Pharmacological Approach to Gastric Acid Suppression: Past, Present, and Future

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Keywords
Gastric acid suppression · H\textsubscript{2}-receptor blocker · Proton pump inhibitor · Potassium-competitive acid blocker · Acid-related disorder · Helicobacter pylori · Gastroesophageal reflux disease · Gastroprotection · Safety

Abstract
Less than 2 centuries have elapsed since the identification of hydrochloric acid in the stomach. The clarification of the molecular mechanisms allowed the effective therapeutic suppression of gastric acid secretion. The spectacular advances in the treatment of acid-related disorders represent a synthesis of the contributions of several brilliant pharmacologists, basic scientists, and clinical physicians. Effective gastric acid suppressive therapy has dramatically improved the therapy and outcome of acid-related disorders. The introduction of proton pump inhibitors (PPIs) in clinical practice has significantly changed the medical management of upper gastrointestinal disorders. PPIs represent the “gold-standard” therapy in acid-related disorders. However, some challenges persist in the therapy of acid related diseases, including management of patients who respond inadequately to PPI therapy, more effective gastroprotection, or more powerful antisecretory treatment for the eradication of Helicobacter pylori infection. New antisecretory drugs are currently being developed and investigated to further provide a more effective and profound gastric acid secretion inhibition. The major advance has been the development of acid pump antagonists, the potassium channel acid blocking drugs (P-CABs). Long-term studies comparing P-CABs with PPIs will help to define the exact place and safety profile of this class of drug in the management of acid-related disorders.

Introduction

The function and secretion of stomach has been a real mystery for centuries. Prior to the 17th century there was a noteworthy confusion regarding the role of stomach in the digestive process. Formulation of several ideas on the nature of the gastric liquid remained for a long time open to controversy. The ancient Greeks identified acid only as bitter-sour liquids [1].

Paracelsus (1493–1541) believed that the stomach contains acid, necessary for digestion, but the source and the nature of the acid were unclear. He thought that the acid in the human stomach originates from the drinking of acidic spa water ("hungry acid") [2].

Lazzaro Spallanzini (1729–1799), who was the professor of Natural History in Pavia, discovered the digestive
power of saliva and confirmed the solvent properties of gastric juice. In 1780, published his observations in this area, but he was uncertain about his findings regarding the acidity of gastric juice. The final resolution of the exact nature of acid produced by the stomach was provided in 1823 by William Prout. He had specifically identified hydrochloric acid in the gastric juice in humans and other animals, and he was able to quantify the total and free hydrochloric acid and chloride present [3, 4].

The scientific research continued with first description of gastric glands as the source of gastric acid (Purkinje and Golgi, mid and late 19th century). The role of the vagus nerves in the control of gastric acid secretion and the theory of “nervism” (the neuro-reflex stimulation of gastric secretion by vagal nerve) was identified by Pavlov (early 20th century). This theory was expanded by the histamine-mediated concept of gastric secretion (Popielski and Code, mid-20th century). The complexity of gastric secretion was completed in 1836 by Schwann, who described a water-soluble factor, named “pepsin,” concluding that gastric acid and pepsin are indispensable for digestion. The impact of gastric acid in etiopathogenesis of mucosal injury is summarized be the famous conclusion of Schwarz (“No acid no ulcer,” 1910). The prostaglandins were demonstrated to influence all components of gastric mucosal defense barriers (Vane, 1970s) [5, 6].

*Helicobacter pylori* was first described to be the causative agent of peptic ulcers by Barry Marshall and Robin Warren (1984) – who later received the Nobel Prize for their findings that bacteria could cause diseases previously believed to be induced by human factors. The discovery has tempted many experts to conclude that physiological factors, and specifically the famous stress theory of Hans Selye are of secondary importance [7].

The identification of the primary pathogenic role of *H. pylori* in peptic ulcer disease (PUD) revolutionized our concept related to mucosal ulceration and enabled to cure the disease [8, 9].

Antacids, protective agents, anticholinergics, gastrin antagonists, and prostaglandins were used for decades in the treatment of PUD with inadequate effects and common side effects.

