REVIEW ARTICLE

Potassium-competitive Acid Blocker: A Newer Target in the Treatment of Acid Peptic Disorder

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Abstract

Acid peptic disorders are a group of disorders that include gastroesophageal reflux disease, gastric ulcer, and duodenal ulcer. The most common causes are nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection. If not treated adequately, it may lead to life-threatening complications like gastrointestinal bleeding and intestinal perforation. H^+K^+-ATPase enzyme in parietal cells is involved in the final step of gastric acid secretion through a conformational change from E_1 to E_2 form. Proton-pump inhibitors (PPIs) are commonly used drugs for the treatment of acid peptic disorders. Proton-pump inhibitors have some limitations such as irreversible inhibition, it is a prodrug. Continuous attempts are made to develop newer targets that overcome these limitations of PPIs in treating acid peptic disorders. Vonoprazan, a novel potassium-competitive acid blocker (P-CAB) approved by the FDA for *H. pylori* infection in combination with antibiotics, could be a potential alternative to PPI in the management of acid peptic disorders. This review mainly highlights the pharmacology of Vonoprazan.

Keywords: Acid peptic disorders, H^+K^+-ATPase (proton pump), Proton-pump inhibitors, Potassium-competitive acid blocker, Vonoprazan.

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Introduction

Acid peptic disorders are a group of disorders that affect the esophagus, stomach, and duodenum due to gastric acid. This mainly includes gastroesophageal reflux disease and peptic ulcer (gastric as well as duodenal ulcer).[1,2] Gastroesophageal reflux disease is characterized by the reflux of acidic content from the stomach into the esophagus. This exposure of esophageal mucosa to acid results in mucosal injury.[2] Peptic ulcer disease is a break in the mucosal lining of either stomach or duodenum due to an imbalance between protective factors (mucous production, mucosal blood flow, bicarbonate, and prostaglandin secretion) and aggressive factors (gastric acid and pepsin).[3,4] *Helicobacter pylori* and NSAIDs are the most common causes of peptic ulcer.[4] The prevalence of peptic ulcer disease was about 8.4% globally, gastroesophageal reflux disease was found to be around 13.98% globally, and 7.6–30% of Indians are found to have GERD.[5–7] It has to be diagnosed and treated early to prevent life-threatening complications like gastrointestinal bleeding, intestinal perforation, gastric outlet obstruction, and gastric carcinoma.[4]

Physiology of Gastric Acid Secretion

The stomach performs its function mainly in the oxyntic gland and pyloric gland area. Acid-secreting parietal cells are present in the oxyntic area and occupy majority of the stomach.[2] Parietal cells have an apical membrane that is present in the luminal side of the cells. An apical membrane of the cells has a secretory canaliculus that invaginates into the interior of the cell. In the resting state, gastric H^+K^+-ATPase (proton pump) is present inside the tubulovesicle in the cytoplasm of parietal cells. Stimulation of parietal cells leads to the fusion of the tubulovesicle with apical canalicular membrane resulting in translocation of the proton pump to the secretory canaliculus.[8–10] Once activated, the proton pump secretes the H^+ ion (acid) into the gastric lumen through exchange of H^+ ion (intracellular) for K^+ (extracellular) by conformational change between E_2 and E_1 form of the enzyme. H^+K^+-ATPase usually exists in two forms: E_1 and E_2. In E_1 form of the enzyme, the ion-binding site of H^+ (primary ion) faces the cytoplasmic side with a higher affinity for H^+ ion and a low affinity for K^+, and in E_2 form of the enzyme, ion-binding site faces the luminal side with higher affinity for K^+. K^+ binds to the E_2 form of the enzyme from luminal side, leading to dephosphorylation of the enzyme then E_2 gets converted into E_1 form as E_1 has low affinity for K^+ ion, it is released from the enzyme leaving the E_1-binding site free of attachment. Now, ATP binds to the E_1 form of the enzyme (in the absence of potassium) followed by binding of H^+ to high-affinity E_1 form. Phosphorylation of the enzyme occurs, leading to conformational change from E_1 to E_2 form resulting in secretion of H^+ (acid) into the gastric lumen.[9–13] This is the final step of acid secretion by parietal cell. Physiology of acid secretion with the mechanism of vonoprazan is illustrated in Figure 1.

