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Vonoprazan and Potassium-Competitive Acid Blockers:A Paradigm Shift from Proton Pump Inhibitors in the Management of Acid-Related Disorders

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ABSTRACT
Acid-related disorders such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Helicobacter pylori infection are among the most common gastrointestinal conditions encountered in clinical practice worldwide [1]. Proton pump inhibitors (PPIs) have long been the mainstay of therapy; however, delayed onset of action, incomplete acid suppression, nocturnal acid breakthrough, interindividual variability due to CYP2C19 polymorphisms, and declining H. pylori eradication rates have highlighted important limitations of this drug class [2–4]. Potassium-competitive acid blockers (P-CABs) are a newer class of antisecretory agents that reversibly inhibit the gastric H /K -ATPase by competing with potassium ions at the luminal binding site [5]. Vonoprazan, the first clinically approved P-CAB, provides rapid, potent, and sustained acid suppression independent of acid activation or CYP2C19 genotype [6]. This review discusses the pharmacological basis, clinical efficacy, safety, and therapeutic applications of vonoprazan and other P-CABs, emphasizing their role as a paradigm shift from conventional PPIs in acid-related disorders.
Keywords: Vonoprazan, potassium-competitive acid blockers, proton pump inhibitors, GERD, Helicobacter pylori

I. INTRODUCTION

Gastric acid secretion is a fundamental physiological process essential for digestion and host defense; however, excessive or prolonged acid exposure contributes significantly to the pathogenesis of acid-related disorders (ARDs) such as GERD, peptic ulcer disease, and Zollinger–Ellison syndrome [1,2]. These conditions impose a substantial global healthcare burden, affecting quality of life and increasing the risk of complications such as gastrointestinal bleeding, esophageal strictures, Barrett's esophagus, and gastric malignancy [3]. Effective acid suppression is therefore central to disease management.

PPIs revolutionized the treatment of ARDs by irreversibly inhibiting the gastric H /K -ATPase, leading to profound and sustained reduction in gastric acid secretion [4]. Despite their widespread use, several limitations have emerged over time. PPIs require activation in an acidic environment, demonstrate a delayed onset of action, and are subject to significant interindividual variability due to genetic differences in CYP2C19 metabolism [5,6]. Moreover, incomplete acid suppression, particularly during the night, contributes to persistent symptoms in a substantial proportion of patients, termed PPI-refractory disease [7].

The development of potassium-competitive acid blockers represents a major advancement in gastric acid suppression. Vonoprazan, the first P-CAB approved for clinical use, has demonstrated superior pharmacodynamic properties compared with PPIs, offering rapid, consistent, and prolonged acid suppression [8]. This review examines the mechanistic differences between PPIs and P-CABs, with particular emphasis on vonoprazan, and evaluates current evidence supporting their clinical utility.

Gastric Acid Secretion and Therapeutic Targets

Acid secretion occurs in gastric parietal cells via the H /K -ATPase proton pump, which exchanges intracellular hydrogen ions for luminal potassium ions [9]. This enzyme represents the final and most critical step in acid production. Regulation of acid secretion involves neural (acetylcholine), hormonal (gastrin), and paracrine (histamine) pathways [10].

PPIs inhibit the proton pump irreversibly but only when the enzyme is actively secreting acid, which explains their requirement for dosing prior to meals and their delayed maximal effect [11]. In contrast, P-CABs directly block the

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potassium binding site of the proton pump, inhibiting both active and resting pumps and resulting in immediate suppression of acid secretion [12].

Mechanism of Action: PPIs versus P-CABs

PPIs such as omeprazole, esomeprazole, and lansoprazole are weak bases that accumulate in the acidic canaliculi of parietal cells, where they are converted into active sulfenamide intermediates [13]. These intermediates covalently bind cysteine residues on the proton pump, leading to irreversible inhibition. Because new proton pumps must be synthesized for acid secretion to resume, PPIs exert prolonged effects despite short plasma half-lives [14].

However, only actively secreting proton pumps are inhibited, and repeated dosing over several days is required to achieve maximal acid suppression [15]. Furthermore, variability in CYP2C19 metabolism significantly influences plasma drug levels and therapeutic response [6].

P-CABs, including vonoprazan, reversibly and competitively inhibit the proton pump by blocking potassium binding [16]. This inhibition is independent of pump activation and does not require acid-mediated conversion [17]. As a result, P-CABs provide rapid onset of action, near-complete acid suppression from the first dose, and minimal influence of genetic polymorphisms [18].

Pharmacokinetics and Pharmacodynamics of Vonoprazan

Vonoprazan is acid-stable and rapidly absorbed following oral administration, achieving peak plasma concentrations within approximately 2 hours [19]. It has a longer elimination half-life (7–9 hours) compared with PPIs, contributing to sustained acid suppression throughout the dosing interval [20].

