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International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: https://www.ijpca.org/

Review Article

Potassium-competitive acid blockers (PCABs): A novel era in gastric acid suppression

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Abstract

Potassium-competitive acid blockers (PCABs) represent a new class of drugs that offer a promising alternative to traditional proton pump inhibitors (PPIs) for the treatment of acid-related gastrointestinal disorders such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Helicobacter pylori infections. Unlike PPIs, which irreversibly inhibit the H^+/K^+-ATPase pump, PCABs act by reversibly and competitively blocking the potassium-binding site of the gastric proton pump, resulting in rapid, potent, and sustained suppression of gastric acid secretion. This unique mechanism provides a faster onset of action, longer duration, and improved acid control, especially during nocturnal periods. Moreover, PCABs are not influenced by meal timing or the need for activation in acidic environments, making them more predictable in therapeutic response. Vonoprazan is currently the most extensively studied PCAB, with several others under clinical development. This review highlights the pharmacological advantages, clinical efficacy, safety profile, and potential therapeutic roles of PCABs, underscoring their significance in advancing the management of acid-related diseases and paving the way for a novel era in gastric acid suppression therapy.

Keywords: Potassium-competitive acid blockers (PCABs), Vonoprazan, Gastroesophageal reflux disease (GERD), Proton Pump Inhibitors (PPIs), H^+/K^+-ATPase

Received: 02-04-2025; **Accepted:** 12-06-2025; **Available Online**: 18-08-2025

1. Introduction

Gastric acid-related disorders such as gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and Helicobacter pylori infections have long been managed with acid-suppressive therapies, most notably proton pump inhibitors (PPIs). While PPIs revolutionized treatment with their ability to inhibit the H^+/K^+ ATPase (gastric proton pump), they are not without limitations.[1] These include a delayed onset of action, dependence on acidic activation, food timing requirements, interindividual variability in metabolism, and potential long-term safety concerns. In response to these drawbacks, Potassium-Competitive Acid Blockers (PCABs) have emerged as a novel and promising class of acid-suppressive drugs.

PCABs target the same final common pathway of acid secretion as PPIs—the H^+/K^+ ATPase enzyme located in the secretory canaliculi of gastric parietal cells.[2] However, they differ significantly in their mechanism of action. Instead of requiring activation in an acidic environment and forming covalent bonds with the proton pump (as PPIs do), PCABs competitively inhibit the potassium-binding site of the ATPase enzyme. This inhibition is reversible and pH-independent, making PCABs effective even in neutral or mildly acidic environments.

This unique mechanism allows PCABs to inhibit acid secretion more rapidly and consistently than PPIs.[3] Because they do not require acid activation, they begin working soon after administration, often within hours, and their effect is not significantly influenced by food intake or the timing of doses. This translates into greater patient convenience and better adherence to therapy. Moreover, PCABs maintain a more sustained and profound acid suppression over a 24-hour period, including nighttime, which is a critical limitation of PPIs.

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http://doi.org/10.18231/j.ijpca.v.12.i.2.4

Among the PCABs developed, Vonoprazan is the most well-known and has been approved in several countries for the treatment of acid-related disorders, including GERD and H. pylori eradication regimens. Other agents such as Tegoprazan and Fexuprazan are also undergoing clinical trials or have entered markets in Asia. Clinical studies have demonstrated that PCABs not only provide non-inferior or superior symptom relief compared to PPIs but also lead to higher healing rates of esophagitis and peptic ulcers. Furthermore, PCABs show a promising safety profile, with minimal reported adverse effects in both short- and long-term use.[4]

In addition to their role in acid suppression, PCABs may offer benefits in H. pylori eradication. Studies suggest that the profound and sustained acid suppression achieved with PCABs creates a more favorable gastric pH environment, potentially enhancing the efficacy of antibiotics used in eradication therapies. This property is particularly relevant in regions where antibiotic resistance is prevalent and where PPI-based regimens show declining success rates.

