International Journal of Health Sciences and Research
[Indexed, Peer-Reviewed Journal]
Volume 16; Issue: 2; February 2026
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

PRAZANs or PCABs, Potassium Competitive Acid Blockers: A New Therapeutic Class in Acid-Related Diseases

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DOI: https://doi.org/10.52403/ijhsr.20260215

ABSTRACT

Acid-related diseases occur due to physiological and protective oscillation of the gastric environment that leads to excessive secretion of acid. The gastric H+/K+-ATPase, an integral membrane protein that belongs to the P2-type ATPase family, is an important enzyme, commonly known as a proton pump, which is responsible for gastric acid secretion. Indeed, it is a site of action of several proton pump inhibitors (PPIs), such as omeprazole, pantoprazole, lansoprazole, rabeprazole, etc., which act by inhibiting this enzyme. The main component of gastric acid is hydrochloric acid, which is secreted by parietal cells and plays a role in regulating the digestion process. Over-secretion or abnormality in this process leads to several acid-related diseases potentiated by the risk factors, such as bacterial infection by Helicobacter pylori, the use of drugs (NSAIDs, oral iron preparations, gastric irritants), and physiological stress that significantly cause peptic ulcer disease. Owing to the irreversible inhibition and limitations associated with the long-term use of PPIs, potassium competitive acid blockers (PCABs), also known as PRAZANs, have been developed as a novel therapeutic approach to treat acid-related diseases, such as gastric ulcers, erosive esophagitis, and gastroesophageal reflux disease (GERD). Indeed, PCABs competitively and reversibly block the potassium-binding site of the H+/K+-ATPase enzyme to reduce the excessive acid secretion with a faster onset of action than PPIs. The present review outlines the clinical development and summarizes the pharmacology and therapeutic effects of PCABs or PRAZANs as a potential alternative to PPIs in the management of acid-related diseases.

Keywords: Fexuprazan, Keverprazan, Potassium competitive acid blockers, Proton pump, Revaprazan, Tegoprazan, Vonoprazan, Zastaprazan, H+/K+-ATPase, NSAIDs, PCAB, PPI

INTRODUCTION

Histamine H2 receptor antagonists (H2RAs; cimetidine, ranitidine, nizatidine, famotidine) and proton pump inhibitors (PPIs; omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) are the earlier acid-suppressive drugs that are involved in the early management of acid-related diseases. Indeed, limitations of chronic long-term use of acid-release suppressants, inadequate response rates and/or treatment failure in a few cases, and poor management of peptic ulcer diseases (PUD), such as Helicobacter pylori (H. pylori)-induced ulcers and non-steroidal anti-inflammatory drug (NSAID)-induced

ulcers, dyspepsia, and gastroesophageal reflux disease (GERD) have increased the need for improvement in anti-secretory therapy [1-4]. Further, several approaches, including a combination of analgesics and anti-inflammatory agents to alleviate symptoms of painful and inflammatory conditions and to reduce the loading amount of those drugs with beneficial synergistic or supradditive therapeutic effects and reduced cost of treatment, have been investigated to manage pain and inflammation and to overcome NSAID-induced PUD [5-7]. Indeed, a widely discussed and breakthrough discovery and development of COXIBs, the selective cyclooxygenase-2 (COX-2) inhibitors without ulceration in the stomach led to the approval of celecoxib in 1998, rofecoxib in 1999, parecoxib, valdecoxib, etoricoxib, and lumiracoxib to treat mild-to-moderate pain and inflammation caused by osteoarthritis, rheumatoid arthritis, juvenile arthritis, gouty arthritis, migraine, post-operative pain, and joint inflammatory conditions [8-12]. However, their approval did not last long due to the pharmacovigilance studies reported a significant risk of cardiovascular death, myocardial infarction, stroke, or heart failure [12,13]. These safety signals have been associated with the use of NSAIDs, strongly correlated with higher COX-2 receptor occupancy, and are associated with an increased cardiovascular risk from NSAIDs [12,14,15]. Therefore, the use of anti-secretory acid blockers remains the mainstay in the management of NSAID-induced ulceration [1,3,16].