### Regulation of Gastric Acid Secretion

Gastric acid secretion is influenced both centrally and peripherally and is precisely regulated by neural (acetylcholine), hormonal (gastrin) and paracrine (histamine, somatostatin) mechanisms. The stimulatory effect of acetylcholine and gastrin is mediated via increase in cytosolic calcium, whereas the effect of histamine is mediated via activation of adenylate cyclase and generation of cyclic adenosine monophosphate. Potentiation between histamine and either gastrin or acetylcholine may reflect post-receptor interaction between the distinct pathways and the ability of gastrin or acetylcholine to release histamine from mucosal enterochromaffin-like cells. The major circulating stimulus of acid secretion is gastrin, which does not stimulate directly the parietal cells, but mobilizes histamine from oxyntic mucosa via enterochromaffin-like cells. The tight regulation of parietal cells ensures the proper secretion of HCl. The final factor in acid secretion is the stimulation of the proton pump (H+, K+-ATPase) enzyme expressed in parietal cells, which regulates the exchange of cytoplasmic H+ for extracellular K+. The H+ secreted into the gastric lumen by the H+, K+-ATPase combines with luminal Cl⁻ to form gastric acid. After appropriate gastric acid secretion occurred, a feedback mechanism finishes gastric acid secretion. The prime inhibitor of acid secretion is somatostatin. A decrease of intragastric pH stimulates somatostatin release from antral D cells. Somatostatin inhibits not only gastric acid secretion but also slows gastrin release. In addition, the duodenal acidification can trigger the release of secretin, which also inhibits gastric acid secretion [10]. In some special circumstances, the gastric acid secretion is deranged resulting in excessively reduced or increased acid output. Chronic atrophic gastritis is a generally asymptomatic condition of great impact because it develops into gastric cancer in a number of patients. There are 2 types of atrophic gastritis. Atrophic gastritis can be associated with long-standing *H. pylori* infection (multifocal atrophic gastritis) and with an autoimmune process that progressively destroys the oxyntic mucosa (autoimmune atrophic gastritis). Autoimmune gastritis is a chronic progressive inflammatory condition that results in the replacement of the parietal cell mass by atrophic and metaplastic mucosa. The pathogenesis of autoimmune atrophic gastritis involves an antibody-mediated loss of parietal cells resulting in hypochlorhydria and then achlorhydria, while autoantibodies against the intrinsic factor impair the absorption of vitamin B₁₂. Autoimmune atrophic gastritis progresses from a mild chronic inflammation of the gastric corpus to an advanced stage associated with a severe form of vitamin B₁₂ deficiency anemia known as pernicious anemia [11]. Gastrinoma is a very uncommon tumor leading to gastrin hypersecretion, hyperchlorhydria, and characterized by Zollinger-Ellison syndrome, that is, severe and multiple gastroduodenal ulcers...
ceration and profuse diarrhea. The disease can be sporadic or familial within multiple endocrine neoplasia type-1 syndrome. Tumors are located usually in the duodenopancreas [12].

**H₂-Receptor Antagonists**

The suppression of gastric acid secretion with antisecretory agents has been the mainstay of treatment for acid-related diseases. The development of the concept of histamine (H₂)-receptor (James Black, 1970s) triggered the way for potent H₂-receptor antagonists (H₂RAs) which partially suppress basal and meal-stimulated acid secretion. Some of these agents can induce an intragastric pH > 3, lasting for approximately 10 h/day when given twice/day at recommended doses. H₂RAs are highly selective, and they do not affect H1-receptors; moreover, they are not anticholinergic agents. The level of gastric acid suppression can facilitate healing of duodenal ulcers; however, the inhibition of gastric acid secretion achieved with H₂RAs have been proved to be suboptimal for effectively controlling more severe acid-related disorders, especially for healing severe erosive esophagitis and has limited efficacy for other indications (e.g., upper gastrointestinal bleeding). In addition, the development of tolerance to H₂RAs further limits their extensive clinical use. Despite these, H₂RAs can be used as part of the step-down strategy of gastroesophageal reflux disease (GERD) treatment, for self-controlling (on-demand treatment) of acid-related symptoms. It has also been suggested that the effectiveness of nighttime dose of H₂RA can be useful for elimination of nocturnal acid breakthrough [13–15].

