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Proton-Pump Inhibitors in Adults and Pediatric Patients: Use and Abuse

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Abstract: *Proton-Pump Inhibitors (PPIs) represent the major therapeutic tool of gastric acid-related disorders in adults and pediatric patients. The proton pump must be activated before the PPI is cleared from the circulation in order to effectively inhibit the H/K ATPase. This is related to time to reach maximum concentration, the absorption and elimination rate of the drug. All these features are modulated by age and genetics. Prolonged inhibition of gastric acid secretion may cause hypergastrinemia and enterochromaffin-like-cell hyperplasia, nutrients deficiency, necrotizing enterocolitis, atrophic gastritis, intestinal dysbiosis and digestive infections. These potential side effects have been described in adults, but pediatric studies are scarce. This review summarizes the pharmacodynamic features of PPIs and clarifies the side effects mechanisms of PPIs in children and adults.*

Keywords: *proton-pump inhibitors; pharmacokinetic; side effects; dysbiosis*

1. Gastric acid secretion

The discovery of gastrin in 1905 by John Edkins, and the elucidation of its function, stimulated further research concerning the production of gastric acid [1]. The secretion of gastric acid has a pivotal utility in maintaining proper digestive function, including iron, calcium and vitamin B12 absorption and protein digestion. Also, it may confer protection against enteric bacterial pathogens infection**,** by preventing bacterial penetration and multiplication in the intestinal lumen [2]. Still, expanded levels of gastric acid in the stomach and/or duodenum may induce a several aggravating conditions as peptic ulcer (PU) or gastro-esophageal reflux disease (GERD) both in adults and children [1].

The synthesis of acid secretion in parietal cells is stimulated by the arrival of foods at the gastric level or their smell and taste. The main triggers of acid corrosive secretion are gastrin - a hormone released from antral G cells, histamine - a paracrine component discharged from oxyntic enterochromaffin-like cells and acetylcholine - a neurotransmitter released from antral and oxyntic intramural neurons [3]. The activation of histamine, acetylcholine or gastrin receptors found within the parietal cells at the level of basolateral membrane is followed by the synthesis of gastric acid. These activated receptors act as triggers for the stimulation of the H+/K+-ATPase that induces gastric acid production [1]. The proton channel H+/K+-ATPase, transports H+ ions at the gastric level and exports K+ ions. [3] This mechanism increases gastric intraluminal acidity.

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Gastric acid inhibition represents the principal therapeutic target of all hyper-acidic disorders such as erosive esophagitis and gastro-duodenal ulcers in adults or pediatric patients. The first element studied in detail was the histamine-2 receptor, a crucial activating parietal cell receptor. The gastric (H+, K+)-ATPase became the second pharmacological target. The ultimate stage of gastric acid synthesis is performed by proton relocation by the gastric (H+,K+)-ATPase. Therefore, researchers centered on drugs acting as proton pump inhibitors (PPIs), considering them to be more effective inhibitors of acid secretion [4].

All drugs contain two heterocyclic halves: a pyridine and a benzimidazole/imidazo-pyridine moiety. A methylenesulfinyl group connect the two halves [4].

2. PPIs classes and pharmacokinetics

Omeprazole was developed in 1989, being the first effective drug of this class [5]. Its chemical structure is: 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole [4]. The common feature of the most used PPIs omeprazole (Figure 1), lansoprazole (Figure 2), pantoprazole (Figure 3), and rabeprazole (Figure 6) is a benzimidazole ring. Researchers developed also a different PPI named tenatoprazole. This new drug contains imidazopyridine that replaces the benzimidazole core. [4]. Omeprazole, the S-enantiomer of omeprazole, lansoprazole, pantoprazole and rabeprazole are the main proton pumps inhibitors clinically marketed but not all drugs of this class are approved for pediatric use, especially in infancy.

Omeprazole contains two enantiomers. The first represents the mirror image of the second, functioning as a racemic mixture [6]. The omeprazole's S-isomer has a superior action to the racemic omeprazole. Pharmaco-kinetics researches showed that PPIs' S-isomers have superior mechanism of action compared to the R-isomers [7]. The chemical structure of the major PPIs classes is delineated below.