Besides, H. pylori eradication therapy in the management of PUD includes the combination of a PPI with two antimicrobial agents, particularly clarithromycin and amoxicillin or metronidazole, whose efficacy is improved by raising the intragastric pH that helps in increasing the bactericidal nature of the antimicrobial agents [17-20]. Although PPIs are effective drugs, they face certain challenges. Indeed, several new drugs were developed that have an extended duration of acid suppression with a half-life longer than that of traditional PPIs, which are called third-generation PPIs, although they were never approved for therapeutic use [1,20,21]. However, these unmet needs are addressed by innovative approaches that led to the discovery and clinical development of a new class of antisecretory medications, potassium competitive acid blockers (PCABs), such as revaprazan, vonoprazan, tegoprazan, fexuprazan, keverprazan, and zastaprazan. All these PCABs are commonly referred to as ‘Prazans’ as all these agents end with the suffix ‘-prazan’, which may potentially inhibit the potassium (K+) ion exchange channel of the gastric enzyme hydrogen potassium ATPase (H+/K+-ATPase) belong to the P2-type ATPase family [2,3,15]. This is an important enzyme, commonly known as a proton pump, and provides more effective acid inhibition than PPIs. Accumulating randomized clinical trial data further supports the superior efficacy of PCABs in a variety of gastric acid-related diseases [2,3,4,16,20,22]. This review summarizes current knowledge on gastric acid release and the evidence-based practice of the current management approaches for gastric acid-related diseases, emphasising the pharmacodynamic and pharmacokinetic differences between PPIs and PCABs, with a focus on best practice advice for the use of PCABs in the pharmacotherapy of these diseases.

PARIETAL CELL - ACID SECRETION - ROLE OF POTASSIUM ION

Gastric acid serves a crucial role in purifying and digesting food and water. Parietal cells are epithelial cells that reside within oxyntic (acid-secreting) glands of the corpus of the stomach and generate hydrochloric acid by secreting proton or hydrogen ion (H^+) and chloride (Cl^-) ions, achieving an extremely low pH of 1 in gastric juice [23,24]. Notably, the pH of the gastric lumen is ~1.4; however, a pH below 1.0 can occur when unbuffered by food and fluids [25,26]. These cells release 1-2 L of

hydrochloric acid daily. In the quiescent phase, tubulovesicular components containing H^+/K^+-ATPase are free, present in inactivated form, and don't merge with the apical (lumen-facing) membrane of parietal cells. The activity of gastric H^+/K^+-ATPase enzyme, the proton pump of the stomach, present in the apical membrane of parietal cells, results in a significantly higher concentration of H^+ in the stomach lumen compared to the bloodstream and functions to acidify the stomach [24,25]. Essentially, K^+ ions are essential for activating this enzyme. Importantly, mastication, excess salivary secretion, food, fluids, and olfactory sensation cause an active phase of acid release wherein a parietal cell is stimulated, and tubulovesicular components containing H^+/K^+-ATPase merge with the apical membrane. Exposed to the luminal fluid containing K^+ ions, the enzyme can then exchange H^+ ions for K^+ ions using energy donated by ATP, which is a critical step in gastric acid production. The enzyme remains inactive at rest due to low K^+ concentrations and impermeable membranes. The chloride channels on the apical membrane allow Cl^- transfer into the luminal side, and react with H^+ ions, resulting in hydrochloric acid (HCl), a chief component of gastric juice (Fig. 1A) [24,25]. PPIs covalently bind to thiol (-SH) residues of cysteine-containing proteins in the α-subunit of proton pumps on the luminal (secretory/canalicular) membranes of gastric parietal cells and continuously inhibit H^+ secretion, resulting in irreversible inhibition of gastric acid secretion. During the active phase of the H^+/K^+-ATPase enzyme and following the administration of a PPI, this class of drugs remains bound to proton pumps for a prolonged period, inhibiting this enzyme activity until new proton pumps are finally synthesized, and replaces the old ones in parietal cells (Fig. 1B) [25-27]. Moreover, H^+/K^+-ATPase has a moderately short half-life of about 2.5 days and is newly synthesized and replaced at a rate of ~20% every 24 h [24,26]. Indeed, about 10% of proton pumps are active in the fasted state, whereas food intake and flavors stimulate about 70% of proton pumps to the active phase [24,28,29]. Therefore, targeting K^+ ions in acid-blocking therapies involves blocking K^+ channels on the apical membrane of the parietal cells by irreversibly inhibiting H^+/K^+-ATPase activity using a PPI or competitively and reversibly inhibiting K^+ ion exchange at the level of H^+/K^+-ATPase using a PCAB (Fig. 1C) [2,3,18,24,25,30,31].