Acid secretion is regulated by neuronal factors [acetylcholine (Ach), gastrin-releasing peptide (GRP)], paracrine (histamine), and endocrine factors (gastrin) through M_3, BB_2, H_2, and CCK_2 receptors, respectively.[2]

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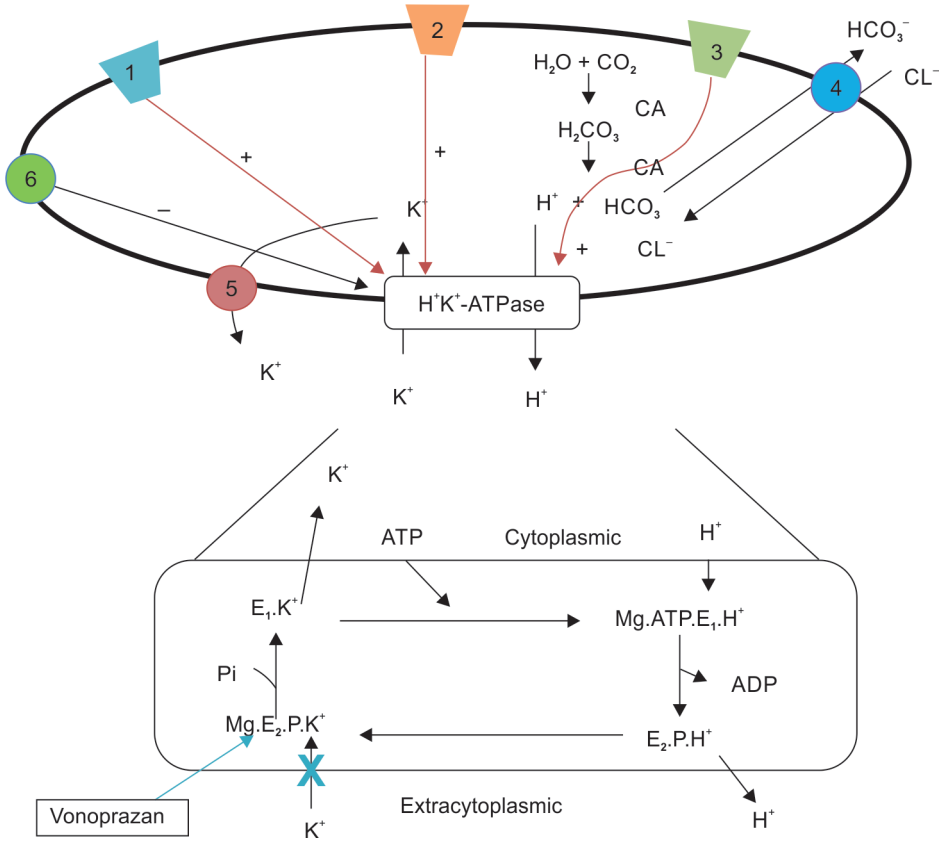

Fig. 1: Physiology of gastric acid secretion and its inhibition by vonoprazan

Methods

A comprehensive search of journals on P-CABs was done by using keywords, including P-CABs, vonoprazan, tegoprazan, and PPIs. We searched in the following databases: PubMed, Google Scholar, ProQuest, and Embase. The reference section of each article was also searched to find out more articles related to our study. In the search process, we found 85 articles related to P-CAB. Out of 85 articles, 46 were selected for review.

Results

Current Status of Drugs for Acid Peptic Disorder

Treatment options available for acid peptic disorders are PPIs, H_2 blockers, antacids, and prostaglandin analogs. Proton pump inhibitors and H_2 blockers are the mainstay in the management of acid peptic disorders. Proton pump inhibitors are preferred as a first-line drug for the management of acid peptic disorders as it causes potent acid inhibition. For *H. pylori* eradication, PPIs are used along with antibiotics (amoxicillin, clarithromycin, and metronidazole) depending on the prevalence of antibiotic resistance.[4] Though PPIs are commonly used drugs for acid peptic disorders, it is still not an ideal antisecretory drug.