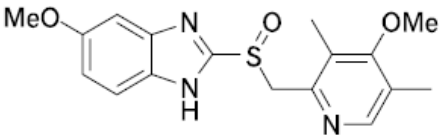

Figure 1. Omeprazole

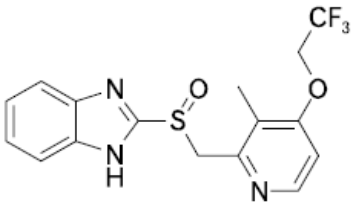

Figure 2. Lansoprazole

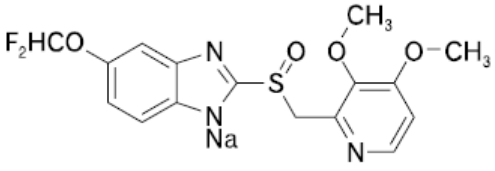

Figure 3. Pantoprazole

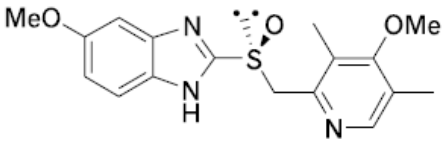

Figure 4. Esomeprazole

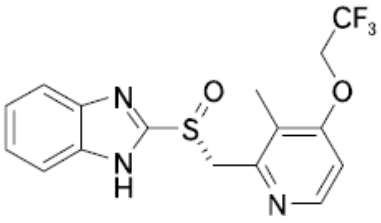

Figure 5. Dexlansoprazole

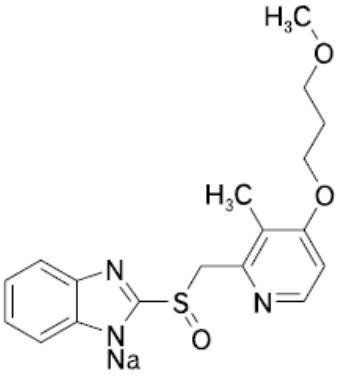

Figure 6. Rabeprazole

A recently developed anti-acid drug class is represented by potassium-competitive acid blockers (P-CABs). This class of drugs seemed a useful therapeutic tool for all disorders induced by increased gastric acid secretion refractory to classic PPIs [8]. Potassium-competitive acid blockers inhibit in a reversibly manner the gastric H+/K+ ionic pump by the mechanism of competition with K+. Pharmacokinetic features of newly developed P-CABs consist in rapid onset, more effective action compare to PPIs and longer duration [8].

Subsequently, potassium-competitive acid blockers were presumed to be a superior therapeutic class for the diseases related to increased gastric acid production. Though, due to severe adverse events such as liver toxicity, attempts to market P-CABs have failed.

The only drug belonging to the P-CABs class that was successfully launched in clinical practice in Korea was revaprazan [9]. A new potassium-competitive acid blocker named vonoprazan fumarate was approved in 2015 by the Japanese health insurance system [10].

In case of PPIs, the constant specific for acid dissociation (pKa1) is approximate 4 whereas the drug will be activated in low *p*H environment.

PPIs are weak bases that usually tend to agglutinate in the parietal cell ducts. At that level, these drugs will be activated by a proton-catalysed mechanism into an acidic complex [1]. The activated complex establishes covalent connections with the sulphydryl radicals of cysteine 813 or 822 residues in the extra-cellular part of the H+/K+ ionic pump in order to produce several disulfide complexes with high stability. In this way, the enzyme will be blocked [1].

A lot of researches pointed to examine the chemical process related to the inhibition of the gastric ATP-ase and to evaluate specific cysteines that react with several PPIs [11,12]. There have been progresses in characterizing the crystal composition of a similar P2 type ionic pump -ATPase. This

promoted the innovation of a 3D model for H+/K+ trans-membrane channel wherein reactive cysteine can be found [13].

For all various PPIs, the stability was established at the *p*H value of 5.1. According to each PPI half live related stability, the value are as follows: for rabeprazole 0.12 h, for omeprazole 1.4 h, for lansoprazole 1.5 h and for pantoprazole 4.7 h [14].

