combined pH/multichannel intraluminal impedance studies revealed that PPI treatment decreases only acid reflux, however, volume reflux (total number of reflux episodes, percentage of time with refluxed material in the esophagus, proximal extent of reflux) remains unchanged (19). Therefore, in comparison with reflux esophagitis, PPIs may be less effective in treatment of extraesophageal manifestations of GERD, such as respiratory tract problems (20,21).

The recent gastroesophageal reflux guidelines of the European and North American Societies of Pediatric Gastroenterology,



	R_1	R_2	R_3	R_4
Omeprazole/ esomeprazole	CH_3O	CH_3	CH_3O	CH_3
Lansoprazole	H	CH_3	CF_3CH_2O	H
Pantoprazole	CF_2HO	CH_3O	CH_3O	H
Rabeprazole	H	CH_3	$CH_3O(CH_2)_3O$	H

FIGURE 1. General chemical structure, routes of absorption and metabolism as well as the mechanism of action of proton pump inhibitors (PPIs). ATPase = adenosine triphosphatase; CYP = cytochrome P450; P-gp = P-glycoprotein; pK_a = negative logarithm of the acid ionization constant. Reproduced with permission from (5).

Hepatology, and Nutrition (ESPGHAN/NASPGHAN) restrict indications for the use of PPIs to diagnostic time limited trials in children with typical symptoms but not infants or patients with extraesophageal symptoms (22). For therapy, the guidelines suggested PPI to be used as first-line for the treatment of reflux-related erosive esophagitis in both infants and children or of typical symptoms of GERD in children. They recommend that PPIs should not be used for the treatment of crying, distress, or visible regurgitation in otherwise healthy infants or for the treatment of extraesophageal symptoms except in which typical GERD symptoms are present.

PEPTIC ULCER DISEASE AND GASTRITIS

Gastric and duodenal ulcers, as well as gastritis can be the consequence of very different causes, such as *H pylori* infection, drugs (eg, nonsteroidal anti-inflammatory drugs (NSAIDs)), stress (eg, shock, multiorgan failure, burns, and major surgery), systemic disease (eg, Crohn disease), and so on; however, in many patients a primary cause may remain unexplained (23). Acid and pepsin cause additional damage to gastric and duodenal mucosa when their defense mechanisms are reduced due to other causes. In contrast with the treatment of GERD, there are practically no published RCTs studying efficacy of PPIs for peptic ulcer disease or gastritis in children; however, based on clinical experience even with relatively low doses of PPIs (0.3−0.7 mg kg^{-1} day^{-1}) ulcer healing is achieved (23). In addition, extrapolation from adult studies may be valid.

HYPERSECRETORY STATES

Hypersecretory states such as Zollinger-Ellison syndrome and antral G-cell hyperplasia are very rare in children. They are characterized by recurrent duodenal and gastric ulcers due to hypersecretion of gastric acid. PPIs in high dose (80 mg or even more per day or up to 3 mg/kg in younger children) are needed to control acid secretion, symptoms, and complications (23).

HELICOBACTER PYLORI INFECTION

PPIs are part of standard triple (PPI + two antibiotics for 14 days) or sequential (PPI + amoxicillin for 5 days, followed by PPI + clarithromycin + metronidazole for 5 days) *H pylori* eradication therapy (24,25). Recommended doses of PPIs for *H pylori* eradication are 1–2 mg/kg/day although the actual dose may vary according to the PPI preparation. Although the goal of treatment is an eradication rate of at least 90%, this is not always achieved

because of antibiotic resistance of individual bacterial strains as well as insufficient compliance.

FUNCTIONAL DYSPEPSIA

In functional dyspepsia (FD), also termed ''nonulcer dyspepsia,'' PPIs can be offered to the patients for pain predominant symptoms (26). PPIs have been shown to be more efficient for pain relief as compared to H2-receptor antagonists (27). Evidence, however, is insufficient to recommend the routine use of PPIs for FD, especially in light of potential side effects from long-term use. There is no rational for the use of PPIs in other functional abdominal pain disorders.