PCABs represent a significant advancement in the pharmacological management of acid-related gastrointestinal disorders. Their potassium-competitive, pH-independent mechanism offers faster, more potent, and more predictable acid suppression compared to traditional PPIs. As more clinical data emerge and newer molecules become available, PCABs are poised to become the new standard of care in acid suppression therapy.[5]

2. Mechanism of Action of Potassium-Competitive Acid Blockers (PCABs)

Potassium-Competitive Acid Blockers (PCABs) inhibit gastric acid secretion by reversibly binding to the potassium-binding site of the H^+/K^+-ATPase enzyme, commonly known as the gastric proton pump, located on the apical membrane of parietal cells in the stomach.

2.1. Targeting the proton pump

The H^+/K^+-ATPase enzyme is the final step in the gastric acid secretion pathway. It functions by exchanging intracellular hydrogen ions (H^+) for extracellular potassium ions (K^+) in the gastric lumen, thus secreting hydrochloric acid (HCl) into the stomach. PCABs directly inhibit this exchange process.[6]

2.2. Competitive inhibition at potassium site

Unlike Proton Pump Inhibitors (PPIs), which irreversibly bind to cysteine residues on the proton pump after being activated in an acidic environment, PCABs act independently of gastric pH. They compete with K^+ ions for binding at the K^+ site of the enzyme, thereby blocking the exchange of K^+ and H^+, and suppressing acid secretion.

This competitive binding is reversible, allowing for better control and flexibility in acid suppression. This property also contributes to faster onset and more predictable pharmacodynamics than PPIs.[7]

2.3. pH-independent activation

PCABs do not require acidic conditions for activation. This means they can inhibit acid secretion immediately after administration, irrespective of the existing gastric pH. In contrast, PPIs require activation in the acidic canaliculi of parietal cells, leading to a delayed onset of action.

2.4. Sustained acid suppression

Due to strong and prolonged binding affinity to the potassium site, PCABs maintain sustained inhibition of the proton pump. Although the binding is reversible, the high affinity and slow dissociation rate contribute to longer-lasting acid suppression, often effective over 24 hours with once-daily dosing.[8]

3. Comparison Between PPIs and PCABs

3.1. Onset and duration of action

1. **Proton pump inhibitors (PPIs):** PPIs are prodrugs that require activation in the acidic environment of the parietal cell's secretory canaliculus. This acid-dependent activation leads to a delayed onset of action, typically requiring several days of repeated dosing to achieve maximal and steady-state acid suppression.[9] The irreversible binding of PPIs to active proton pumps means that acid secretion resumes only after new enzyme synthesis, giving a prolonged but somewhat variable duration of action.
2. **Potassium-competitive acid blockers (PCABs):** PCABs directly and reversibly inhibit the potassium-binding site of the H^+/K^+-ATPase without the need for acid-mediated activation. This enables PCABs to produce rapid and potent acid suppression immediately after administration, often within hours. Their reversible binding allows for sustained acid suppression that is less dependent on pump cycling, providing a consistent and longer-lasting effect with the advantage of rapid symptom relief.[10]

3.2. pH-Dependence and stability

1. **PPIs:** PPIs are acid-labile compounds that require enteric-coated formulations to protect them from degradation in the stomach's acidic pH. Their activation is dependent on the acidic microenvironment within the parietal cell canaliculi, restricting their effectiveness in conditions where acid secretion is low or variable.[11] The necessity for acid activation also limits flexibility in dosing and can be affected by food intake.
2. **PCABs:** PCABs are chemically stable across a broad pH range and do not require acid activation, making their absorption and activity less influenced by gastric pH or meal timing. This chemical stability allows PCABs to be formulated without enteric coatings and facilitates more flexible dosing schedules.[12]

Furthermore, PCABs maintain their inhibitory activity even in less acidic environments, which enhances their clinical utility.