REASONS FOR THE DISCOVERY AND DEVELOPMENT OF POTASSIUM COMPETITIVE ACID BLOCKERS

Proton pump inhibitors (PPIs) stand out as effective medications for inhibiting gastric acid secretion; however, they come with certain limitations. Importantly, all the currently available PPIs have similar pharmacological characteristics owing to their similar molecular structure. Notably, (1) PPIs are prodrugs [28,31] and (2) require gastric acid secretion to be converted to the active sulfenamide or sulfenic acid form of the drug to provide their pharmacological effect [27,31,32]. Indeed, (3) a PPI is unstable in an acidic condition and (4) administration of enteric-coated tablets, modified release formulations, or co-administration with an acid-neutralizing agent, such as sodium bicarbonate, is essential to achieve peroral bioavailability [32-34].

Moreover, (5) omeprazole and lansoprazole, the first-generation PPIs, are metabolized by hepatic enzymes including CYP2C19, wherein genetic polymorphisms of CYP2C19 impact the metabolism of some PPIs, (6) thereby they exhibit a slow onset of action and (7) necessitate premeal dosing. On the other hand, (8) esomeprazole and rabeprazole, the second-generation PPIs, are more stable and are not strongly influenced by different CYP2C19 hepatic enzyme activities. However, (9) their plasma half-life is only 2-3 h, and (10) only a part of the

proton pump (enzyme) is in an active acid-secreting state when a PPI is administered, (11) repeated per oral or parenteral administrations of the drug are necessary for adequate and complete inhibition of proton pumps [27,28,34]. Further, (12) following several initial peroral doses, a period of stable acid inhibition is achieved; however, nocturnal acid inhibition is weaker with a once-daily morning dose. Moreover, (13) ~25% of proton pumps are replaced by newly synthesized enzymes within 24 h, and the newly biosynthesized proton pumps after the morning PPI dose will start to secrete gastric acid during the nocturnal period [3,26,27,32]. Owing to this, (14) 3 to 5 days of administration is required to reach their peak acid-inhibitory effects. (15) This delayed effect can be a consideration in cases where prompt acid suppression is crucial. (16) PPIs covalently bind to proton pumps and cause irreversible inhibition of this enzyme activity [3,26,27].

