



Potassium Competitive Acid Blockers: A New Paradigm for The Management Of Stomach Acid Disorders

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ABSTRACT

Proton pump inhibitors (PPIs) are the main therapy for stomach acid disorders to date. The disadvantage of PPI is the difficulty of controlling symptoms at night, such as tightness, chest pain, and coughing cough. Potassium competitive acid blockers (P-CAB) are a new class in the management of stomach acid disorders. Potassium competitive acid blockers work by a different mechanism, which binds non-covalently to H⁺/K⁺-ATPase. This mechanism results in a faster, stronger, and long-lasting suppression effect of gastric acid production. Besides being able to cure gastric complaints at night, P-CAB increases the success of Helicobacter pylori eradication. The safety of the use of this P-CAB drug, according to research is quite mild and acceptable. Currently, examples of P-CAB groups on the market are vonoprazan and tegoprazan. This narrative review is intended to provide further insight into this potassium competitive acid blocker (P-CAB) class of drugs.

1. Introduction

Since the discovery of proton pump inhibitors (PPIs) in 1985, the management of patients with stomach acid disorders has improved. Patients with peptic ulcer disorders, gastroesophageal reflux disease (GERD), and helicobacter pylori infection have new hope of recovery. But at this time, the next target is obtained that has not been overcome by PPI. Complaints such as heartburn or tightness at night, as well as decreased success of helicobacter pylori eradication, have not been overcome by PPI.^{1,2}

Potassium competitive acid blockers (P-CAB) are a new class that works differently from proton pump inhibitors (PPIs) by H⁺/K⁺-ATPase inhibition. P-CAB has many advantages, including not requiring an acidic atmosphere, faster onset of gastric acid production suppression, more stability in suppressing stomach acid in the long term, and resistance to cytochrome P (CYP)2C19 polymorphism. Based on these advantages, P-CAB is better able to overcome complaints at night. P-CAB is also reported to have advantages in increasing the success of eradication of Helicobacter pylori infection.

3-5

Currently, two types of drugs are still used, namely, vonoprazan which appeared in 2015 and tegoprazan which appeared in 2019. The first P-CAB is revaprazan, but because the gastric acid suppression effect is not better than PPIs, its use is limited. Side effects of vonoprazan and tegoprazan are still mild and tolerable.¹

2. Potassium competitive acid blocker (P-CAB) Mechanism of action

Potassium competitive acid blockers (P-CAB) are a class of drugs that decrease stomach acid production by a different mechanism than proton pump inhibitors (PPIs). Proton pump inhibitors (PPIs) enter parietal cells in an inactive form so they need acid to become active. This prodrug will then turn into sulphenamide and give covalently with the cysteine group H⁺/K⁺-ATPase which causes H⁺/K⁺-ATPase inactivation. Unlike PPI, P-CAB enters the canaliculi of gastric parietal cells in an active form so it does not require acid to become active. The P-CAB will create a non-covalent bond with H⁺/K⁺-ATPase so that it has a slower and longer dissociation speed.²

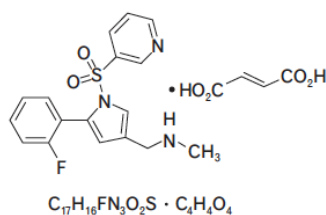


Figure 1. Chemical structure of vonoprazan²

Table 1. Difference between P-CAB (vonoprazan) and PPI²

	P-CAB (vonoprazan)	PPI
Maximal acid suppression after dosing (day)	1	3-5
Influence of CYP2C19 polymorphisms	-	+
Influence of meal	-	+
Stability in acidic conditions	>	
Acid suppression at night (pH + HTR) (mean ± SD,%)	67,9 ± 28,3 84,3 ± 20,3	12,9 ± 10,9 (E) 15,3 ± 13,3 (R)
<i>H. pylori</i> eradication rate (First line Triple Therapy) (%)	92,6	75,9 (L)
Healing rate of sever reflux esophagitis (LA, Grade C/D) (%)	88,0 – 96,0	53,9 – 82,6 (L)
PPI – refractory GERD	>	

Pharmacokinetics and pharmacodynamics

Vonoprazan is very quickly absorbed in the stomach and small intestine and has a rapid onset. Maximum plasma concentration (C_{max}) from 10 to 60 ng/mL in between 1.5 and 2 hours. The effect of maintaining a pH of 4 is very long when compared to esomeprazole and rabeprazole. P-CAB is metabolized in the liver via CYP 3A4 and partially metabolized via CYP2B6, CYP2C19, CYP2D6, and SULT2A1. This causes stomach acid suppression can be fast, strong, and stable for a longer time. PPIs are metabolized primarily by CYP2C19, which has polymorphisms that reduce the effectiveness of PPIs in most people. Research shows that P-CAB can be eaten before or after meals. There was no significant difference in suppressing gastric acid secretion.^{6,7}

