NEW DRUG

Vonoprazan – A Potassium-Competitive Acid Blocker: An Overview

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ABSTRACT

Vonoprazan helps in management and treatment of heartburn, peptic ulcers and gastroesophageal reflux disease. The structure, mechanism of action, and clinical applications have been discussed in this article. A brief review of literature is carried out.

Keywords: Acid peptic disorders, gastroesophageal reflux disease, peptic ulcer

Acid peptic disorders stem from unique yet interrelated pathogenic mechanisms, characterized by either heightened acid secretion or compromised mucosal defense. The diagnosis of gastroesophageal reflux disease (GERD), peptic ulcer disease, and acid peptic disorders is further complicated by frequent overlap with conditions such as functional dyspepsia and irritable bowel syndrome posing challenges in clinical identification[1]. GERD is expected to remain a common cause for primary care consultations[2].

The incidence of GERD is 15.6 (range 11.046-20.714). The risk factors are age, body mass index (BMI), nonvegetarian diet, tea and coffee, tobacco, and alcohol consumption[3]. Chavan and Bhaktavatsalam found the prevalence of acid peptic disease to be very high, i.e., 38.1% in Indians[4]. Clinically, acid peptic disorders present as heartburn and regurgitation in GERD patients. They also experience extraesophageal symptoms with reflux cough syndrome, which is the most common symptom. Other symptoms include lower abdominal pain and constipation[1].

The impact of acid peptic disorders affects quality of life and causes work absenteeism and if left untreated, it may lead to complications like peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma. However, the frequency, severity, and complications of GERD depend on geographic and ethnic factors. Dietary factors are responsible to lower the frequency and severity of GERD and Barrett's esophagus[3].

POTASSIUM-COMPETITIVE ACID BLOCKERS

A novel treatment in acid-related diseases are potassium-competitive acid blockers, which include fexuprazan, revaprazan, tegoprazan, and vonoprazan. Among these, vonoprazan has undergone extensive study and was initially approved in Japan in 2015 for various acid-related diseases including gastric ulcer, duodenal ulcer, reflux esophagitis, and prevention of recurrence of ulcers as well as adjunct therapy for *Helicobacter pylori* eradication[5]. The US Food and Drug Administration (FDA) approved two vonoprazan-containing regimens for *H. pylori* treatment and also accepted a new drug application for vonoprazan for the treatment of erosive esophagitis[5]. Potassium-competitive acid blockers act at the final step in the acid secretory pathway by inhibiting the hydrogen potassium ATPase (H^+/K^+-ATPase) transporter on the luminal membrane of gastric parietal cells, the same proton pump targeted by proton pump inhibitors (PPIs). After systemic absorption, potassium-competitive acid blockers concentrate in parietal cell canaliculi and ionically bind to H^+/K^+-ATPase transporters to prevent acidifying proton secretion. Once bound, the potassium-competitive acid blockers block K^+ ion access to the proton pump. Unlike PPIs, potassium-competitive acid blockers are acid stable and thus do not require enteric coating or optimal dosing administration 30 minutes prior to meals. Additionally, they are not prodrugs and act immediately at the

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proton pump. These mechanistic differences facilitate more rapid attainment of peak plasma levels and onset of action[5].

Patients in whom lifestyle modifications are ineffective in controlling GERD symptoms can benefit from pharmacologic therapy. Acid suppression forms the cornerstone of pharmacological management for GERD. Therapeutic agents include PPIs, histamine 2 receptor antagonists, and antacids. Additionally, medications affecting gastrointestinal motility such as prokinetics are also utilized in treatment of GERD[6].

The alternative formulations of PPIs include immediate-release omeprazole and modified-release dexlansoprazole in certain regions. Dexlansoprazole MR achieves a higher percentage of time with intragastric pH >4 compared to lansoprazole. However, these formulations offer only modest advantages in acid secretion control compared to conventional PPIs[7].