CYSTIC FIBROSIS

Antisecretory drugs have been used as an adjunct to pancreatic enzyme therapy to improve absorption of fat and treat gastrointestinal symptoms in patients with cystic fibrosis (CF). In a recent Cochrane Database systematic review, the authors concluded that there is limited evidence that the use of antisecretory drugs in CF patients is associated with improvement in gastro-intestinal symptoms and fat absorption (28). It is recognized, however, that GERD presents a more frequent problem in CF patients, especially with increasing age, supporting the need for esophageal assessment and treatment of GER as standard components of clinical care (29).

EOSINOPHILIC ESOPHAGITIS

According to the results of a meta-analysis, PPI therapy induces clinical response in 60% and histologic remission in 50% of patients with EoE (30). No significant differences were noted between responders and nonresponders with regards to patient age or the specific PPI used but the efficacy of PPIs increased when they were administered twice compared to once daily. The remission rate was slightly higher in patients with documented pathological acid exposure when compared to those with normal pH-monitoring results (65% vs 49%), pointing to the fact that both antisecretory and anti-inflammatory mechanisms of action of PPIs may be important. These patients were until recently classified as having PPI-responsive esophageal eosinophilia (PPI-REE).

According to previous guidelines, a therapeutic trial with at least 8 weeks of therapy with high dose of PPIs ($1-2\,mg\,kg^{-1}\,day^{-1}$) was an initial part of the diagnostic algorithm in patients with symptomatic esophageal eosinophilia in order to differentiate between PPI-REE and EoE. (31); however, it has been found that EoE and PPI-REE are virtually indistinguishable from one another regarding phenotypic, genetic, and pathophysiological features (32). Consequently, the term PPI-REE was retracted in more recent EoE guidelines and PPI therapy is now considered not as a diagnostic criterion for EoE but as a therapeutic agent (33). In PPI responders, long-term PPI therapy is recommended, because after discontinuing the therapy, symptoms and esophageal eosinophilia typically recur over a 3- to 6-month period. Although both esophageal eosinophilia and symptoms may reappear despite maintenance therapy, a recently published prospective study reported that 78% of children with PPI-responsive EoE remained in remission at 1-year follow- up on low dose PPI therapy (34). The long-term therapeutic strategy and best maintenance dose of PPIs are yet to be defined, however, an approach where the dose is progressively decreased to the lowest dose that keeps the disease in remission seems reasonable (33).

DOSING AND ADMINISTRATION

The main indications and suggested dose ranges for commonly used PPIs are shown in Table 1, although these must be reviewed in accordance with current guidance and local prescribing guidelines. Because PPIs are acid labile, their oral formulations consist of enteric-coated tablets or granules contained in capsules. For patients unable to swallow tablets or capsules, including those reliant on enteral feeding (eg, gastrostomy or jejunostomy), locally prepared dispersible preparations and suspensions of PPIs have been used. Given that meal-induced stimulation of acid production may be necessary to optimize acid suppression it is suggested that PPIs are administered 15–30 minutes before meals. Total daily doses can be given once daily or split into two doses generally taken before breakfast and the evening meal where possible.

SAFETY

According to a recently published review of GERD treatment in children, adverse events with PPI therapy appear in up to 34% of cases, with headaches, diarrhea, nausea, and constipation being the most frequent (35). The authors, however, stated that ''it is not always clear which (adverse events) were truly related to the drug, as opposed to the disease itself or a randomly acquired illness.'' It is also reported in the literature that PPIs may also increase the risk for more serious adverse events, such as lower respiratory tract infections, gastroenteritis, necrotizing enterocolitis (NEC) in premature infants, and nosocomial infections (36). These potential safety issues are discussed especially in the context of inappropriate or prolonged use, noting areas where evidence is strong as well as those where it is lacking and/or in need of further exploration.