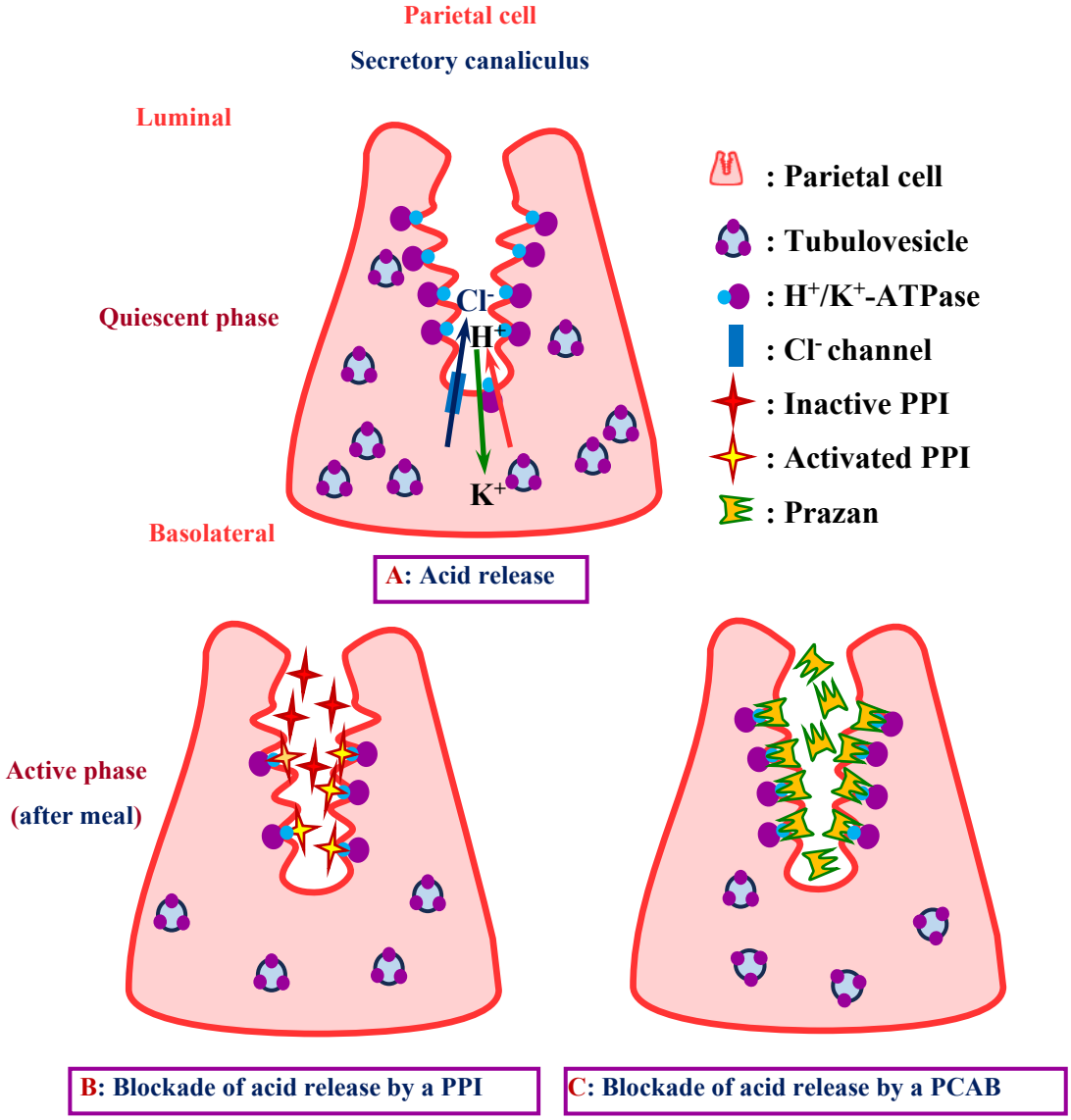

Fig. 1: (A) Physiology of gastric acid release by a parietal cell and mechanism of action of antisecretory drugs, (B) proton pump inhibitors (PPIs), and (C) potassium-competitive acid blockers (PCABs) [22,24,25,30,31].

Additionally, despite their efficacy in reducing acid production, (17) PPIs may show limited resolution of symptoms associated with acid-related diseases [21,28]. Additional challenges include (18) low bioavailability, meaning only a fraction

of the administered dose reaches the systemic circulation, potentially impacting overall effectiveness [28,33,34]. (19) The fast metabolism of PPIs may require frequent dosing to maintain sustained acid suppression. Additionally, (20) concerns about drug interactions and the variable sustainability of acid suppression further complicate their use [3,22,24,27-29,33-39]. Adding to this, several adverse events related and unrelated to acid inhibition have been reported in patients treated with PPIs. Accumulating data reported adverse events chiefly associated with the use of PPIs include pneumonia, gastrointestinal infection, gastric carcinoid tumor, gastric fundic mucosal hypertrophy, changes in gut microbiome, small intestinal bacterial overgrowth, iron deficiency, bone fracture, vitamin B12 deficiency, hypomagnesemia, gastric fundic gland polyps, gastric cancer, colon cancer, spontaneous bacterial peritonitis, hepatic encephalopathy, and drug interaction [3,21,28,29,33,34,38-41].