In an acidic environment with the *p*H around 1.2 that is similar to the parietal cell interior *p*H, all PPIs became active more quickly. All PPIs half lives were modified in the low pH environment, ranging from 1.3 min to 4.6 min. Pantoprazole had the slowest activation rate in these conditions [4].

Elaboration of drug metabolites is an vital subject. Enzymatic conversion is more beneficial than synthetic chemistry [15]. These important compounds are difficult to produce, but they have a major importance for safety assessment. Many of these drugs are metabolized via the cytochromes P450 by oxidations. The PPIs are transformed by human cytochromes P450, creating several metabolites according to each characteristic substance [15].

Initially, the native PPIs are inactive drugs, being subsequently rapidly metabolized in the liver. It is fundamental to preserve increased PPI serum level until the gastric secretion is initiated because PPI is an acid-activated prodrug. The metabolism velocity balances the drug plasma level.

Human cytochrome P450 directs the metabolism of PPIs. Cytochromes P450 systems drive the initial metabolism phases in humans, synthesizing drug metabolites obtained by oxidation mechanisms. These are further eliminated or adjusted and targeted for excretion by phase II enzymes such as glutathione transferases. P450s are also responsible for the generation of activated drugs from their prodrug forms [15].

Butler at al. [15] showed that the mutation A82F/ F87V in P450 BM-3 enzyme of Bacillus megaterium will alter the substrate selectivity. Consequently, several drugs belonging to PPIs class can become substrates for these mutations [15]. Active conversion of different PPIs to human like compounds by BM-3 enzyme variants guarantees innovative pathways of synthesis for these substances.

3. Mechanism of PPIs action at the gastric level

An acidic environment characterized by a *p*H lower than 4 is found in humans only at the gastric level [16]. It is known that all drugs belonging to PPIs class act as weak bases and their pKa ranges between 4 for pantoprazole, lansoprazole and omeprazole and 5 for rabeprazole. Therefore, it is obvious that these drugs would initially be located in the low pH environment of parietal cells ducts [4]. The PPIs therapeutic index is determined by the acid space dependent concentration of the drug. The PPI's level at the surface of the transmembrane ionic channel is more than 1000 time increased over the serum concentration of the drug [16]. Another important mechanism is related to the prodrug activation to a cationic substance with high reactivity. The conversion is dependent to the acidic environment where the inactive prodrug is initially located. In order to be activated, the prodrugs will react by protonation in order to create disulfides bounds with the cysteines molecules of the $H+/K+$ ionic pump. Several studies have proved that acid stability for PPIs increases as follows: rabeprazole<lansoprazole<omeprazole<pantoprazole [16].

Several factors are critical for PPI pharmaco-kinetics features: PPIs' storage at the level of parietal ducts, the amount of the ionic pump enzyme situated in the ducts, the additional enzyme synthesis, the specific metabolism pathways of the PPI and the specificity of the PPIs binding and stability in the parietal ducts [17].

4. The stability of PPIs binding

A crucial ascertainment highlighted that additional enzymatic synthesis contributes to total restoration of ionic pump mechanism due to the formation of a tight covalent bond of the drug with the enzyme [16]. The half life of the pump will be equivalent to the half life of drug connected to the

enzyme. Several studies depicted different half lives for the drug binding, the ionic pump enzyme and PPIs' activity inhibition [18].

The ionic pump enzyme in rats has a half life of 54 h [19]. The enzyme function recovered following PPI administration after 15 h [20]. Similar studies showed that the half time for acid secretion recovery in lab rats treated with omeprazole was 20 h [21].

There are disulfide bridges between the activate drug and the molecule cysteine of the enzyme. Disulfide connections are weak, facilitating cleavage. The glutathione from the parietal ducts split these bounds. The cleavage of the glutathione that contacted the disulfide from the PPI connected to the enzyme will restore the enzyme activity [16].

In this manner, the stability of PPI binding is the most important factor that influence the duration of the inhibitory mechanism. The pharmacokinetic features of the marketed PPIs in adults and pediatric patients are depicted in Figure 7 [22-24].