**Proton Pump Inhibitors**

The ultimate step in acid secretion is the stimulation of the proton pump (H⁺, K⁺-ATPase) to secret hydrogen ions into the gastric lumen in exchange for potassium ions. The discovery of proton pumps in parietal cells (Ganser, Forte and Sachs, late 1970) and the recognition that proton pump (H⁺, K⁺-ATPase) is the final step of acid secretion instructed the way for more potent and profound acid inhibition and culminated in the development of proton pump inhibitors (PPIs; late 1980s) which are targeted at directly inhibiting this enzyme [16–18]. PPIs revolutionized the therapy of acid-related disorders, and they represent one of the most commonly prescribed classes of drugs. Once-daily PPI dosing inhibits maximal acid output by about 66% after 5 days. The PPIs can induce an intragastric pH above 3 lasting for approximately 17 h/day, and an intragastric pH above 5 for approximately 9 h/day after once-daily oral administration for recommended doses. It is possible to obtain even higher target pH values with higher doses and with continuous intravenous administration of PPIs. They are most effective when the parietal cell is stimulated to secrete gastric acid postprandially. This phenomenon has practical clinical implications for timing of administration. Maximal gastric acid secretory capacity may not be restored for up to 24–48 h after discontinuing PPI therapy [19, 20].

Chemically, all available PPIs consist of a benzimidazole ring and a pyridine ring, but vary in the specific ring substitution. All PPIs have a broadly similar mechanism of action. However, there are some differences between the PPIs in their pharmacokinetics, pharmacodynamics, and potential for drug interactions. Although the individual PPI have similar efficacy in many cases, differences between them should be considered when choosing a treatment regimen [21, 22].

Many studies have shown the clear-cut superiority of PPIs over H₂RA as a treatment for acid-related disorders. It has been shown that there is a significant correlation between healing and the degree, duration of gastric acid suppression, and length of treatment [23].

Several meta-analyses did show that PPIs are more effective than H₂RAs in the treatment of PUD, severe GERD, Zollinger-Ellison syndrome, or upper gastrointestinal bleeding [24–27]. The presence of acid is essential for nonsteroidal anti-inflammatory drug (NSAID)- and aspirin-induced gastroduodenal mucosal injury. There is strong evidence that PPIs effectively can prevent and treat NSAID- and aspirin-associated gastroduodenal mucosal lesions [28, 29]. Raising intragastric pH by PPIs improves the antimicrobial and bactericidal effectiveness of antibiotics against *H. pylori* eradication. As a consequence, the combination of a PPI with antibiotics is the well-established standard first-line regimen for eradication of *H. pylori* infection [30].

The key messages regarding main indications and appropriate use of PPIs are summarized in Table 1 [31–33].

**Safety of Long-Term PPI Therapy**

PPI therapy is commonly used outside of clear-cut indications, resulting in widespread inappropriate use or for indications with little benefit; therefore, the inap-
Appropriate long-term treatment is a matter of concern. Although overuse and misuse may challenge the safety profile, the tolerability of PPIs is remarkable good. Adverse events generally can occur at a rate of 1–3%. Long-term trials suggest a similar tolerability rate to that found in short-term studies. The main indications, appropriateness and improper long-term PPI use, and some concerns about long-term therapy with PPI have been recently extensively reviewed by Scarpignato et al. [31], Yadlapati and Kahrilas [32], and Freedberg et al. [33]. Observational studies have raised concern that PPIs can be associated with increased risk of pneumonia, osteoporosis, Clostridium difficile-associated diarrhea, cardiovascular disease, liver disease, chronic renal disease, microscopic colitis, dementia, or gastric carcinoid. Despite a large number of studies, the overall quality of evidence for PPI adverse effects is low [31, 34–38]. Very recently, in a large placebo controlled randomized trial of 17,598 participants, long-term adverse events were similar in the PPI (pantoprazole) group compared to placebo arms with 53,000 patient years of follow-up: pantoprazole was not associated with any significant adverse events when used for 3 years, with the possible exception of an increased risk of enteric infections (1.4 vs. 1.0% in the placebo group; OR 1.33; 95% CI 1.01–1.75) [37].