Apart from this, GERD associated with nocturnal symptoms was improved in 79% of patients with PPI therapy, but in cases of chronic GERD, (21) patients experienced acid reflux during NAB (nocturnal acid breakthrough). To improve the treatment efficacy, an H2RA was combined with a PPI that resulted in a significant decrease in acidity on day 1, however, (22) acidity increased on long-term use due to tolerance to H2RA [42-44]. These unmet needs of acid-related diseases have been continuously highlighted and encouraged to investigate new treatment modalities that lead to the discovery and development of PCABs (Table 1). This class of drugs has a fast onset of action and dose-dependent effect, binds reversibly, and competitively blocks the final step of acid secretion with respect to K^+ binding to the gastric parietal cell H^+/K^+-ATPase [1,36]. The PPIs are generally metabolized by the CYP2C19 genotype, whereas the PCABs effect is not influenced by the CYP2C19 genotype. Owing to these advantages, the use of vonoprazan, the first Prazan as well as the first PCAB, is an evidence-based and well-established therapy which is approved for clinical practice in Japan in 2014 [2-4,18,22,45]. These Prazans or PCABs were not available outside of the US until recently, when the USFDA approved vonoprazan use in 2023 [22]. Intriguingly, PCABs exert their acid-suppressive activity via the H^+/K^+-ATPase of the parietal cell, the ion pump responsible for gastric acid secretion, but they are otherwise distinct from PPIs in terms of physicochemical characteristics, pharmaceutical aspects, pharmacodynamics, particularly, mechanism of action, target site of binding, and not prodrugs in that they do not need metabolic activation in the stomach, pharmacokinetics, mainly absorption, stability in acidic pH, and metabolism (Table 2 and 3) [2-4,24,38]. Therefore, Prazans or PCABs offer a potential alternative to PPIs with a markedly different clinical profile [2-4,18,22,45].

Table 1. Pharmacodynamic comparison of PPIs and PCABs [2-4,16,18,32,45-49]

Proton pump inhibitors (PPIs)	**Potassium competitive acid blockers (PCABs) or PRAZANs**
Need acidic condition for activation of a PPI pro-drug and conversion to the active form, sulphenamide	Direct action on H^+/K^+-ATPase
Binds covalently to H^+/K^+-ATPase	Binds reversibly to the K^+ site of H^+/K^+-ATPase
Irreversible binding to the proton pump	Reversible ionic binding to the proton pump
Optimum therapeutic effect occurs after 3-5 days	Full effect is seen after the first dose
1000-fold higher concentration in a parietal cell acid space than in plasma	100000-fold higher concentration in a parietal cell acid space than in plasma
Affected by genetic polymorphism	Not affected by genetic polymorphism
Unable to inhibit new proton pumps	Able to inhibit new proton pumps
Pharmacodynamic effect is greater during the daytime	Pharmacodynamic effect lasts for both daytime and nocturnal hours

DRUG DEVELOPMENT

During the 1980s, a novel class of antisecretory drugs, known as PCABs, was introduced. These drugs have been undergoing development and trials for several years and are anticipated to potentially replace conventional PPIs that are used to suppress gastric activity. The first drug of PCABs is SCH28080, an imidazopyridine compound developed 36 years ago that showed successive inhibition of gastric acid secretion in animals and humans, but the studies on SCH28080 were discontinued owing to hepatotoxicity. This led to the manoeuvre of discovery and development of several of its derivatives, such as linaprazan (AZD0865), an imidazopyridine derivative, revaprazan (YH-1885), a pyrimidine derivative, vonoprazan, keverprazan, fexuprazan, pyrrole derivatives, and soraprazan, an imidazonaphthyridine derivative [3,17,18,45,50,51]. Linaprazan initially demonstrated comparable efficacy to esomeprazole in addressing esophagitis and providing symptomatic relief for non-erosive reflux disease during phase 1 and phase 2 trials. However, subsequent studies were impeded as linaprazan failed to exhibit superior effectiveness to esomeprazole and unveiled an adverse reaction, hepatotoxicity characterized by reversible elevation of hepatic transaminases [3,14,45,46].

Table 2. Clinical development status of PRAZANs, the potassium-competitive acid blockers (PCABs) [1-4,16,18,20,25,45-49,52-54].