Metabolism occurs predominantly via CYP3A4, with minimal involvement of CYP2C19, resulting in predictable pharmacokinetics across different patient populations [21]. Pharmacodynamic studies demonstrate that vonoprazan maintains intragastric pH >4 and >6 for significantly longer durations than standard-dose PPIs, both during daytime and nighttime periods [22]. This potent acid suppression is particularly relevant for conditions requiring high intragastric pH, such as H. pylori eradication and severe erosive esophagitis.

Clinical Applications

Gastroesophageal Reflux Disease

GERD is one of the most prevalent gastrointestinal disorders worldwide, with increasing incidence in both Western and Asian populations [23]. Although PPIs are effective in many patients, up to 30–40% experience incomplete symptom relief [7].

Randomized controlled trials have demonstrated that vonoprazan is non-inferior and, in severe cases, superior to PPIs in healing erosive esophagitis [24]. Vonoprazan has also shown improved maintenance of healing and reduced relapse rates compared with lansoprazole [25]. Importantly, vonoprazan has demonstrated efficacy in PPI-refractory GERD, offering a valuable therapeutic option for this challenging patient population [26].

Peptic Ulcer Disease

PPIs are standard therapy for gastric and duodenal ulcers; however, P-CABs provide comparable or superior healing rates [27]. Vonoprazan has been shown to effectively heal peptic ulcers and prevent recurrence, particularly in patients receiving long-term NSAID therapy [28]. Meta-analyses confirm that P-CABs are non-inferior to PPIs for ulcer healing, with similar safety profiles [29].

Helicobacter pylori Eradication

Eradication of H. pylori is critical for preventing peptic ulcer recurrence and reducing gastric cancer risk [30]. Rising antibiotic resistance has reduced the efficacy of traditional PPI-based regimens [31]. Potent acid suppression enhances antibiotic stability and bacterial susceptibility [32].

Vonoprazan-based regimens achieve higher eradication rates than PPI-based therapies, particularly in clarithromycin-resistant strains [33]. Vonoprazan-amoxicillin dual therapy has emerged as a simplified and effective regimen, reducing antibiotic exposure while maintaining high eradication success [34].

Safety and Tolerability

Short-term studies indicate that vonoprazan has a safety profile comparable to PPIs, with common adverse effects including diarrhea, constipation, headache, and nausea [35]. Vonoprazan induces greater hypergastrinemia due to potent acid suppression; however, long-term studies up to five years have not demonstrated clinically significant gastric neuroendocrine tumors or dysplasia [36].

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Rare adverse effects such as hypomagnesemia and QT prolongation have been reported, emphasizing the importance of monitoring during prolonged therapy [37]. Overall, available evidence supports the favorable safety profile of vonoprazan and other P-CABs.

Other Potassium-Competitive Acid Blockers

In addition to vonoprazan, other P-CABs such as tegoprazan, fexuprazan, and keverprazan have been approved in selected countries [38]. These agents share similar mechanisms of action but differ in pharmacokinetic profiles and regional availability. Ongoing studies aim to further define their comparative efficacy and safety.

II. LIMITATIONS AND FUTURE DIRECTIONS

Despite promising clinical data, long-term safety beyond five years remains under evaluation [39]. Comparative studies between individual P-CABs and cost-effectiveness analyses are needed. Integration of P-CABs into international treatment guidelines and personalized acid suppression strategies represent important future directions [40].

III. CONCLUSION

Vonoprazan and other potassium-competitive acid blockers represent a significant advancement in the management of acid-related disorders. By providing rapid, potent, and consistent acid suppression with minimal pharmacogenetic variability, P-CABs address several limitations of PPIs. Current evidence supports their use as effective alternatives—and in selected cases superior options—to PPIs in GERD, peptic ulcer disease, and H. pylori eradication. Continued research and pharmacovigilance will further clarify their optimal role in clinical practice.

REFERENCES

[1]. Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: a comprehensive review. Gut Liver. 2017;11(1):27–37.
[2]. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD: an overview of their pharmacology, efficacy and safety. Pharmacol Res. 2009;59(3):135–153.
[3]. Scarpignato C, Hunt RH. Acid suppression therapy: where do we go from here? Gut. 2019;68(7):1355–1367.
[4]. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–328.
[5]. Furuta T, Shirai N, Sugimoto M. Influence of CYP2C19 polymorphism on proton pump inhibitor therapy. Pharmacogenomics. 2007;8(9):1199–1210.
[6]. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. J Neurogastroenterol Motil. 2018;24(3):334–344.
[7]. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2005;22(2):79–94.
[8]. Sugano K. Vonoprazan fumarate, a novel potassium-competitive acid blocker. Ther Adv Gastroenterol. 2018;11:1756283X17745776.
[9]. Scott DR, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan to the gastric H /K -ATPase. Aliment Pharmacol Ther. 2015;42(11–12):1315–1326.
[10]. Abdel-Aziz Y, Metz DC, Howden CW. Potassium-competitive acid blockers for the treatment of acid-related disorders. Aliment Pharmacol Ther. 2021;53(7):794–809.
[11]. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528–534.
[12]. Echizen H. The first-in-class potassium-competitive acid blocker, vonoprazan. Clin Pharmacokinet. 2016;55(4):409–418.
[13]. Mulford DJ, Leifke E, Hibberd M, et al. Pharmacokinetics and pharmacodynamics of vonoprazan. Clin Pharmacol Drug Dev. 2022;11(2):278–284.
[14]. Scarpignato C, Howden CW. Translational PK/PD of vonoprazan. Aliment Pharmacol Ther. 2023;58(1):16–25.
[15]. Laine L, DeVault K, Katz P, et al. Vonoprazan versus lansoprazole for erosive esophagitis. Gastroenterology. 2023;164(1):61–71.