The overall clinical benefits of PPI therapy outweigh potential risks, but those without clear indication are only exposed to the potential minor risks of PPI treatment. Therefore, adherence to evidence-based indications is mandatory for a safe and effective PPI treatment. Reducing inappropriate prescribing of PPIs can minimize potential for adverse events [31, 34–38].

### Limitations of PPI Therapy

Despite the overall effectiveness of PPIs, they have some shortcomings, at least to their pharmacological limitations, including a delay onset of action, incomplete acid suppression, the need for ingestion before a meal to achieve maximum efficacy. That’s why some challenges remain in the treatment of acid-related diseases. These include management of patients with GERD who do not respond adequately to PPI therapy (PPI refractory GERD), more effective gastroprotection (treatment and prevention of NSAID-aspirin induced gastrointestinal mucosal injury), or optimal medical

<table>
<thead>
<tr>
<th>Table 1. Current indications and appropriate use of PPI therapy [31–33]</th>
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<tbody>
<tr>
<td><strong>Short-term PPI therapy appropriate</strong></td>
</tr>
<tr>
<td>– Healing of erosive esophagitis (Los Angeles grade A and B)</td>
</tr>
<tr>
<td>– <em>Helicobacter pylori</em> eradication (in combination with antibiotics)</td>
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<tr>
<td>– Functional dyspepsia</td>
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<tr>
<td>– Peptic ulcer disease</td>
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<tr>
<td>– Acute upper gastrointestinal bleeding</td>
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<tr>
<td>– Stress-ulcer prophylaxis in high-risk patients</td>
</tr>
<tr>
<td>– Eosinophilic esophagitis</td>
</tr>
<tr>
<td><strong>Long-term PPI appropriate</strong></td>
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<tr>
<td>– Barrett’s esophagus</td>
</tr>
<tr>
<td>– Severe erosive esophagitis (Los Angeles grades C and D)</td>
</tr>
<tr>
<td>– Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>– Idiopathic peptic ulcer disease</td>
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<tr>
<td>– Gastroprotection in high-risk patients (long-term nonselective NSAID-users)</td>
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<tr>
<td>– Anti-platelet therapy in patients at high risk for upper GI complications</td>
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<tr>
<td>– PPI-responsive Eosinophilic esophagitis</td>
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<tr>
<td><strong>PPI use – no benefit</strong></td>
</tr>
<tr>
<td>– Corticosteroid treatment (unless used in combination with NSAIDs)</td>
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<tr>
<td>– Acute pancreatitis (no benefit form acid inhibition)</td>
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<tr>
<td>– Hypertensive gastropathy (no need for acid suppression)</td>
</tr>
<tr>
<td>– Chronic pancreatitis (standard dose of PPI only in patients with steatorrhea, refractory to enzyme replacement treatment)</td>
</tr>
<tr>
<td>– Stress ulcer prophylaxis in noncritically ill hospitalized patients and low risk for upper GI complications</td>
</tr>
<tr>
<td>– Anticoagulant therapy (no need for gastroprotection unless used in combination with NSAIDs)</td>
</tr>
</tbody>
</table>

PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; GI, gastrointestinal.
therapy of nonvariceal upper gastrointestinal bleeding. Current PPIs are also suboptimal for “on-demand” therapy in nonerosive reflux disease. Despite PPI therapy, overnight recovery of gastric acid secretion, termed “nocturnal acid breakthrough,” is also an issue [39, 40]. Among the challenges, the increasing rate of unsuccessful *H. pylori* eradication is also of great concern and requires modification of therapeutic strategies with optimal combination of potent antisecretory and antibiotic regimens. There are several explanations for the decrease in efficacy of PPI-clarithromycin containing standard triple therapy: compliance, high gastric acidity, high bacterial load, and bacterial strains, but the most important is the increase in *H. pylori* resistance to clarithromycin. It has been demonstrated that *H. pylori* resistance rate to antibiotics is increasing in most parts of the world [30].