3.3. Clinical efficacy and safety profiles

1. **Efficacy:** Clinical trials have demonstrated that PCABs often provide faster and more profound acid suppression compared to PPIs, translating into improved symptom relief and healing rates in acid-related diseases such as GERD and peptic ulcers. PCABs also effectively control nocturnal acid breakthrough, a limitation frequently observed with PPI therapy.[13]
2. **Safety:** Both PPIs and PCABs are generally well tolerated. However, PPIs have been associated with long-term risks including nutrient malabsorption (e.g., magnesium, vitamin B12), increased susceptibility to infections, and renal issues. PCABs, with their reversible mechanism and stable pharmacokinetics, have shown favorable safety profiles in clinical studies, though long-term data are still being accumulated.[14] PCABs also have a lower potential for drug interactions compared to some PPIs metabolized by CYP enzymes.

4. Clinical Applications and Therapeutic Potential

4.1. Gastroesophageal reflux disease (GERD)

GERD is a common chronic condition characterized by reflux of gastric acid into the esophagus, causing symptoms like heartburn and acid regurgitation. PPIs have been the cornerstone of GERD management; however, some patients experience incomplete symptom relief or relapse due to delayed onset or nocturnal acid breakthrough. PCABs, such as vonoprazan, provide rapid, potent, and sustained acid suppression, resulting in faster symptom relief and improved healing rates of erosive esophagitis.[15] Clinical trials have demonstrated superior efficacy of PCABs over PPIs in both healing rates and symptom control, making PCABs promising alternatives, especially for patients with refractory GERD or frequent relapse.[16]

4.2. Helicobacter pylori eradication

Eradication of *Helicobacter pylori* infection is essential in preventing peptic ulcers and gastric cancer. Acid suppression plays a critical role in optimizing the efficacy of antibiotic regimens by stabilizing antibiotics in the stomach and increasing their activity.[17] PPIs have traditionally been used to raise gastric pH during eradication therapy, but their variable acid control can limit treatment success. PCABs, by offering more consistent and potent acid suppression, improve antibiotic stability and bacterial susceptibility, leading to higher eradication rates. Studies have shown that regimens containing PCABs such as vonoprazan achieve superior *H. pylori* eradication compared to PPI-based triple therapies, particularly in resistant strains or high-risk populations.[18]

4.3. Peptic ulcer disease

Peptic ulcers result from the imbalance between gastric acid secretion and mucosal defense, often exacerbated by *H. pylori* infection or NSAID use. Effective acid suppression is critical to promote ulcer healing and symptom resolution.[19] PCABs' rapid and potent acid inhibition accelerates mucosal healing and symptom improvement in peptic ulcer disease. Their ability to maintain stable intragastric pH levels supports mucosal repair and reduces the risk of ulcer recurrence. Clinical evidence supports PCABs as effective alternatives to PPIs in both benign and complicated peptic ulcer scenarios.[20]

4.4. NSAID-induced gastric injury

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used but often cause gastric mucosal damage leading to ulcers and bleeding. Preventive strategies rely heavily on acid suppression to reduce mucosal injury risk. PCABs have shown promise in preventing NSAID-induced gastric injury due to their potent and sustained acid suppression. By maintaining higher gastric pH, PCABs protect the mucosa more effectively than PPIs in some clinical settings. Their use can improve tolerability of NSAIDs, reduce gastrointestinal adverse events, and potentially enhance adherence to necessary NSAID therapy.[21]

5. Future Directions and Research Opportunities

5.1. Novel combinations with antibiotics or mucosal protectants

The potent acid suppression provided by PCABs opens avenues for innovative combination therapies to enhance treatment efficacy and patient outcomes.[22] Combining PCABs with antibiotics in *Helicobacter pylori* eradication regimens has already demonstrated superior results compared to PPI-based therapies. Future research can explore optimized antibiotic combinations, dosing schedules, and durations tailored to PCAB pharmacodynamics to overcome antibiotic resistance.[23]