Compound	Chemical Class	Development phase	Company
Compounds whose development has been stopped			
Linaprazan (AZD0865)	Imidazopyridine	Stopped after phase 3	AstraZeneca
CS526 (R105266)	Pyrrolopyridazine	Stopped after phase 1	Sankyo and Ube/Novartis
Soraprazan (BY359)	Imidazonaphthyridine	Stopped after phase 2	Altana
YH-4808	Pyrrolo-pyridine	Stopped after phase 2	Yuhan
Currently available compounds			
Revaprazan (YH1885)	Pyrimidine	Marketed in South Korea and India	Yuhan
Vonoprazan (TAK-438)	Pyrrole	Marketed in Japan, the Philippines, Singapore, Thailand, USA, Argentina, Peru, South Korea, Malaysia, Ecuador, China, Indonesia, Brazil and Mexico	Takeda and Phathom
Tegoprazan (RQ-00000004)	Benzimidazole	South Korea, China, Mongolia, Philippines Phase 3 in Europe/US	Raqualia
Keverprazan	Pyrrole	Marketed in China	Jiangsu Carephar Pharmaceuticals
Fexuprazan (DWP14012)	Pyrrole	South Korea, Philippines	Daewoong
Compounds under active development			
X842 (Linaprazan pro-drug)	Imidazopyridine	Phase 2 in Europe	Cinclus Pharma

On the other hand, revaprazan emerged as the first PRAZAN or the first PCAB approved globally for treating duodenal and gastric ulcers in 2005, marking a significant milestone in South Korea [47,50,55]. Vonoprazan, a modified compound designed for improved safety and efficacy, gained approval as the second drug for managing GERD and other acid-related diseases in Japan in 2015 [56]. Notably, tegaprazan, in randomized controlled trials, exhibited superior efficacy compared to PPI-based triple therapy and was deemed safe for first-line H. pylori eradication

therapy [57]. However, its limitation in overcoming clarithromycin resistance in H. pylori within the Korean population should be acknowledged. Despite this drawback, tegaprazan entered the market in 2018 for the treatment of erosive esophagitis and gastroesophageal reflux [3,22,58-60]. Further research and clinical experience may provide additional insights into its long-term effectiveness and potential solutions to address its limitations.

PHARMACOLOGY OF CURRENTLY AVAILABLE PRAZANs or PCABs

PCABs competitively and reversibly bind to the proton pump at the K^+ site and dissociate when blood K^+ concentration decreases. Originally, Prazans or PCABs are commonly referred to as acid pump antagonists due to their acid-suppressive activity exerted by their inhibitory effect via the H^+/K^+-ATPase of the parietal cell, the ion pump responsible for gastric acid secretion [3,4,18,20,22,45]. Pharmacologically, PCABs differ from PPIs as they are not prodrugs but rather weak bases. In their protonated form, they inhibit the K^+ exchange channel of H^+/K^+-ATPase, the final step in acid secretion. The pKa value is a crucial indicator, with lower values indicating stronger acidity [1,18,46,61]. The overview of the pharmacology of PCABs is summarized in Table 3.

Revaprazan

Globally, revaprazan was the first PRAZAN or PCAB approved for human use in South Korea in 2006, and later in India; however, it is not yet approved in Europe or the United States [25,46]. The pharmacokinetic profile of revaprazan was examined in a double-blind and three-way crossover clinical trial involving 30 healthy male volunteers. The study included daily oral doses of 100, 150, or 200 mg of revaprazan for a period of 7 days. After a single dose on day 1, the concentration of revaprazan in the blood peaked at approximately 1.7-1.8 h, with a gradual decrease thereafter and a half-life ranging from 2.2 to 2.4 h. Higher doses resulted in increased maximum concentration (Cmax) and area under the curve (AUC0-24) of revaprazan [58]. For 100 and 200 mg doses on day 1, Cmax ranged from 196.0 to 402.2 ng/mL, and AUC0-24 ranged from 661.6 to 1452.3 ng per h/mL. There were no significant differences in oral clearance among the groups. On day 7, the concentration and pharmacokinetic characteristics of revaprazan remained similar to those observed on day 1. However, a 17% increase in AUC0-24 and a 5% increase in Cmax were noted with a 100 mg dose. The estimates for AUC0-24 and Cmax were 1.17 and 1.05 for 100 mg, 1.23 and 1.02 for 150 mg, and 1.32 and 1.13 for 200 mg, respectively. The time to reach maximum concentration (Tmax) and oral clearance were not affected by the dose. There was a slight increase in half-life observed on day 7 in all groups [16,25,46,57,58,61]. In the single-dose study, YH1885 (revaprazan) caused an increase in intragastric pH, especially in the higher dose groups, while the placebo group showed minimal changes. The pH-time profiles in the multiple-dose study were similar to those in the single-dose study, with day 7 being comparable to day 1. The daily mean pH and percentage of time at pH >4 varied significantly [46,57,69].