**New Drug Development**

Several novel approaches to correct the pharmacological limitations of PPIs are being explored. Attempts to overcome these issues have included the development of potent H$_2$-receptor agonists, gastrin agonists, non-benzimidazole PPI, extended and delayed release PPIs, PPI combination, new agents with longer half-lives, and new generation of PPIs. Whether these new approaches offer a significant clinical benefit or carry with them new unexpected side effects remain to be determined (Table 2) [41–43].

### Potassium-Competitive Acid Blockers

The major advance has been the development of acid pump antagonists, the potassium channel acid blocking drugs (P-CABs), which block the K$^+$, H$^+$-ATPase K$^+$ channel. P-CABs block the K-exchange channel of the proton pump, resulting in competitive, reversible, food independent inhibition of gastric acid secretion, have a rapid onset of action, and maintain a prolonged and consistent elevation of intragastric pH. The main differences in the mechanism of action between PPIs and P-CABs are shown in Table 3.

*Vonoprazan fumarate (Takecab®)* is a first-in-class potassium-competitive acid blocker that has been available in Japan since February 2015 and has so far been introduced only into a small number of Asian countries [44–47]. The main pharmacological properties of vonoprazan are summarized in Table 4.

*Vonoprazan 20 mg was shown to be effective and non-inferior to lansoprazole 30 mg in terms of endoscopic erosive esophagitis healing rate at 8 weeks. In addition, esophagitis healing rates at 2 and 4 weeks were slightly higher with vonoprazan 20 mg versus lansoprazole 30 mg treatment. The safety profile of vonoprazan 20 mg was similar to that of once-daily lansoprazole 30 mg [48]. The extremely potent antisecretory effect of vonoprazan might be especially useful in long-term treatment of patients with severe esophagitis and Barrett’s esophagus. Indeed, it has been suggested that vonoprazan is more effective than most PPIs for patients with severe erosive esophagitis and the efficacy of vonoprazan in GERD maintenance treatment may be higher than that of some PPIs [49, 50].

#### Table 2. New drug development for gastric acid inhibition [41–43]

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
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<tbody>
<tr>
<td>H$_2$RAs</td>
<td>Lavoltidine, Loxitidine</td>
</tr>
<tr>
<td>CCK/gastrin receptor antagonist PPIs</td>
<td>Loxiglumide, spiroglumide, itriglumide</td>
</tr>
<tr>
<td>Delayed release</td>
<td>Pantoprazole magnesium</td>
</tr>
<tr>
<td></td>
<td>Dextansoprazole (MR; modified release)</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole (ER; extended release)</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole stronium delayed-release</td>
</tr>
<tr>
<td></td>
<td>IR-omeprazole (instant release)</td>
</tr>
<tr>
<td>New agents</td>
<td>Ilaprazole</td>
</tr>
<tr>
<td></td>
<td>Tenatoprazol (non-benzimidazole PPI)</td>
</tr>
<tr>
<td>PPI combination</td>
<td>AGN-201904-Z (omeprazole pro-drug)</td>
</tr>
<tr>
<td></td>
<td>Omeprazole + lansoprazole</td>
</tr>
</tbody>
</table>

H$_2$RAs, H$_2$-receptor antagonists; PPIs, proton pump inhibitors.

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Gastric Acid Suppression: History

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DOI: 10.1159/000505204
It is also suggested that vonoprazan has the possibility to become a new treatment option for the prevention of NSAID or aspirin-related gastroduodenal mucosal adverse events in high-risk patients [51, 52].

