Effects of long term proton pump inhibitors use in pediatrics

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ABSTRACT

We review the physiology of gastric acid secretion and main clinical complications of hypochloridria in childhood. It has become a common practice to treat infants and children who have suspected gastroesophageal reflux disease by using acid-suppressive medications empirically. Multiple studies in adult patients indicate an increase in risk of infection, nutritional impairment and immunological complications. Literature update is revisited in order to summarize acid-suppressive medications adverse effects in infants and children on long-term use.

INTRODUCTION

Gastric physiology and acid secretion

The stomach has had an increasing importance in the GI tract pathology due to the multiple actions related to acid production that go well beyond nutritional functions.

Processing ingested food is a major function of the stomach through mechanical physiology using kinetic tri-dimensional muscular structure but also through secretion of hydrochloric acid with pH between 1.0 and 3.5. Extreme acidity is produced by oxyntic cells located in stomach fundus and body. These cells actively transport chloride and hydrogen ions into the glandular lumen in a mixture with pH 0.8 allowing persisting maintenance of acidity in gastric lumen with various consequences:

1. Activation of a pro-enzyme, pepsinogen, secreted by pyloric glands located in the antrum thus transforming it into an active enzyme that catalyses the hydrolysis of protein macromolecules.

2. Optimization of enteric absorption of vitamins and minerals like vitamin B12 which requires intrinsic factor (IF) to promote absorption. IF is produced in antrum cells when pH is low. Acidity of the stomach is very important for transformation of ingested iron from ferrous to ferric form and maintenance of its chemical stability allowing subsequent intestinal absorption. Active secretion of ascorbic acid from plasma into gastric juice enhances this reaction and iron absorption. Acid pH is also needed to ionize calcium carbonate and transform it into ionized form to be absorbed.

3. In addition to the above mentioned nutritional benefits, gastric microenvironment has a relevant role as antimicrobial defence barrier thus protecting the gastrointestinal tract from various ingested germs. The acid gastric pH is one of the most relevant non-specific defence mechanisms of the body. In vitro studies have shown that pH 3.0 or below cause a bacterial depletion that lasts for 15 minutes and bactericidal properties are kept when pH rises up to 4. Studies conducted in rats and subsequently confirmed in humans revealed that gastric juice is almost sterile, having bacterial colony count below $10^5/ml$. Additionally to the chemical bactericidal properties, the acid causes closure of the pylorus inhibiting the gastric motility and this allows the gastric alimentary content to be kept for a considerable period of time exposed to these conditions. Therefore, it potentiates the bacterial clearance and sterilization of alimentary contents that passes into the gut where mucosal permeability is much higher.

4. Acid pH inhibits growth of nitrites and other N-containing compounds generated from protein digestion. N-containing products are transformed into nitrates that are also secreted by the oral glands. Nitrate conversion into nitrites leads to some toxicity and may have a role in gastric epithelium metaplasia. This experimental evidence seems to have clinical confirmation from studies in adults that show higher nitrite levels after omeprazole treatment in HP
positive patients. Thus, production of nitrous compounds in neutral pH may have some carcinogenic effect as seen in patients with chronic atrophic gastritis and persistent hypochlohydria. Maintenance of pH below 4.0 is due to secretion of gastrin by the parietal cells. Gastrin is an important secretagogue produced by G cells, part of the pyloric glands located in the antrum. Emotional factors, initiation of the cephalic phase of digestion or any other vagal stimulus, as well as the presence of proteins in the gastric lumen, kick-off secretion of gastrin. Whenever there is decrease in the production of acid there is a compensatory hypergastrinemia. Production of gastrin is the strongest stimulus for the secretion of hydrochloric acid, which is fortunately accompanied by the secretion of mucus essential to keep homeostasis in the mucosal barrier. Disturbance or variation of the gastric acidity can be divided into overproduction of acid causing a reduction of the pH, named hyperchlorhydria, or reduction of the secretion causing hypo or achlorhydria. This is defined as a persistent pH above 6.5 after maximum stimulation with pentagastrin, synthetic analogue of the gastrin hormone. In hypochlohydria pH is usually between 4.0 and 6.5, and may be due to several causes. In this new century one of the most important causes of hypochlohydria in children is the overuse of prescription of gastric acid suppressants as histamine-2 receptor antagonist (H2R) and proton pump inhibitors (PPI).