Table 3: The overview of the pharmacology of PRAZANs or PCABs [2-4,12,16,18,20,25,45,46,53,54, 57,60-68].

PRAZAN or PCAB	Pharmacokinetics	Side effects/ADRs	Caution/Warnings
Revaprazan Dose: 200 mg, once daily	Administration: orally, usually 30 min before food Absorption: Peak plasma concentrations are reached in	Diarrhea, nausea, abdominal pain, constipation, flatulence, headache,	Reduce absorption of ketoconazole Shows synergistic antifungal activity with triazoles, such as

	about 1.7 to 1.8 h BA: Inherently low due to poor water solubility, but various advanced formulations like nanosuspensions, self-nanoemulsifying systems (SNEDDS), and solid supersaturable micelles (SSuM) significantly enhance its absorption $t_{1/2}$: 2.2 to 2.4 h Metabolism: Liver Duration of action: 19.7 h Excretion: Kidney, as metabolites	rhinorrhea	posaconazole In patients with hepatic and renal impairment During pregnancy and breastfeeding
Vonoprazan Dose: 20 mg, once daily	Administration: Oral BA: Not clinically affected by food Metabolism: Liver, by cytochrome P450 (3A4, 2B6, 2C19, 2D6) $t_{1/2}$: 7.7 h Duration of action: > 24 h Excretion: Kidney, as metabolites	Constipation, diarrhea, stomach pain, headache, nausea, rash, edema	Reduces levels of clopidogrel and amlodipine Long-term use may lead to vitamin B12 deficiency, hypomagnesemia, fundic gland polyps, *Clostridioides difficile* infection, and increased risk of fractures in the hip, wrist, or spine
Tegoprazan Dose: 50 mg, once daily	Administration: Oral BA: Not clinically affected by food intake $t_{1/2}$: 3.7 to 5.4 h Metabolism: Liver, CYP3A4, but not affected by CYP2C19 Duration of action: 24 h Excretion: Kidney and feces, as metabolites	Headache, diarrhea, nausea, vomiting, abdominal pain or discomfort, dysgeusia	Strong CYP3A4 inhibitors like clarithromycin increase tegoprazan levels (up to 2.5-4.5-fold), while inducers like rifampicin decrease May reduce the absorption of drugs requiring low gastric pH (e.g., ketoconazole, atazanavir, nelfinavir, rilpivirine, iron salts) During pregnancy and breastfeeding
Fexuprazan Dose: 40 mg, once daily	Administration: Oral BA: Not clinically affected by food intake $t_{1/2}$: 7.5 to 9.7 h Metabolism: Liver, CYP3A4, but not affected by CYP2C19 Duration of action: 24 h Excretion: Mainly through feces (approx. 80%) and bile, with minimal renal excretion (less than 2%)	Indigestion, diarrhea, nausea, abdominal discomfort, stomach inflammation, erythema (skin redness), headache, back pain	May reduce the absorption of drugs requiring low gastric pH (e.g., ketoconazole, atazanavir, nelfinavir, rilpivirine, iron salts) During pregnancy and breastfeeding *Clostridioides difficile* infection, increased risk of fractures in the hip, wrist, or spine
Keverprazan Dose: 20 mg, twice daily	Administration: Oral BA: Not clinically affected by food intake $t_{1/2}$: 7.5 to 9.7 h Metabolism: Liver, CYP3A4, but not affected by CYP2C19 Duration of action: 24 h Excretion: Mainly through feces (approx. 80%) and bile, with minimal renal excretion (less than 2%)	Dysgeusia, nausea, abdominal pain, hyperuricemia, hyperlipidemia, diarrhea	Strong CYP3A4 inhibitors like clarithromycin increase keverprazan levels Prolonged use may increase the risk of bone fractures, specifically in the hip, wrist, and spine, in individuals already at risk for osteoporosis
Zastaprazan Dose: 20	Administration: Oral BA: Can be taken with or	Diarrhea, constipation, nausea, abdominal	May reduce plasma levels of drugs, such as atazanavir,