Finally, the utility of vonoprazan as an alternative to PPI therapy for *H. pylori* eradication, especially in resistant and difficult to treat groups, has also been considered. The vonoprazan-based triple therapy showed superior efficacy in terms of *H. pylori* eradication as compared to the PPI-based triple therapy. Moreover, seems that vonoprazan is superior to conventional PPI-based therapy for the eradication of clarithromycin-resistant *H. pylori* strains. The vonoprazan-based triple therapy showed comparable tolerability and incidence of adverse events [53, 54]. It has also been suggested that dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin, and clarithromycin, suggesting that vonoprazan-based dual therapy can provide and acceptable eradication rate of *H. pylori* infection (92.9% intention-to-treat analysis, 95% CI 82.7–98.0%) without the need for second antimicrobial agents, such as clarithromycin [55, 56].

Long-term studies comparing P-CABs with PPIs will help to clearly define the exact place and safety profile of this new class of drug in the management of acid-related disorders.

**Disclosure Statements**

The authors have no conflict of interest to declare.

**Author Contributions**

L.H.: conceiving the idea of the review, preparation, and correction of manuscript. T.B.: preparation of the manuscript. L.B.: preparation of the manuscript, search of references. Z.T.: critical review of the manuscript. All authors approved for the final manuscript.

### Table 3. The main differences in the mechanisms of action between PPIs and P-CABs [20, 41]

<table>
<thead>
<tr>
<th></th>
<th>PPIs</th>
<th>P-CABs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires transformation to the active sulfonamide form</td>
<td>Lower concentration in parietal cell acid space (1,000-fold higher than those in plasma)</td>
<td>Acts directly on the proton pump (K⁺, H⁺-ATPase)</td>
</tr>
<tr>
<td>Lower concentration in parietal cell acid space (1,000-fold higher than those in plasma)</td>
<td>Covalent binding to K⁺, H⁺-ATPase</td>
<td>Super concentration in parietal cell acid space (100,000-fold higher than those in plasma)</td>
</tr>
<tr>
<td>Covalent binding to K⁺, H⁺-ATPase</td>
<td>Irreversible binding to K⁺, H⁺-ATPase</td>
<td>Competitive binding to K⁺, H⁺-ATPase</td>
</tr>
<tr>
<td>Irreversible binding to K⁺, H⁺-ATPase</td>
<td>Duration of effect related to half life of the sulphonamide-enzyme complex</td>
<td>Reversible binding to K⁺, H⁺-ATPase</td>
</tr>
<tr>
<td>Duration of effect related to half life of the sulphonamide-enzyme complex</td>
<td>Delay onset of action</td>
<td>Duration of effect related to half life of drug in plasma</td>
</tr>
<tr>
<td>Delay onset of action</td>
<td>Food-dependent inhibition of gastric acid</td>
<td>Full effect from first dose</td>
</tr>
<tr>
<td>Food-dependent inhibition of gastric acid</td>
<td>Incomplete acid suppression</td>
<td>Food independent acid inhibition</td>
</tr>
<tr>
<td>Incomplete acid suppression</td>
<td></td>
<td>Complete, prolonged acid suppression</td>
</tr>
</tbody>
</table>

PPIs, proton pump inhibitors; P-CABs, potassium channel acid blocking drugs.

### Table 4. The main pharmacological properties of vonoprazan [44–47]

- First-in-class potassium competitive acid blocker
- It inhibits the H⁺, K⁺-ATPase mediated-gastric acid secretion in a selective, reversible, and potassium competitive manner with a slow dissociation rate
- Food independent
- Rapid onset of action
- It possesses approximately 350 time more potent inhibitory effect than lansoprazole (in in vitro experiments)
- Stronger and longer lasting effect than lansoprazole
- Prolonged and consistent elevation of gastric pH
- A single oral dose of 20 mg increases the gastric pH above 4.0 as early 4 h after and maintained the gastric pH above 4.0 until 24 h postdose
- It undergoes important metabolic elimination, but the influence of a genetic polymorphism is limited

It is also suggested that vonoprazan has the possibility to become a new treatment option for the prevention of NSAID or aspirin-related gastroduodenal mucosal adverse events in high-risk patients [51, 52].
References


55 Furuta T, Yamada M, Kagami T, Uotani T, Suzuki T, Higuchi T, et al. Dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin and clarithromycin for eradication of Helicobacter pylori. Digestion. DOI: 10.1159/000502287.