Effects of hypochlohydria and long term use of gastric suppression medication

Proton pump inhibitors induce a hypochloridric status. There is increasing medical evidence about adverse effects secondary to long term use. Most of the knowledge arises from large studies in adults. However a special interest should be devoted to its effects in children, because its use is increasing very much but also because the particularities of the paediatric background.

One of the expected effects of long term use of gastric suppression drugs is the stimulation of neuroendocrine pathway. Gastrin regulation by the parietal cells and its effect in enterochromaffin cells is regulated by a negative feedback system. In animal models the inhibition of secretion leads to a rise in secretin in plasma with proliferation of enterochromaffin cells. Safety studies in children with long use of PPI described elevated gastrinemia. The sustained hypergastrinemia (≥500pg/ml) seen in atrophic chronic or autoimmune gastritis leads to proliferation of ECC which raise the risk of gastric carcinoids or neuroendocrine tumors (NET) mainly when permanent acid secretion occurs with Hp coinfection. The higher NET incidence is a serious long term complication but it is unlikely that this process occurs during childhood.

As previously mentioned, persistent hypochlohydria favours the overgrowth of nitrous compounds producing bacteria that convert nitrates into nitrites and facilitate carcinogenesis of the gastric epithelium. At the same time at neutral pH acid ascorbic loses stability leading to low intragastric levels of vitamin C which prevents nitrites from transforming into nitric oxide and causes a higher exposure to metaplastic nitric compounds. More than half of patients with common variable immunodefficiency (CVID) have hypochlohydria and atrophic gastritis, and there have been rare cases of gastric carcinoma in children with this immune disorder. It has been shown that the concentration of nitrites in gastric juice of patients with CVID is much higher than those with isolated chronic gastritis. Carcinoma may occur in 5-10% of these patients which is a prevalence 50 times the general population, providing support to the above mentioned.

Nutritional consequences

Malabsorption of vitamin B12 is clearly associated with chronic gastritis and hypochlohydria. Among PPI and H2R users there’s a remarkable vitamin B12 deficiency shown in adults. This is related to long term use in H2 antagonists but it seems to occur even in short term use of PPI. However results seem to be different in children: in a cohort of children with cystic fibrosis there was no evidence of vitamin B12 deficiency among PPI users. Absence of Vitamin B12 deficiency has been described in other paediatric studies.

Vitamin A is formed from its precursor β-carotene in ingested food. Bioavailability depends on several factors, namely ingestion of fresh foods. Tang et al have shown that hypochlohydria and achlorhydria affect and reduce its bioavailability. Hypocalcemia and hypochlohydria were correlated in clinical studies performed in adults. A recent meta-analysis reviewed 18 studies regarding the risk of fracture. The risk of spine, hip and all site fracture was moderately associated to the use of PPI, and was not related to length of exposition to PPI (less than 1 year vs more than 1 year). This seems to provide additional evidence about the oral calcium reduced absorption as a consequence of decreased acid secretion. Hypomagnesemia has been strongly associated to long term PPI use in adults, but this effect is still under an unclear mechanism. In a systematic review of paediatric studies in GERD and PPI use children there is no evidence of such a consequence. Some anecdotal reports also document the use of pantoprazole as a cause of false-positive urine cannabinoid screen.

Microbiome changes

The gut microbiome plays an important role in enteric infections, as it seems a modulator of immune response and may lead to some homeostasis disruption. Microbiota changes are now connected to development of IBD, IBS symptoms, obesity and NAFLD among many other diseases. The microbiota is composed of a diversity of classes, the most representative phyla are Firmicutes, Actinobacteria and Proteobacteria. In an elegant study comprising 1815 adult patients, PPI users showed a significant reduction in the microbiota alfa diversity, with a deviation from the controls of 20% of gut bacteria. Moreover, in PPI users there may be an increase in bacteria genera Enterococcus, Streptococcus,
**Staphylococcus** and the potentially pathogenic species *Escherichia coli*. The oral bacteria were over-represented in the faecal microbiome *(Lactobacillus salivarius).*\(^{35}\) This may represent a shift toward the colonization in gut from species that usually were not viable at lower digestive tube due to acid barrier. This may be of major importance to understand how microbiota can be modulated earlier in infancy and which consequence can be derived from this later in life.