DYSBIOSIS, SMALL INTESTINAL BACTERIAL OVERGROWTH, AND INFECTIONS

As gastric acid represents one of the first lines of defense against pathogenic micro-organisms, reduction of gastric acidity due to PPIs may, in theory, lead to increased bacterial colonization in the gastrointestinal tract (37,38). From there pathogens may translocate into the upper and lower respiratory tract. In addition, increased gastric pH may also result in decreased gastric mucus viscosity, increased bacterial translocation and impaired leucocyte function (39,40). The use of PPIs may, therefore, result in intestinal dysbiosis. Indeed, a significant increase of *Streptococcaceae* and *Enterococcaceae*, which are risk factors for *Clostridium difficile* infection, and decrease of *Faecalibacterium*, a commensal anti-inflammatory microorganism, were observed secondary to PPI therapy (41). A number of studies have reported evidence of small intestinal bacterial overgrowth and associated symptoms in children receiving prolonged PPI therapy (42–45).

A number of studies in neonatal and pediatric intensive care unit patients have suggested that the use of acid-suppressive medications, both PPIs and H2-receptor antagonists, may be associated with increased risk of NEC and bacteremia/sepsis, although the association with ventilator-associated pneumonia is conflicting (46). In a multicenter prospective Italian study on 4- to 36-month-old children treated for GERD, the authors found that the rates of acute gastroenteritis and community-acquired pneumonia were significantly higher in patients treated with either PPIs or H2-receptor antagonists in comparison with healthy controls during 4 months of follow-up (47). Similarly, Orenstein et al (48) reported a higher rate of adverse events, particularly lower respiratory tract infections, in 1- to 12-month-old infants with GERD treated with lansoprazole compared to placebo. In another study including 6- to 17-year-old patients with asthma but without overt GERD a significantly higher prevalence of upper respiratory tract infections and bronchiolitis was seen in the group treated with lansoprazole compared to placebo (49); however, an association between PPIs and respiratory infection was not observed in other studies (50,51). A retrospective case-control study of children with *Salmonella*

TABLE 1. Indications, minimum, and maximum doses of commonly used PPIs in children

PPI	Indication	Standard dose	Maximum dose	Reference
Omeprazole	GERD	1–4 mg/kg/day	40 mg/day	(22)
	H. Pylori Infection	15–24 kg – 20 mg BD 25–34 kg – 30 mg BD >35 kg – 40 mg BD	15–24 kg – 40 mg/day 25–34 kg – 60 mg/day >35 kg – 80 mg/day	(25)
	Eosinophilic Esophagitis	Induction: 0.5–1 mg/kg BD Maintenance: to be defined	To be defined (40 mg BD in adults) Maintenance: to be defined	(33)
Esomeprazole	GERD	10 mg/day (weight <20 kg) or 20 mg/day (weight >20 kg)	40 mg/day	(22)
	H. Pylori Infection	0.8–1.3 mg/kg BD OR 15–24 kg – 20 mg BD 25–34 kg – 30 mg BD >35 kg – 40 mg BD	15–24 kg – 40 mg/day 25–34 kg – 60 mg/day >35 kg – 80 mg/day	(103) (25)
	Eosinophilic Esophagitis	Induction: 0.5–1 mg/kg BD Maintenance: to be defined but doses of 0.5–1 mg/kg OD have been used	Induction doses of 1mg/kg BD (maximum 40 mg BD for 8 weeks have been used) Maintenance: to be defined	(33,104)
Lansoprazole	GERD	2 mg/kg/day for infants	30 mg/day	(22)
	H. Pylori Infection	0.6–1.2 mg/kg/day	To be defined given current target ER of 90% (previously 30 mg/day but ER <90%)	(1,25)
	Eosinophilic Esophagitis	15 mg BD Maintenance: to be defined	30 mg/day Maintenance: to be defined	(105)
Pantoprazole	GERD	Ages 5–11 years 20 mg OD Ages > 12 years 20 mg OD	40 mg/day 40–80 mg/day	(106) (107)
	H. pylori infection	Ages > 12 years 40 mg BD	80 mg/day	(107)

Suggested doses only: before use need to check with current guidance as well as local or national formulary and dosing guidelines. PPI use is generally not recommended in preterms, neonates and infants apart for specific indications, where lower doses may be used. BD = twice daily, ER = eradication rate, GERD = gastroesophageal reflux disease, *H. pylori* = Helicobacter pylori, OD = once daily, PPI = Proton Pump Inhibitor.

enteritidis and *Salmonella typhimurium* revealed an increased risk for infection with these pathogens in children taking PPIs (52).