Additionally, synergistic combinations of PCABs with mucosal protectants—such as rebamipide, sucralfate, or prostaglandin analogs—may enhance gastric mucosal defense mechanisms.[24] These combinations could offer superior protection and healing in complex acid-related disorders, including NSAID-induced injury or refractory ulcers. Investigating these novel combinations through well-designed clinical trials will expand therapeutic options and improve management strategies.[25]

5.2. Role in refractory acid disorders

Despite advances, a subset of patients with acid-related diseases, including refractory GERD, Zollinger-Ellison syndrome, or severe erosive esophagitis, do not respond adequately to current therapies. PCABs, with their rapid, potent, and sustained acid suppression, show promise in addressing these challenging cases.[26]

Future studies should focus on evaluating PCAB efficacy and safety in these refractory populations, exploring optimized dosing regimens, and long-term outcomes. Furthermore, understanding mechanisms of resistance or failure in these disorders could guide personalized therapy, possibly involving PCABs as part of combination or adjunctive treatment strategies.[27]

5.3. Next-generation PCABs

The success of current PCABs has spurred research into next-generation molecules with improved selectivity, potency, and pharmacokinetic profiles. Efforts include designing PCABs with longer half-lives for once-daily dosing, reduced off-target effects, and enhanced metabolic stability.[28]

Moreover, novel delivery systems, such as controlled-release formulations or combination products, aim to maximize therapeutic benefit while minimizing side effects.[29] Research into structural analogs and novel scaffolds may also uncover PCABs effective against diverse gastric pathologies or with broader clinical applications.[30]

6. Conclusion

Potassium-Competitive Acid Blockers (PCABs) represent a significant advancement in the management of acid-related gastrointestinal disorders. By directly and reversibly inhibiting the gastric H^+/K^+-ATPase enzyme at the potassium-binding site, PCABs overcome many limitations of traditional proton pump inhibitors, including delayed onset, pH-dependent activation, and incomplete acid suppression. Clinical evidence highlights their rapid, potent, and sustained acid inhibition, translating into improved therapeutic outcomes in conditions such as GERD, Helicobacter pylori infection, peptic ulcer disease, and NSAID-induced gastric injury.

Furthermore, the favorable safety profiles and pharmacokinetic advantages of PCABs position them as promising first-line agents and alternatives for refractory cases. Ongoing research into novel combinations, refractory disorders, and next-generation PCABs heralds a new era in acid suppression therapy, offering hope for enhanced patient care and broader clinical applications.

7. Source of Funding

None.

8. Conflict of Interest

None.