Parameter	Omeprazole 20mg	Lansoprazole 30 mg	Pantoprazole 40 mg	Rabeprazole 20 mg	Esomeprazole 20 mg/40 mg
T_{max} (hr)	1-4	1.2-2.1	2-4	3-5	1.0 – 3.5
C_{max} (µmol/L)	0.23-23.2	1.62-3.25	2.87-8.61	1.14	2.1-2.4 at 20 mg; 4.7-5.1 at 40 mg
AUC (µmol *hr/L)	0.58-3.47	4.6-13.5	5.22-13.04	2.22	4.2 at 20 mg; 12.6 at 40 mg
V (L/kg)	0.13-0.35	0.4	0.15		0.22-0.26
CL (mL/min)	400-620	400-650	90-225		160-330
$T_{1/2}$ (hr)	0.5-1.2	0.9-2.1	0.8-2	0.6-1.4	1.3-1.6

T_{max} time to maximal plasma concentration; C_{max} maximal plasma concentration; AUC area under the plasmatic concentration curve; V apparent volume of distribution; CL clearance; $T_{½}$ elimination half-life.

Figure 7. Pharmacokinetic characteristics of PPIs

Safety concerns regarding PPIs

Both in adults and children, PPIs are frequently used for the treatment of gastric acid-induced disorders. Previous research established that the majority of the PPIs are located in the most acidic environments in human body - near the gastric parietal cell and specifically interacted with its therapeutic targets at that place. These drugs proved to have reduced short-term side effects, being well tolerated. Yet, concerning the increasing rate of gastric acid-related conditions, several adverse reactions after long term administration started to be published. But so far, there is no publication which clarifies completely the exact mechanisms by which PPIs' side effects occur in children or adults.

The main adverse effects are represented by nutritional deficiencies, bacterial or fungal infections, neurological disorders or ophthalmic impairment [25]. Besides, as shown in Table 1 [25], a lot of other rare adverse reactions have been reported such as autoimmune disorders, allergies including angioedema, renal impairment or different myopathies.

Table 1. Publications concerning PPIs related side effects after long term use in pediatric and adult patients [25]

PPIs related side effects	Reference
Gastro-intestinal system	
Diarrhea/constipation, abdominal pain, nausea	26
Enteric infection	27, 28
Hypergastrinemia	29
Gastric polyps	30
Drug-induced hepatitis	31
Peritonitis	32
Nervous system	
Emotional disorders	33
Ophthalmic impairment	34
Immune system	
Allergic reactions	35, 36
Systemic Lupus Erythematosus	37
Circulatory System	
Ischemic heart disease	38
Anemia	39
Angioedema	40
Urinary system	
Interstitial nephritis, proteinuria	41
Musculo-skeletal system	
Myalgia	38, 42
Rhabdomyolysis	42
Polymyositis	42
Endocrine and reproductive systems	
Endocrine glands disorders	43
Respiratory system	
Community-acquired pneumonia	44, 45
Others	
Nutritional deficiencies	46, 47
Skin-related conditions	48
Alopecia	49
Drug-drug interactions	50

The safety of adding concomitant medication on PPIs raised important concerns. Wedemeyer et al. [51] published a review concerning drug interactions in patients receiving PPIs and other medications. The results indicated that omeprazole has a major risk regarding interactions with other medications due to its affinity for CYP2C19 and CYP3A4.

On the other hand, pantoprazole seems to interact less with other drugs. Lansoprazole and rabeprazole have been shown to interact less with other drugs compared to omeprazole. The paper concluded that there are few drug-PPIs interactions with major clinical significance. As an example, the review proved that mycophenolate mofetil pharmacokinetics is *p*H dependent, so it is altered by PPIs concomitant administration. The mechanism is based on the decreased gastric acidity that implicit will reduce the mycophenolic acid availability.

The paper also reported that co-administration of PPIs with methotrexate may alter methotrexate absorption and may interact with protease inhibitors pharmacokinetics.