### Infectious complications

Hypochlorhydria reduces the strong natural bactericidal filter leading to bacterial proliferation not only within the stomach but throughout the gastrointestinal tract.\(^{26,27}\) *In vitro* studies using chemical simulation of gastric juice have demonstrated that gastric juice has a bactericidal effect over *E. coli* O157:H7, which is a rather frequent agent in paediatric patients.\(^{28}\) Elevation of gastric pH may be an important facilitator of infection in humans through agents like *Vibrio cholerae*, *Campylobacter jejuni*, *Giardia lamblia*, *Serratia* and several strains of *Salmonella*.\(^{1,2,28-30}\) PPIs have also been shown to retard gastrointestinal motility,\(^{31}\) delay gastric emptying rate\(^{32}\) and decrease gastric mucus viscosity,\(^{33}\) all of which may have direct effects on gut microflora and survival of enteric pathogens.

*H pylori* has been associated to hypochloridria, which can lead to infectious complications. In a study among children from Peru, the presence of cholera was significantly associated with infection with *H pylori* children below 10 years of age, and this was an independent risk factor.\(^{34}\) In this study the use of antacids was not associated to cholera, which may be a result of better health care and access to potable water.

For a long time ago there has been noticed that adult immunocompromised patients treated with inhibitors of acid secretion were at risk to infection. However paediatric studies on this issue are sparse.

In hospital setting there was increased risk of diarrhoea by *Clostridium difficile* among inpatients after intake of PPI’s\(^{35}\) and this results were recently replicated in children.\(^{35,36}\) Various authors report a higher incidence of pneumonia in hospitalised patients taking PPI’s.\(^{36,38}\) A meta-analysis of 23 studies, comprising almost 300,000 patients showed a 65% increase in the incidence of *Clostridium difficile*-associated diarrhoea among patients who used PPI.\(^{39}\) This issue raised several controversies as has been debated in recent publications.\(^{40,41}\)

The use of omeprazole in preterm newborns has been associated to increased risk of necrotizing enterocolitis and potential systemic infections.\(^{42}\) Terrin et al. conducted a study with infants of gestational age between 24 and 32 weeks. Two cohorts, exposed and not exposed to ranitidine, were observed over a 1-year period for infections, NEC, and death. Ranitidine use in VLBW newborns was associated to raised rate of NEC and poor outcome.\(^{43}\) Other NICU studies were conducted regarding the risk factors for bloodstream infection in patients and there was a consistent finding of increased risk of infection, namely gram-negative bacteremia and late-onset bacteremia, in newborns receiving PPI’s or H2-blockers.\(^{44-49}\)

It is well recognised that these complex patients in intensive neonatal units have a number of other factors that need separate assessment besides hypochlorhydria and changes in the intestinal microbiota, but it seems plausible that the inhibition of gastric acid may play a role in increasing susceptibility to infection.

Paediatric intensive care unit (PICU) patients have been associated to routine gastric acid inhibition in several PICU scenarios, mostly for prevention of stress ulcer and to minimize the risk of enteral intolerance. Elward et al conducted a prospective cohort study on risk factors associated with ventilator-associated pneumonia (VAP) in PICU patients, with 595 enrolled patients. On univariate analysis H2 antagonists were significantly associated with VAP.\(^{50}\) Other studies had confounding results derived from observational and retrospective studies.\(^{51-53}\) Ambulatory patients are also prone to PPI effects on increased infectious risk. Recently an outbreak of *Salmonella* infection in UK adult patients was associated to PPI use as well as community acquired pneumonia.\(^{54,55}\)