There is growing interest in potassium-competitive acid blockers as promising alternatives, poised to overcome some limitations associated with PPIs[5,7]. When protons are transported by H^+,K^+-ATPase from cytoplasm to the canalicular space across the apical membrane of parietal cells, an equal amount of K^+ ions are counter transported into cytoplasm of parietal cells, so that total process is electrically balanced.

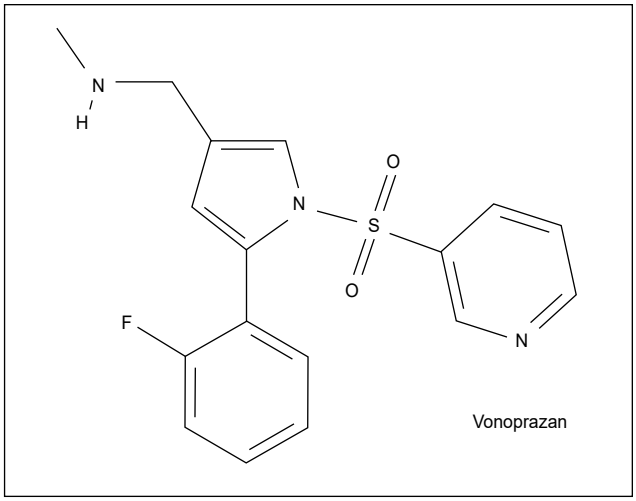
As a result, the activity of H^+,K^+-ATPase in the parietal cells is regulated by the availability of extracellular K^+. Studies on molecular mechanisms of H^+,K^+-ATPase, therefore, led to discovery of potassium-competitive acid blockers, which is a new class of antisecretory agents and a novel treatment in acid-related diseases. This class of drugs exhibits their antisecretory effects by competitively blocking availability of K^+ for H^+,K^+-ATPase[8].

VONOPRAZAN

Vonoprazan is a novel, orally active potassium-competitive acid blocker that has demonstrated rapid, potent and long-lasting gastric acid suppression. It has been approved in Japan and 14 other countries in Asia and South America for a number of years for the treatment of a variety of acid-related diseases[7].

Vonoprazan Structure

Vonoprazan is a potassium-competitive acid blocker with the chemical structure $C_{17}H_{16}FN_3O_2S$. It is a pyrrole derivative that binds to the potassium ion binding site on the gastric proton pump, preventing the pump from activating and blocking gastric acid secretion.



Vonoprazan

Vonoprazan Uses

The principal use of vonoprazan is in management of GERD. It binds and inhibits H^+,K^+-ATPase at the final step in the acid secretory pathway in gastric parietal cells and it has different mechanisms of action than conventional PPIs. It can inhibit the proton pump even in neutral environments with an inhibitory constant (Ki) of 10 nM at pH 7 and 3 nM at pH 6.5. It has stronger potential to inhibit the gastric proton pump than other potassium-competitive acid blocker and lansoprazole[7].

The treatment of acid peptic disease is based on providing symptomatic relief and enhancement of ulcer healing in affected area, i.e., esophagus, stomach and duodenum and to heal and maintain remission of erosive esophagitis. The aim of treatment is also to prevent complications and recurrence and to improve the quality of life[6,9]. The medical management of GERD comprises of lifestyle modifications and pharmacologic agents[10]. Lifestyle modifications to treat GERD should remain the first line of therapy and it includes weight loss, avoiding late night meals, elevating head of bed and steering clear of habits or foods that may worsen symptoms[11].

PHARMACODYNAMICS AND PHARMACOKINETIC

The half-life of vonoprazan dissociation by potassium chloride is 12.5 hours in isolated proton pumps. Vonoprazan has high affinity and slow clearance from gastric parietal cells, accumulating in both resting and stimulated conditions. The acid dissociation constant of vonoprazan is 9.37, which is higher than that of conventional PPIs and other potassium-competitive acid blockers. When vonoprazan is exposed to acidic conditions, it is instantly protonated and remains stable. It can accumulate, function, and bind the proton pump