The Food and Drug Administration (FDA) raised attention about the administration of several PPIs concomitant with clopidogrel, advising against this combination [16]. Yet, a randomized controlled trial assessed the adverse effects of clopidogrel administration concomitant to omeprazole. This study didn't find increased adverse reactions related to cardiovascular system. By contrary, the results showed less adverse gastrointestinal events due to omeprazole [52].

As yet, the authors issued two hypotheses to describe the potential adverse effects of PPIs. Hagiwara [53] supposed that PPIs administration on a long period of time will decrease the intra-

gastric acidity, increasing the risk of intestinal infections and exacerbating the adverse inflammatory reaction until gastric adenocarcinoma.

Liu et al. [54] reported that in the environment of lysosomes with *p*H=5, PPIs can be activated. Consecutively, this will have an impact on certain lysosomal enzymes activity with further impairment to the immune system. These could be the base of certain severe adverse events such as infections and oncogenesis. Although the proposed mechanisms to explain PPIs toxicity have been presented, these two pathways are not able to clarify all the adverse effects described in routine practice.

Thus, Dingfeng et al. [25] aimed to explain at the molecular level the mechanisms of PPI's adverse effects. The authors used gene expression microarray to connect human genes to PPIs and adverse reactions. They indicated that PPIs can inhibit acid hydrolases and V-ATPases in all acidic intracellular medium. Furthermore, the synthesis and secretion of coagulation factors, cytokines and complement, as well as antigen presentation may be affected by these drugs [27]. This paper demonstrated that the complement cascade pathway and cellular retinol metabolism are altered by PPIs. These two pathways with different genes expression could contribute to the PPIs toxic action [25].

Corsonello et al. [55] reported that PPIs may induce severe side effects as previously depicted, including endothelial alteration, impaired immune response, malabsorbtion, small intestine bacterial overgrowth and certain drug interactions. Not all these severe side effects attributed to long term PPIs treatment are connected to clinical evidence in routine practice because the investigations in clinical trials are conducted in ideal conditions in order to assess certain drugs efficacy. As an example, patients with comorbidities and severe conditions are usually excluded from randomized clinical studies. Therefore, it is crucial to develop further large clinical studies enrolling pediatric and adult patients to quantify the risk of long-term PPI therapy.

The influence of PPIs on the gut microbiota

PPIs administration become the first line drug recommended for pediatric patients aged more than one year old and adult with gastric acid related disorders. These drugs are in a great measure well tolerated as shown before, but long-term administration may lead to a significant diminish of gastric acid secretion and will create the premises of gut microbiota imbalance. The complex human gut's ecosystem is interacting with the host, conferring high relevance to health or diseases in case of dysbiosis. The human gut microbiota has a vital role for nutrition, modulates the immune system and regulates the brain activity and behavior.

Any disturbance in the normal balance of intestinal ecosystem will result in various extra-intestinal or intestinal diseases. Recent publications highlighted the implication of chronic PPIs administration in the initiation of intestinal dysbiosis with the appearance of small intestinal bacterial overgrowth (SIBO) [56]. Long term PPIs administration has a great potential to alter the intraluminal digestive microbiota [28]. SIBO is characterized by the proliferation of more than 10^5 colony forming units (CFU) / mL in the small intestine lumen [56]. Pediatric or adult patients diagnosed with SIBO can be pauci-symptomatic or asymptomatic, but a great majority of these patients associate digestive symptoms as recurrent abdominal pain, bloating, chronic diarrhea or malabsorption syndrome [57].

A recent study published by Belei et al. [28], showed that concomitant administration of probiotics in children with gastro-esophageal reflux treated with PPIs, decreased the rate of SIBO and reduced rate of digestive symptoms. The authors concluded that chronic administration of anti-acid drugs should be combined with probiotic treatment to minimize the risk of intestinal dysbiosis [28].

Bruno et al. [58] evaluated the predominance of microbiota disturbance induced by long term PPI's administration and highlighted the implication of gut flora alteration in the pathogenesis of several digestive conditions.

Actually, a few data have been published regarding the interaction between PPIs and oral bacterial flora. A recent publication [59] showed that short time administration of esomeprazole had a great impact on oral cavity and gut microbiota: Leptotrichia and Fusobacterium periodontal concentrations

increased, salivary Veillonella and Neisseria decreased and Streptococcus concentrations in stool increased. These results support the idea that PPIs may alter both oral and gut microbiota [59].