An association may also exist between *C difficile* infection and PPI use, mostly reported from adult studies. Three retrospective studies in children infected with *C difficile* revealed that the use of PPIs was significantly associated with the presence and severity of infection (53–55), and in another study, an increased risk for *C difficile* infections in children was found for H2-receptor antagonist but not for PPI use (56). A systematic review and meta-analysis including 67 studies found a significant association between PPI use and an increased incidence of *C difficile* infection not only among adult but also among pediatric patients (OR 3.00, 95% CI 1.44–6.23; $P < 0.00001$) (57).

The long-term consumption of PPIs in patients with cirrhosis appears to be associated with the development of bacterial infection (58). Several studies in adults suggested that PPI use may also increase the risk of hepatic encephalopathy in patients with liver cirrhosis, probably due to changes in the composition and metabolism of intestinal microbiota (59,60). We do not know whether these findings are relevant also for the population of pediatric patients and hypothetically the risk in posttransplant immunocompromised children of bacterial translocation from the gut needs to be borne in mind.

ABSORPTION OF NUTRIENTS AND BONE FRACTURES

PPIs can, in theory, interfere with calcium absorption by a number of mechanisms (64). Hypochlorhydria *may* interfere with absorption of calcium, magnesium, and B vitamins, resulting in hyperparathyroidism and affect bone remodeling and mineralization as well as affect connective tissue and muscle strength. Net bone resorption and increased secretion of the parathyroid hormone-like hormone have also been reported to occur with hypergastrinemia (61).

Several studies and meta-analyses suggest that long-term use of PPIs is associated with an increased risk of fractures in adults but fall short of causal implication (62,63). In a population-based study including 125,000 patients receiving PPIs and 600,000 controls they observed a dose-related increased risk for fractures in young adults between the age of 18 and 29 years but not in children younger than 18 years of age (64). The results of two studies including pediatric patients on long-term PPI therapy did not find significant changes in serum calcium levels or bone mineral density (65,66); however, some may argue that the short duration of these studies and small sample sizes may not have been sufficient to show an impact of PPIs on calcium and bone metabolism in children (11). A recently published retrospective study of a cohort of 850,000 children revealed that those who were treated in infancy with PPIs alone or in a combination with histamine H2-receptor antagonists have an increased childhood fracture hazard, which appears amplified by days of use and earlier initiation of such therapy (67). In addition, a retrospective analysis of 32,000 pediatric healthcare encounters with documentation of PPI use, matched with the same number of encounters without PPI use, found a statistically significant higher rate of fractures among the PPI exposed group (68).

Gastric hypoacidity caused by PPIs may theoretically interfere with absorption of other minerals and vitamins. A number of observational studies and meta-analyses in adults suggested an association between the use of PPIs and the development of

hypomagnesemia (69,70). PPIs also appear to directly affect iron metabolism by suppressing iron absorption by upregulating hepcidin, which inhibits duodenal ferroportin (71). An association between PPI use, especially chronic, and sideropenic anemia likely due to the negative effects of PPIs on iron absorption, has been proposed by a number of studies, but data in children remains limited (72–74). Gastric acid and activated pepsin are also needed to release vitamin B12 from its protein bond and its subsequent binding with intrinsic factor suggesting that PPIs may interfere with vitamin B12 absorption; however, the results of adult studies on the influence of long-term PPI use on vitamin B12 status are conflicting (75,76) and pediatric studies are lacking (3,11).

GASTRIN SECRETION AND GASTRIC CANCER

With long-term PPI therapy elevated gastrin levels and enterochromaffin-like cell hyperplasia are observed (77,78). Clinical relevance of these effects is probably minor, since there is no evidence that children develop atrophic gastritis or carcinoid tumors; however, published epidemiological studies in adults reveal that long-term PPI use may be associated with an increased risk of gastric cancer [reviewed in (79)], with some experts advocating circumspection in the long-term use of PPIs in children and young adults (80). A recent large case–control study failed to show any association between PPI exposure, even long-term, and gastric cancer (81).