3. Potassium competitive acid blocker (P-CAB) in clinical practice

P-CAB with GERD

GERD is a condition where there is discomfort or pain in the middle chest due to reflux or rising stomach acid into the esophagus. GERD causes complaints that are very disturbing so it often reduces the quality of life. The prevalence of GERD in Indonesia ranges from 20% to 50% of the population.⁸

Before P-CAB appeared, the main pharmacological treatment of GERD was using PPIs. However, the disadvantage of PPIs is that it is difficult to cure GERD attacks at night. Patients often have cough, and tightness, especially during sleep at night. Increasing the dose of PPI and frequency did not show satisfactory results. Based on the competitive

bonding mechanism, P-CAB shows its advantages in reducing complaints at night. The slow speed of dissociation creates a stomach acid suppression effect that lasts until night. The dose of vonoprazan for GERD therapy is 10mg or 50mg tegoprazan taken at night before bedtime. GERD therapy can be continued for up to 4 or 8 weeks.^{4,9}

P-CAB with helicobacter pylori eradication

Helicobacter pylori is a unique, human specific pathogen, survives in the acidic environment of the stomach and carcinogenic. *H. pylori* can survive against acid in the stomach in the presence of the enzyme urease. The prevalence of *H. pylori* infection in the world ranges from 40-50% of the population, while in Indonesia it ranges from 22.1%. *H. pylori* is closely associated with the long-term incidence of mucosal-associated lymphoid tissue (MALT), gastric cancer.^{5,10}

Eradication of *H. pylori* is currently using a combination of PPIs with two antibiotics for 7-14 days. Currently, the success of eradication is declining due to increasing antibiotic resistance and ineffective gastric acid suppression. The main antibiotics in eradication management are clarithromycin, metronidazole, and levofloxacin. Some regions and countries already report resistance to clarithromycin of up to 60% - 70%. Resistance to metronidazole as a second line is also increasing, especially in the Southeast Asian region. Levofloxacin resistance increases to 20% - 40%. Gastric acid suppression that has been done with the PPI group seems to show a decrease in effectiveness so that in the end it decreases the success of eradication. The guidelines of the Japan Gastroenterology Association have

suggested vonoprazan shift as the first line of *H. pylori* eradication. Tegoprazan has not been suggested as the first line of eradication of *H. pylori* because no recent studies have been obtained. Recent research shows that tegoprazan is not inferior when compared to lansoprazole in the eradication of *H. pylori*.^{5,11}

P-CAB with gastric ulcer and duodenal ulcer

Gastric ulcers and duodenal ulcers are diseases that common in the elderly and people with cardiac stents. The double-blind, randomized trial showed that vonoprazan 20 mg per day was not inferior to lansoprazole 30 mg in the management of gastric ulcers and duodenal ulcers. So P-CAB, especially vonoprazan, can be used as gastric ulcer therapy or

duodenal ulcer.¹²⁻¹⁵

P-CAB as ulcer prevention in users of low-dose aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs)

Low-dose aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to cause the risk of stomach disorders to ulcers. Elderly patients usually take NSAID for a long time because of osteoarthritis. Patients with coronary stents are also prone to bleeding because of gastric ulcers. Study in Mohammad Hoesin hospital also showed that patients with acute myocardial infarction given mostly aspirin (53,3%). PPIs have been the main therapy for gastric ulcer prevention.¹⁶