There are certain limitations for PPIs in treating acid peptic disorder, as it causes irreversible inhibition of proton pumps leading to hypochlorhydria. Also, it is a prodrug that requires the presence of acid secretion for its conversion into an active metabolite, PPIs block only the proton pump that is active during the period in which PPI is available as an active compound, resulting in incomplete inhibition of proton pump and thereby the acid secretion is inhibited. Continuous attempts are made to develop newer targets that overcome these limitations of currently used drugs for acid peptic disorders. Vonoprazan, a P-CAB, has been developed as a newer drug target for peptic ulcers. This review will focus on the pharmacology of vonoprazan.[12,14–17]

Vonoprazan – Potassium-competitive Acid Blocker

Vonoprazan is the first-in-class drug approved by the FDA on 3rd May 2022 for the treatment of *H. pylori* infection in adults as a dual therapy with amoxicillin and as triple therapy along with amoxicillin and clarithromycin.

Mechanism of Action

Vonoprazan, after reaching the gastric lumen, enters the H^+K^+-ATPase enzyme through the space between transmembrane 1/2 and 5/6 loops and extra-cytoplasmic ends of transmembrane 4, 8, and 9. Then, it docks in the cleft between $Alanine_{375}$ and $Cysteine_{813}$ in the E_2P form of the enzyme. Once it docks in the cleft hydrogen bonding between the hydroxyl group of $Tyrosine_{799}$ and the oxygen molecule of sulfonyl group of vonoprazan occurs, this hydrogen bonding is responsible for slow dissociation and prolonged acid inhibition than other drugs. As mentioned previously, the K^+ ion usually binds in the E_2 form of the enzyme during acid secretion, here, vonoprazan already binds to E_2 form and competitively prevents K^+ binding to the E_2 form and inhibits further steps reversibly in the process of acid secretion.[18,19]

Mechanism, indications, and adverse effects of vonoprazan are highlighted in Table 1.

Table 1: Vonoprazan mechanism, indication, and adverse effect

Mechanism of vonoprazan	*Indication*
Vonoprazan ↓ Reaches gastric lumen ↓ Binds to the E_2 form of the enzyme ↓ Prevents K^+ binding to the enzyme ↓ Inhibits K^+-dependent dephosphorylation of enzyme ↓ Prevents the conformational change of enzyme from E_2 to E_1 ↓ Reversibly inhibits H^+K^+-ATPase ↓ Inhibits acid secretion	*Approved indication* • *Helicobacter pylori* eradication *Other indications* • Gastric ulcer • Erosive esophagitis • Prevention of endoscopic submucosal dissection-induced ulcer • PPI-resistant reflux esophagitis *Adverse effects* • Erythema multiforme, skin rashes, nephrotoxicity, antibiotic-associated hemorrhagic colitis in vonoprazan-based *H. pylori* eradication regimen. • Plasma gastrin and pepsinogen II level increased with vonoprazan. • Nasopharyngitis, abdominal pain, and diarrhea.

Table 2: Comparison between proton-pump inhibitors and potassium-competitive acid blocker

Sl no.	*Characteristics*	*PPI*	*P-CAB vonoprazan*
1	Prodrug	+	–
2	Acid stability	Labile	Stable
3	Need for enteric-coated formulation	+	–
4	Influence of CYP2C19 polymorphism	+	–
5	Acid inhibition	Irreversible	Reversible
6	Onset of action	Slow	Rapid
7	H^+K^+-ATPase inhibition	Inhibit only active pump	Inhibit both active and inactive pump
8	Steady-state acid suppression (maximum) in days	3–4	1
9	pH > 4 holding time ratio 0–24 hours[16]	Esmoprazole 61.2 ± 17.1% Rabeprazole 65.1 ± 14.2%	85.8 ± 14.7%
10	*H. pylori* eradication rate[26]	72.8%	87.9%

P-CAB, potassium-competitive acid blocker; PPI, proton-pump inhibitor

Pharmacokinetics

Vonoprazan is a pyrrole derivative that is well absorbed after oral administration.[20] It is stable in an acidic environment for more than 8 hours, hence it does not need enteric coating, unlike PPIs.[21] The half-life of vonoprazan is 6–9 hours, and T_{max} is 1.5–2 hours.[14] Onset of action is rapid with slow dissociation from the proton pump making vonoprazan more potent and a prolonged acid inhibitor.[14,19] It inhibits both active and inactive proton pumps as compared with PPIs that inhibit only the active proton pump.[22] Also, P-CABs do not require acidic pH for their action as it blocks the proton pump in mid-cycle as compared with PPIs that require acidic pH for their activation.[20,22]