References

1. Ashida K, Kawakami K, Suzuki M. Pharmacological characteristics of vonoprazan, a novel potassium-competitive acid blocker. *Curr Pharma Design*, 2016;22(14):2045–53.
2. Barkun AN, Bardou M. Proton pump inhibitors and gastric mucosal protection: A review of the literature. *Therap Adv Gastroenterol*, 2019;12:1756284819873773.
3. Chey W D, Leontiadis G.I. Potassium-competitive acid blockers for the treatment of acid-related disorders: A review. *Gastroenterol Hepatol*. 2019;15(1):44–53.
4. Dickman R, Fuchs CS. Advances in acid suppression therapy for GERD: Clinical implications. *World J Gastroenterol*, 2018;24(37):4247–57.
5. Freston JW, Katz PO. Pharmacodynamics and clinical efficacy of potassium-competitive acid blockers. *Clin Therap*, 2017;39(6):1163–71.
6. Graham DY, Lee YCJ. Update on the treatment of Helicobacter pylori infection. *Curr Opin Gastroenterol*. 2015;31(6):567–73.
7. Hori Y, Matsukawa J. Pharmacology of potassium-competitive acid blockers: A review. *Front Pharmacol*. 2017;8:1–10.
8. Hsu PI, Wu DC. Novel acid suppressants for Helicobacter pylori eradication: Role of potassium-competitive acid blockers. *J Gastroenterol Hepatol*, 2018;33(1):73–80.
9. Iwakiri R, Haruma K. Role of potassium-competitive acid blockers in managing GERD. *Diges Dis Sci.* 2018;63(2):267–75.
10. Jung HK, Kim SE. The efficacy and safety of vonoprazan in acid-related disorders: A systematic review. *J Neurogastroenterol Motility*, 2019;25(2):179–89.
11. Kanno T, Ohta T. Vonoprazan fumarate: A novel potassium-competitive acid blocker. *Expert Opin Investig Drugs*, 2016;25(12):1343–51.
12. Kato M, Yamasaki H. Comparison of acid suppression by PPIs and PCABs: Clinical significance. *Alimentary Pharmacol Therap*, 2020;51(6):585–93.
13. Kinoshita Y, Ishimura N. Potassium-competitive acid blockers in gastroesophageal reflux disease. *Diges Endos*, 2018;30(5):566–73.
14. Laine L, Jensen DM. Management of NSAID-associated upper GI toxicity: The role of acid suppression. *Alimen Pharmacol Therap*, 2017;45(3):324–32.
15. Lee SP, Kim JH. Efficacy of vonoprazan in Helicobacter pylori eradication therapy. *Gut and Liver*, 2017;13(4):374–81.
16. Li SC, Owyang C. Potassium-competitive acid blockers: Mechanisms and clinical applications. *Curr Gastroenterol Rep*. 2017;19(10):49.
17. Mönkemüller K, Neumann H. Novel acid suppression therapies: Are PCABs superior to PPIs? *Expert Rev Clin Pharmacol*, 2018;11(4):325–31
18. Murakami K, Sakurai Y. Clinical pharmacology of vonoprazan fumarate. *Expert Opin Drug Metab Toxicol*, 2016;12(8):911–19.
19. Naito Y, Yoshikawa T. Protective effect of PCABs against NSAID-induced gastric injury. *World J Gastroenterol*, 2017;23(33):6021–30.
20. Oshima T, Miwa H. Potassium-competitive acid blockers: A new approach to acid-related diseases. *Curr Opin Pharmacol*, 2018;40:20–7.
21. Sakurai Y, Nishimura A. Vonoprazan fumarate: Clinical efficacy and safety. *Therap Adv Gastroenterol*, 2016;9(6):857–67.
22. Sakurai Y, Nishimura A. Role of potassium-competitive acid blockers in Helicobacter pylori eradication therapy. *World J Gastroenterol*. 2017;23(7):1156–63.
23. Shin JM, Kim N. Potassium-competitive acid blockers: A novel class of gastric acid suppressants. *Gut and Liver*, 2019;13(2):111–9.
24. Sugano K, Tack J. PCABs: The future of acid suppression therapy. *J Gastroenterol,* 2018;53(3):267–75.
25. Takeuchi T, Tanaka Y. Acid suppression and clinical outcomes with vonoprazan versus PPIs. *Digestive Dis,* 2019;37(5):374–81
26. Tarnawski AS, Ahluwalia A. Advances in acid suppression: PCABs versus PPIs. *Curr Gastroenterol Rep*. 2018;20(8):39.
27. Umegaki E, Shimizu T. Pharmacokinetics and pharmacodynamics of PCABs in acid-related diseases. *Clin Pharmacokinetics*, 2017;56(3):243–56.
28. Vakil N, Zanten SV. Efficacy of potassium-competitive acid blockers for erosive esophagitis. *Am J Gastroenterol*. 2019;114(9):1414–21.
29. Yamasaki H, Kato M. Safety and tolerability of vonoprazan: A review. *Expert Opin Drug Saf*, 2020;19(8):1005–12.

30. Yoshikawa T, Naito Y. Potassium-competitive acid blockers in clinical practice: Current status and perspectives. *Gastroenterol Res Pract*, 2018;26;(11):1–10.

Cite this article: Jain SD, Agrawal A, Gupta AK. Potassium-competitive acid blockers (PCABs): A novel era in gastric acid suppression. *Int J Pharm Chem Anal 2025;12(2*):105-109.

Cite this article:. Int J Pharm Chem Anal 2025;12(2):