A prospective cohort study was performed by Canani et al in a paediatric population on chronic treatment with PPI’s for GERD in children between the ages of 4 and 36 months, to evaluate the association of acid-suppressive medications with acute gastroenteritis or pneumonia. Children diagnosed with GERD according to results of esophageal pH monitoring and esophageal biopsy were randomized. One-half of this cohort received omeprazole (1 mg/kg per day) and the other half received ranitidine (10 mg/kg per day) for a 2-month course. There was a significant increase in the incidence of pneumonia and gastroenteritis in GERD patients in the PPI group.\(^{56}\) Orenstein et al conducted a multicentre, prospective study evaluating the efficacy and safety of PPIs in infants between 28 days and 12 months of age with symptomatic GERD. Patients were randomized to lansoprazole or placebo. There was a significant increase of lower respiratory tract infections in the lansoprazole group.\(^{57}\)

### Immunological consequences

Protein digestion starts in the stomach and it has benefits beyond nutrition. Hydrolysis of proteins may have immune consequences that were unknown until recently. The identification of adults with chronic gastritis developing *de novo* immunogenicity to alimentary antigens that were previously tolerated prompted for research in this area. Reduction of proteolysis adds an allergic potential to ingested proteins. Mechanisms of alimentary intolerance, specially IgE-mediated are mainly related to the size of macromolecules presented to the intestinal mucosa, although some intact proteins may be found in the small intestine and even in the bloodstream.\(^{58}\) It is possible to simulate gastric juice *in vitro* in a way to promote proteolysis of food fragments that would otherwise be allergenic.\(^{59}\) If pH rises in controlled setting this hydrolytic capacity becomes compromised thereby increasing the risk of sensitisation. The same experiment was simulated in...
experimental animal models after injection of omeprazole. The same investigators showed that the lack of proteolytic potential increases in patients under treatment that inhibits gastric secretion along with increased de novo production of IgE. Perception that gastric hypoacidity may be the first obstacle to modulation of food tolerance has a prominent role in paediatrics as the incidence of alimentary allergy is twice that found in adults given the progressive tolerance with age. In this context avoidance of sustained gastric acid suppression may play an important role in prevention of food allergy.

CONCLUSION

Hypochlorydria in infancy and childhood seems to be a far more common phenomenon than usually recognised. PPI’s complications are rare but must be anticipated especially in infants because the usual dose recommended compared with its acid secretion capacity is much higher than in adults. Empirical anti-secretory treatment is widely prescribed for long periods in small infants hoping to abolish signs and symptoms presumably linked with gastric acid exposure. Prevalence of GERD is high in infants and small children. However there is enough evidence that symptoms usually associated with GERD persist after PPI treatment but have little relation with reduction of acid secretion. This raises the hypothesis that non-acid reflux may contribute to the clinical picture that prompts for therapy.

In small infants there is a subgroup with feeding or swallowing difficulties to which PPI’s are often prescribed empirically, assuming that there is GERD. In the latest years, prescription of PPI’s worldwide puts this drug in the top ten of prescriptions. In some communities gastric suppression medication became as common as antipyretics in children.

In a paediatric gastroenterology clinic, referrals for regurgitation nearly doubled from 14% to 23%, and 85% of these infants were already started on acid-suppressive medications before evaluation by the gastroenterologist. A recent meta-analysis showed that excessive infant crying is not ameliorated with PPI treatment.

Consequences of prolonged reduction acid secretion may be deleterious or even outgrow potential benefits. Among those there is reduced absorption of iron, calcium and vitamins (potentially B12) as well as exposure to ingested bacteria increasing the risk of infection (not only gastrointestinal). Infectious complications in hospitalized and ambulatory children are not negligible and maybe serious. The role of allergic sensitization, although paediatric studies are lacking, may also be considered. Finally, there may be a small increase in the risk of malignancy that may evolve slowly from child to adulthood.

Medically induced hypochlorydria especially for prolonged periods should only be undertaken after clear analysis if benefits outweighs potential risks. Strict selection of high risk patients for treatment with PPI’s may minimize the above discussed.

Further paediatric studies may shed additional light in to this topic but current evidence recommends that the use of gastric acid suppression must be used cautiously for limited periods of time.

REFERENCES