SENSITIZATION TO FOOD ANTIGENS

Increase of gastric pH due to therapy with PPIs prevents activation of pepsinogens and the initiation of protein digestion in the stomach (82). That in turn increases the possibility that, despite subsequent proteolysis by pancreatic and intestinal proteases and peptidases, some peptides serve as antigenic epitopes for intestinal immune cells and induce immune responses. Both animal experiments and prospective studies in adults receiving PPIs have revealed that PPI therapy may lead to sensitization to food antigens (82–85). It is not known if these observations have any clinical relevance regarding the development of food allergies; however, a small case series of pediatric patients that developed de novo EoE on long term PPIs may raise some concern (86). In a case–control study about possible associations of different prenatal, intrapartum and postnatal factors with subsequent development of pediatric EoE, maternal fever, preterm birth, cesarean delivery, and antibiotic use in neonates were found to be associated with the increased risk for EoE, but the adjusted odds ratio was the highest for the use of acid-suppressive medications (aOR 6.05; 95% CI 2.55–14–4) (87). Moreover, a recently published retrospective cohort study showed that treatment with acid-suppressive medications, both PPIs and H_2-receptor antagonists, in the first 6 months of life, significantly increases the risk for development of food allergy, medication allergy, anaphylaxis, allergic rhinitis, and asthma (88).

In a single case–control based study including 2934 celiac disease (CD) patients and 14,584 matched controls (42% younger than 20 years) exposure to antisecretory medications was associated with an increased incidence of CD, especially in younger individuals (89). Lebwohl et al addressed the possibility that symptoms of undiagnosed CD were the cause rather than the consequence for the prescription of PPIs (protopathic bias); however, when they excluded all initial PPI prescriptions made in a year preceding the diagnosis of CD, the association remained significant. Although the mechanisms involved in this association are still to be elucidated, the influence of acid suppression on protein digestion, increased gastric permeability, immunomodulatory effects of PPIs, an increased risk for gastrointestinal infections with pathogens and alterations in the small-intestinal microbiome may be implicated.

OTHER CONDITIONS

Numerous studies and their meta-analyses suggest that PPI use may be associated with an increased risk of acute kidney injury and chronic kidney disease including end-stage renal disease in adults [reviewed in (90)]; however, apart from a single observational study of children with acute kidney injury which suggested a possible association with exposure to PPIs no pediatric studies regarding this adverse effect appear to have been published (91).

Several studies have also suggested a link between prolonged PPI use and dementia and Alzheimer disease (AD) in elderly patients (92–95). Conversely, other studies found that PPI use may offer a protective effect against dementia and AD (96,97). Two recently published systematic reviews and meta-analyses suggested that there was no statistical association between PPI use and an increased risk of dementia or AD (98,99). There are, however, no studies to suggest CNS effects of PPI use in children.

Finally, in addition to the potential association with gastric cancer discussed above, some studies have implicated an increased risk of cancers of the liver (100), pancreas (101), and colorectum (102). More recent studies do not support an increased risk of gastrointestinal cancers with 2 or more years of PPI use, although the risk with use >10 years needs to be better defined (92). Therefore, although risk may link to prolonged use of PPIs, data regarding their use in, or from, the pediatric age group is currently lacking as is clear evidence of direct causation.

CONCLUSIONS

PPIs are used for the prevention and treatment of gastric acid-related conditions. They are formally approved by regulatory agencies for the treatment of symptomatic GERD and erosive esophagitis in children after the first year of life. No PPI is approved for the use in patients younger than 1 year old as clinical trials have not proven to date that PPI are be effective in infants with symptomatic GER or profound crying or fussing.

Although PPIs are generally well tolerated, their use may be associated with an increased risk of infections, *C difficile*-associated diarrhea, impaired digestion of proteins, and possibly malabsorption of minerals and vitamins. There may be an association with cancer, but this is tenuous and causation not confirmed.

The decision on when and in whom to the use PPIs should be, wherever possible, evidence-based in the pediatric age group. In addition, their use, especially long-term, must be monitored, and any possible benefits must always be balanced with potential risks from PPI use.

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