of gastric parietal cells in strongly acidic secretory canaliculi. The dissociation rate of vonoprazan from H^+,K^+-ATPase is slow and acid does not decompose it. Nonionic type of vonoprazan is decreased in a strong acidic secretory canaliculi and passive transport from the acidic secretory canaliculus to the cytoplasm is inhibited. It is therefore retained for a long time inside the parietal cells and can inhibit H^+,K^+-ATPase that is activated by further stimulation of acid secretion. The concentration of vonoprazan is up to 10^8-fold higher in secretory canaliculus of parietal cell than in plasma. It can stay in the protonated form and binds to H^+,K^+-ATPase subunit to compete with potassium binding and inhibits function of pump. The binding of vonoprazan to the proton pump is ionic, and its effects are reversible and dose-dependent. Vonoprazan can be taken regardless of meal ingestion and the rate of absorption is not affected by meals. It is rapidly absorbed and the time taken to reach maximum concentration in plasma is less than 2 hours after oral administration. After absorption, the half-life in plasma is approximately 2 hours for conventional PPIs, but up to 9 hours for vonoprazan. Thus, vonoprazan stays in blood longer and can block acid secretion continuously[7].

Vonoprazan demonstrated noninferiority and superiority compared to PPI lansoprazole in both healing and maintenance of erosive esophagitis. This advantage was particularly notable in cases of more severe erosive esophagitis[12]. Vonoprazan has noninferior efficacy compared to lansoprazole in terms of erosive esophagitis healing rate[13]. Transitioning from a PPI to vonoprazan is significantly linked to symptom improvement in GERD patients resistant to PPI therapy. Hence, vonoprazan presents a promising treatment option for PPI-resistant GERD[14]. It significantly improved heartburn and patient satisfaction, among patients with PPI-resistant GERD[15]. Vonoprazan 20 mg shows a similar tolerability profile to lansoprazole 30 mg and is noninferior in terms of gastric ulcer healing. It also demonstrates similar efficacy for duodenal ulcer healing, despite not meeting the noninferiority criteria[16]. Vonoprazan 10-20 mg demonstrated efficacy comparable to lansoprazole 15 mg in preventing peptic ulcer recurrence during low-dose aspirin therapy, exhibited a similar long-term safety profile and was well-tolerated[17].

A vonoprazan-based regimen is more effective than a PPI-based regimen as a first-line *H. pylori* eradication therapy[18]. Vonoprazan triple therapy and vonoprazan quadruple therapy regimens demonstrated increased *H. pylori* eradication rates compared to traditional quadruple therapy. Vonoprazan triple therapy exhibited fewer side effects, suggesting its potential applicability for *H. pylori* eradication in clinical practice[19].

Vonoprazan Dosage and Administration

Vonoprazan film-coated tablets of 10 and 20 mg are available. They can be taken without regard to food or timing of food and should be swallowed and not chewed. The recommended dosage of vonoprazan is 20 mg once a day for 4 to 8 weeks in reflux esophagitis, 10 mg once a day for maintenance of healing esophagitis, 20 mg once a day for 8 weeks and 6 weeks for gastric and duodenal ulcers, respectively, 10 mg once a day for prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer and 20 mg twice daily with triple drug regimen for 1 week for *H. pylori* eradication.

Vonoprazan Contraindications

Vonoprazan is contraindicated in patients with known hypersensitivity to vonoprazan or any component of vonoprazan, rilpivirine containing products. As a precaution, vonoprazan should not be given during pregnancy and lactation.

Vonoprazan Side Effects

The side effects of vonoprazan include nausea, headache, dysgeusia, dyspepsia, gastritis, pain abdomen, abdominal distension, diarrhea, nasopharyngitis, vulvovaginal candidiasis, urinary tract infection, and hypertension.

CONCLUSION

Vonoprazan plays a significant role in management of acid peptic diseases, especially in the treatment of GERD, peptic ulcer disease, and *H. pylori* infection. It causes potent acid suppression, rapid symptom relief and has better outcome as compared to traditional PPI therapies. Further, it can be given empty stomach as well as after meals.

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