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[16]. Iwakiri K, Fujiwara Y, Manabe N, et al. Evidence-based GERD guidelines 2021. J Gastroenterol. 2022;57(4):267–285.
[17]. Hoshino S, Kawami N, Takenouchi N, et al. Efficacy of vonoprazan for PPI-resistant reflux esophagitis. Digestion. 2017;95:156–161.
[18]. Mizokami Y, Oda K, Funao N, et al. Vonoprazan prevents ulcer recurrence during long-term NSAID therapy. Gut. 2018;67(6):1042–1051.
[19]. Wang WX, Li RJ, Li XF. P-CABs versus PPIs for peptic ulcer disease. Clin Transl Gastroenterol. 2024;15(9):e1.
[20]. Furuta T, Yamade M, Higuchi T, et al. Acid suppression and H. pylori eradication. J Clin Med. 2023;12(9):3110.
[21]. Rokkas T, Niv Y, Gisbert JP. P-CAB-based regimens for H. pylori. Am J Gastroenterol. 2025;120(4):787–798.
[22]. Gao W, Teng G, Wang C, et al. Vonoprazan–amoxicillin dual therapy. Helicobacter. 2022;27(5):e12918.
[23]. Eusebi LH, Ratnakumaran R, Yuan Y, et al. Global prevalence of GERD. Gut. 2018;67(3):430–440.
[24]. Xiao YL, Qian JM, Zhang ST, et al. Vonoprazan maintenance therapy. Chin Med J. 2024;137(8):962–971.
[25]. Akiyama J, Hosaka H, Kuribayashi S, et al. Long-term vonoprazan in GERD. Digestion. 2020;101(2):174–183.
[26]. Savarino E, Zentilin P, Savarino V. NERD and refractory GERD. Nat Rev Gastroenterol Hepatol. 2013;10(6):371–380.
[27]. Liu Y, Gao Z, Hou X. P-CABs vs PPIs in erosive esophagitis. Ther Adv Gastroenterol. 2024;17:1756284824125156.
[28]. Marabotto E, Ziola S, Savarino V, et al. Vonoprazan in peptic ulcers. Clin Exp Gastroenterol. 2020;13:99–104.
[29]. Ouyang M, Zou S, Cheng Q, et al. P-CABs for peptic ulcer disease. Pharmaceuticals (Basel). 2024;17(6):698.
[30]. Liou JM, Malfertheiner P, Lee YC, et al. H. pylori eradication consensus. Gut. 2020;69(12):2093–2112.
[31]. Zhong Z, Zhan B, Xu B, et al. Antibiotic resistance in H. pylori. Am J Cancer Res. 2022;12(3):1215–1221.
[32]. Sue S, Maeda S. P-CABs in H. pylori eradication. Gut Liver. 2021;15(6):799–810.
[33]. Shirley M. Vonoprazan in H. pylori infection. Drugs. 2024;84(3):319–327.
[34]. Shih CA, Wu DC, Shie CB, et al. Dual therapy for H. pylori. Microorganisms. 2025;13(4):715.
[35]. Gong H, Han D, Liu S, et al. Adverse events of vonoprazan. Rev Esp Enferm Dig. 2023;115(6):294–300.
[36]. Haruma K, Kinoshita Y, Yao T, et al. Long-term safety of vonoprazan. BMC Gastroenterol. 2023;23(1):139.
[37]. Okamoto M, Wakunami Y, Hashimoto K. Hypomagnesemia with vonoprazan. Intern Med. 2022;61(1):119–122.
[38]. Ramani A, Merchant A, Cash BD. Newer P-CABs in development. Eur J Clin Pharmacol. 2023;79(8):1023–1029.
[39]. Scarpignato C, Gatta L, Zullo A, et al. Long-term acid suppression safety. BMC Med. 2016;14:179.
[40]. Patel A, Laine L, Moayyedi P, et al. Integrating P-CABs into clinical practice. Gastroenterology. 2024;167(6):1228–1238.

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