The esophagus contains a distinctive colonisation. Healthy individuals have an esophageal microbiota formed mainly by gram positive bacteria as Streptococcus. In patients with esophagitis or Barret esophageal alterations gram negative bacteria predominates as Fusobacterium, Actinomyces, Prevotella or Granulicatella [60]. Actually, studies regarding the involvement of PPIs in altering the esophageal microflora and induction of Barret esofageal lesions are inconclusive. Chronic PPIs treatment may alter esophageal microflora by increasing the Firmicutes strains and decreasing the concentration of Bacteroidetes [61].

Another recent epidemiological research showed that in patients without comorbidities, chronic administration of PPIs increased the risk of esophageal adenocarcinoma [62].

The stomach is not sterile. The gastric colonization pattern is mainly based on Bacteroidetes and Firmicutes. Streptococcus strains predominate in the gastric microbiota, beside Prevotella and Veillonella [63]. It has been shown that PPIs chronic administration was associated to several adverse events as increased bacterial concentration and translocation and gastric stasis [64]. Hypochlorhydria has a negative role by diminishing microbial diversity. It promotes development of genotoxic bacterial strains that could increase the nitrate/nitrite reductase functions involved in malignancy [65].

Most studies are focalizing to the fact that long treatment with PPIs significantly alters small intestine microbiota causing SIBO due to the reduction of protective gastric acid barrier [66, 67]. As shown before, the chronic use of PPIs favors the development of enteral infection and secondary alterations in microbiota composition. By inducing dysbiosis, PPIs may influence gut–brain axis functions, causing irritable bowel syndrome onset [68].

The colon is colonized with the largest number of microbial strains of the whole gastrointestinal tract [69]. By diminishing gastric acid barrier, PPIs will alter the colonic microbiota, basically by decreasing the commensal bacteria. This will have an implicit impact in reduction the variety of the microflora at this level [70]. Hence, it is very likely that the microbiota alteration induced by PPIs will alter host equilibrium. PPIs can precipitate the onset of enteric contaminations with Clostridium difficile or other bacterial strains as Campylobacter or Salmonella [71]. There are scarce published data regarding the relationship between PPI-driven microbial imbalance and inflammatory bowel disease (IBD) onset. By altering the intestinal flora, chronic administration of PPIs can decompensate the IBD course, inducing relapses. This is due to the fact that IBD patients are more prone to bacterial coinfections [58]. It is not to be ignored that chronic hypergastrinemia, induced by PPIs long term administration may favor the development of certain digestive malignancies according to some authors [72, 73].

Conclusions

PPIs remain the first-line treatment for all conditions induced by increased gastric acidity. These drugs have been shown to have a high safety profile, being well tolerated and free of major side effects during short-term administration in pediatric as well as in adult patients. However, in recent years there has been an increase in the number of publications reporting adverse effects of PPIs after long-term use.

PPIs exert a strong action of suppressing gastric acidity. Consequently, this mode of action could induce morphological and functional injuries at the gastric level, including gland hyperplasia or hypergastrinaemia. Other important side effects have been reported after long-term administration of PPIS, such as nutritional deficiencies, enteral infections, ocular and renal damage and neurological impairment. Most of the major side effects attributed to long-term administration of PPIs are not based on strongly significant evidence due to various error factors in clinical trials.

More and more evidence has been published that long-term administration of PPIs can disrupt the gastrointestinal tract microbiota at any level by removing the gastric acid barrier. This may favor the onset of dysbiosis, precipitating the development of other gastrointestinal or extra-digestive disorders.

Given the potential risks associated with long-term administration of PPIs, physicians should determine the correct indication for administration, as well as the optimal dose and duration of administration.

In both pediatric and adult patients who require long-term administration of PPIs, probiotics association could be indicated in order to decrease the intestinal microbiota alteration. However, this strategy remains to be tested in future large clinical trials. Chronic administration of PPIs should be avoided as much as possible and in case of need for prolongation of therapy "on demand" strategy should be adopted.

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