Vonoprazan is metabolized in the liver mainly by CYP3A4 into various metabolites such as M-I, M-II, M-III, M-IV-Sul, N-demethylated vonoprazan, and vonoprazan N-sulfate. It is also metabolized by CYP2B6, CYP2C19, and CYP2D6.[23,24] A small fraction of the drug is excreted in urine as an unchanged form.[14] Unlike PPIs, acid suppression by vonoprazan is not affected by the CYP2C19 genotype as they are mainly metabolized by CYP3A4.[14,25]

Several structural types of P-CAB, such as imidazopyridines (SCH28080, AZD0865, and PF-03716556), pyrimidines (YH1885), and imidazonaphthyridine (soraprazan) have been investigated as P-CABs, but toxicity profile (hepatic toxicity) and efficacy profile limited their further developments. Comparison of features between PPIs and P-CABs is given in Table 2. The study conducted by Jung et al. showed a comparison of the eradication rate of *H. pylori* between PPIs and P-CABs.[26]

Adverse Effects

Nasopharyngitis, abdominal pain, neck pain, headache, dizziness, diarrhea, oral herpes, and epistaxis.[14,25] Plasma gastrin and pepsinogen II levels increased with vonoprazan.[14,25] Kamiya et al. reported a case of erythema multiforme with vonoprazan-based first-line therapy along with amoxicillin and clarithromycin, it subsided with the treatment of steroid pulse therapy and immunotherapy.[27] Suzuki et al. reported that occurrence of skin rashes was higher with vonoprazan-based therapy compared with PPI-based therapy.[28] Suzuki et al. demonstrated that combined treatment with vonoprazan and lafutidine produces a lesser elevation of serum gastrin level but effective gastric acid inhibition compared with vonoprazan alone.[29] Tanaka et al. reported a case of antibiotic-associated hemorrhagic colitis with vonoprazan-based second-line therapy.[30] Nishimura et al.

Table 3: Summary of clinical trial data of vonoprazan

Study	*Study outcome*
Chey et al. 2022[33]	A randomized clinical trial comparing vonoprazan triple and dual therapy with standard therapy (PPI-lansoprazole) for *H. pylori* infection in the United States and Europe. This study results showed that both vonoprazan-based dual (78.5%) as well as triple therapy (84.7%) was found to be superior in eradicating *H. pylori* infection compared with PPI-based triple therapy (78.8%). Vonoprazan was also superior in eradicating clarithromycin-resistant *H. pylori* infection.
Ashida et al. 2016[34]	In this multicenter randomized clinical trial, vonoprazan a novel potassium acid blocker compared with lansoprazole for the healing of erosive esophagitis showed a better healing rate of erosive esophagitis even in severe cases with vonoprazan treatment and was not affected by CYP2C19 genetic polymorphism.
Kagawa et al. 2016[35]	This study compared vonoprazan with PPIs for preventing bleeding from endoscopic submucosal dissection-induced gastric ulcers and showed that vonoprazan reduces endoscopic submucosal dissection-induced bleeding significantly in comparison with PPI.
Hoshino et al. 2017[36]	This prospective study evaluated the efficacy of vonoprazan in treating proton-pump inhibitor-resistant reflux esophagitis. This study result showed that 87.5% of PPI-resistant reflux esophagitis healed with vonoprazan.

reported a case of vonoprazan-induced gastric polyp and reduced on discontinuation of vonoprazan.[31] Ishida et al. reported that vonoprazan also causes tubulointerstitial nephritis.[32]

Clinical Trial Data

A summary of clinical trial data is given in Table 3.[33–36]

Other Clinical Trial Data

Open-label cross-over study conducted by Sakurai et al. in 2015 comparing the acid-inhibitory effect of vonoprazan and rabeprazole reporting pH holding time ratio on day 1 to be 84.2 ± 12.4% with vonoprazan and 26.3 ± 13.4% with rabeprazole, on day 7, it was 93.8 ± 7.35% with vonoprazan and 65.1 ± 14.2% with rabeprazole. The ratio of 24-hour pH 4 HTR day 1 to day 7 is >0.8. This study indicates that vonoprazan inhibits gastric acid secretion better even on day 1 compared with rabeprazole.[16]