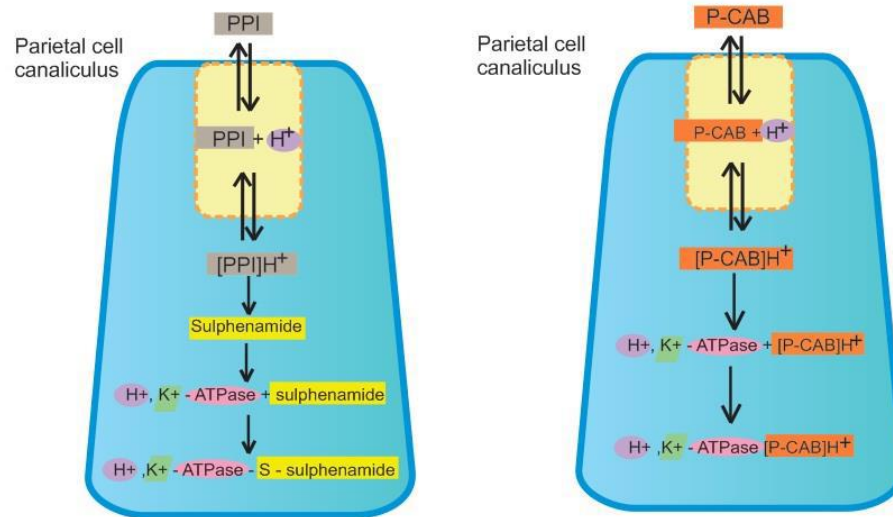


Figure 2. Differences in PPI and P-CAB mechanisms⁵

Table 2. List of problems and plans for solving them at the beginning of the observation period

	American College of Gastroenterology Indonesian Society of Gastroenterology	Japanese Society for Helicobacter Research	The Toronto Consensus	The Maastricht V/ Florence Consensus Report
First Line	If Clarithromycin – resistant strains < 20% PPI Amoxicillin Clarithromycin If Clarithromycin – resistant strains > 20% PPI Bismuth subsalicylate Metronidazole Tetracycline	PPI or vonoprazan Amoxicillin Clarithromycin	If Clarithromycin – resistant strains < 15% PPI Amoxicillin/metronidazole Clarithromycin If Clarithromycin – resistant strains > 15% PPI Amoxicillin Metronidazole Clarithromycin or PPI Bismuth subsalicylate Metronidazole Tetracycline	If Clarithromycin – resistant strains < 15% PPI Amoxicillin Clarithromycin If Clarithromycin – resistant strains > 15% PPI Amoxicillin Metronidazole
Second Line	PPI Bismuth subsalicylate Metronidazole Or PPI Amoxicillin Levofloxacin	PPI Amoxicillin Metronidazole	PPI Amoxicillin Levofloxacin Or PPI Bismuth Metronidazole Tetracycline	PPI Amoxicillin Levofloxacin Or PPI Bismuth Metronidazole Tetracycline
Third line	PPI Amoxicillin Levofloxacin Rifabutin	PPI Amoxicillin/Metronidazole Sitafloxacin	PPI Amoxicillin Rifabutin	Regimens based on the bacterial culture susceptibility test

Vonoprazan has been conducted a non-inferiority trial with lansoprazole, and the results show that vonoprazan 10 mg is not inferior. Long-term use of at least 24 weeks has been shown to reduce the incidence of gastric ulcers with minimal side effects.²

P-CBA and other clinical effects

Currently, tegoprazan is expected to have an effect on improving inflammatory bowel disease (IBD). Studies in mice have shown tegoprazan improves dysbiosis of the colon microbiota by increasing the growth of *Bacteroides vulgatus*. *Bacteroides vulgatus* reduces intestinal inflammation by inhibiting the adhesion of pathogenic bacteria. More research is needed in patients to prove the effectiveness of tegoprazan.¹²

4. Side effects

The use of P-CAB, especially vonoprazan in a short time, has been shown not to cause side effects. However, concerns about the use of vonoprazan for a long time (> 8 weeks) are feared to increase the incidence of hypergastrinemia, malabsorption, and hypochlorhydria if used for a long time. Most cases of side effects are still mild. The large VISION study evaluating the long-term use of vonoprazan as an esophagitis therapy has found no side effects. However, the interim analysis of VISION is still within 3 years while the end point of the VISION research is still within 2 years so there is still the possibility of side effects appearing.¹³

Tegoprazan was initially feared to cause more frequent hepatotoxicity than PPIs. However, large studies have shown that tegoprazan has lower hepatotoxicity effects compared to all six types of PPIs.¹⁴

5. Drug interactions

Vonoprazan is reported to decrease the effectiveness of atorvastatin (HMG-coA inhibitor) if used together. However, this does not seem to be the same if atorvastatin is used in conjunction with tegoprazan. So at this time vonoprazan should not be used in conjunction with statins. Cons of Vonoprazan current indications are hypersensitivity and concomitant use with drugs atazanavir sulphate, nelfinavir or rilpivirine hydrochloride.¹⁵

6. Conclusion

Potassium competitive acid blockers (P-CAB) are a new class of stomach acid production-suppressing drugs that show better effectiveness. The different mechanism of action with proton pump inhibitors (PPIs) makes the effect of suppressing stomach acid production longer and is able to overcome PPI deficiencies such as complaints at night and the effectiveness of helicobacter pylori eradication. Further research on the effectiveness of P-CAB, including its safety in the long term is still needed.

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