In a multicenter randomized controlled trial by Murakami et al. in 2016 showed that *H. pylori* eradication rate with vonoprazan 20 mg was 92.6% and lansoprazole 30 mg was 75.9% as first-line therapy (primary endpoint) along with amoxicillin and clarithromycin, and eradication rate with vonoprazan was 98% and lansoprazole was 99.9% as second-line therapy (second-line therapy) along with amoxicillin and metronidazole. This shows vonoprazan is superior in eradicating *H. pylori* infection as first-line therapy and comparable efficacy as second-line therapy in eradicating *H. pylori* in comparison with lansoprazole.[37]

Dose-ranging randomized trial conducted by Ashida et al. 2015 with vonoprazan and lansoprazole showed that the healing rate of erosive esophagitis was 92.3%, 92.5%, 94.4%, 97%, and 93.2% for vonoprazan 5 mg, 10 mg, 20 mg, 40 mg, and lansoprazole 30 mg, respectively. The healing rate of erosive esophagitis increases with dose as it inhibits gastric acid secretion in a dose-dependent manner.[38]

Randomized control trial by Iwakiri et al. 2017 evaluates the acid-inhibitory effect of vonoprazan in PPIs-resistant erosive esophagitis and showed that pH >4 HTR increases from baseline in both vonoprazan 20 mg and 40 mg group (from 73.21 to 96.46% and 69.97 to 100%, respectively). Healing rate of PPIs-resistant erosive esophagitis is >60%.[39]

A randomized control trial conducted by Takahashi et al. on gastric ulcers induced by submucosal dissection showed no significant difference between vonoprazan and lansoprazole on ulcer healing rate and most of the ulcers reduced to less than 10% from their baseline size on both groups. This indicates vonoprazan also can be used for the management of submucosal-induced gastric ulcers, and ulcer healing is comparable with lansoprazole.[40]

A phase III randomized trial in multiple centers by Kinoshita et al. 2016 evaluated the efficacy and safety of vonoprazan in non-erosive gastroesophageal reflux disease and showed that the proportion of days without the symptom of heartburn was not statistically significant from placebo. The severity of heartburn was reduced significantly in the vonoprazan group.[41]

Tegoprazan

Tegoprazan has been approved in Korea, but not by US FDA for the treatment of GERD. It has a similar mechanism of action as that of vonoprazan with rapid onset of action. After a single dose, it elevates pH >6 within an hour.[42] It rapidly distributes to the stomach and remains there for 12 hours after the oral administration.[43] T_{max} is around 0.5–1.5 hours, and elimination $t_{1/2}$ is 3.6–5.3 hours. Plasma concentration increases dose proportionally. The mean renal excretion of tegoprazan was found to be less than 6%.[44] It is metabolized in the liver mainly by CYP3A4 and also by CYP2C19. CYP2C19 genotype does not affect the acid suppression by tegoprazan as it is mainly metabolized by CYP2C19.[42]

Adverse Effects

Most of the side effects reported are mild in intensity, such as diarrhea, headache, myalgia, and eye pain. Additionally, serum gastrin levels increase with tegoprazan.[44,45]

In vivo animal studies with tegoprazan showed that tegoprazan reduces the severity of colitis by improving the intestinal epithelial barrier function and growth of *Bacteroides vulgatus* that reduces the intestinal inflammation.[46]

Conclusion

Vonoprazan is a novel potassium-competitive acid blocker approved by FDA on May 2022 for *H. pylori* infection in adults. It is advantageous over PPIs in being acid-stable with faster onset of action and sustained acid inhibition, does not require acidic medium for its activation, does not need enteric-coated formulation, and is not influenced by CYP2C19 polymorphism. It inhibits both active and inactive proton pumps. Also, its safety and efficacy have been proven in treating peptic ulcer diseases by various studies in comparison with PPIs. It is also effective in reducing bleeding caused by gastroesophageal reflux disease, endoscopic submucosal

dissection, PPI-resistant gastric ulcers, and erosive esophagitis. We conclude that vonoprazan could be a better alternative to PPIs in treating acid peptic disorders. Further studies are needed to prove its long-term efficacy and safety over PPIs.

Orcid

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