mg, once daily	without food, as food do not have a clinically significant impact on its overall effectiveness $t_{1/2}$: 7.0 to 10.0 h Metabolism: Liver, primarily metabolized by CYP3A4 and CYP3A5. CYP3A4, but not affected by CYP2C19, and its genetic variants Duration of action: 24 h Excretion: Mainly through feces (approx. 80%) and bile, with minimal renal excretion (less than 2%)	pain, or flatulence, headaches	nelfinavir, ketoconazole, and itraconazole. Potentially interferes with the absorption of iron salts, erlotinib, dasatinib, and digoxin

Vonoprazan

It is a well-recognized and first-in-class PRAZAN or PCAB approved as Vonoprazan fumarate, also known as Takecab, in Japan in 2015, in Russia in 2021, and recently in the United States in 2023 under the brand name Voquezna [2,70,71]. It is used alone for the treatment of gastroduodenal ulcers, drug-induced peptic ulcers, and reflux esophagitis, and in combination with antibiotics for the eradication of H. pylori [2,3]. It has satisfactory effects and a good safety profile in clinical studies of gastric and duodenal ulcers, reflux esophagitis, NSAID-associated ulcers and H. pylori eradication [53,59,63]. Vonoprazan has a high P^{Ka} (9.3), so it is protonated easily to show its effect. It has high efficacy because the protonated forms do not cross the cell membrane; therefore, it gets concentrated in the acid-secreting canaliculi of parietal cells [36,46]. It is rapidly absorbed and reaches peak plasma concentration within 1.5-2.0 h after oral administration. Food has minimal impact on its absorption. The bioavailability in humans is still unknown. Vonoprazan has a high plasma protein binding of 80% in healthy individuals and extensively distributes into tissues with a large apparent volume of distribution. Due to its acid-resistant properties, it concentrates in the gastric parietal cells and provides long-lasting acid suppression for over 24 h after a 20 mg dose. The drug has an average terminal half-life of approximately 7.7 h in healthy adults. Vonoprazan is mainly metabolized by enzymes such as CYP3A4, CYP2B6, CYP2D6, and SULT2A1. Metabolism is extensive, as shown by a mass balance study where a significant portion of the administered dose was recovered as metabolites in urine [70-72]. In a subsequent clinical study, the plasma TAK-438 (vonoprazan) concentration-time profiles showed rapid absorption, with a median Tmax of ≤2 h under fasting conditions. The elimination half-life ($T_{½}$) ranged from 5.7 h on Day 1 to 7.0 h on Day 7 in the Japanese population, and from 6.1 h on Day 1 to 8.8 h on Day 7 in the UK population. The $T_{½}$ and T_{max} for TAK-438 were independent of the dose. The pharmacokinetic parameters were similar for each dose on Days 1 and 7. On Day 7, TAK-438 was found in low amounts in the urine after all doses. In Japan, 4.0-6.3% of the dose was excreted, while in the UK it was 4.0-4.4% [46,72,73]. Further, vonoprazan 20 mg, a single dose, can increase gastric PH within 4 h. This rapid action treats acid-related disease in a short duration. The PH above 4 at nighttime after administration of vonoprazan is higher than rabeprazole or PPIs. During day time, the mean percentage of time of vonoprazan was 85.3% and 100.0% of PH above 5 after administration of multiple doses of 40 mg vonoprazan [4,53,71,72].

Tegoprazan

Third PRAZAN or PCAB, which was developed by CJ Healthcare and first approved and launched in South Korea in

2019 for the treatment of GERD [3]. In a study on tegoprazan, the drug had shown a linear pharmacokinetic profile. This means that the drug levels in the body increased proportionally with the dose. Additionally, tegoprazan effectively reduced acid secretion in a dose-dependent manner. The study also estimated that the bioavailability of the drug was between 86% and 100%, and most of the drug was eliminated through the stool, with only a small amount (3-6%) being excreted in the urine [46,53,54,64,74]. As the dose of tegoprazan increased, the plasma drug concentrations also increased in a dose-dependent manner. The average maximum plasma concentration (Cmax) values were observed as 383, 970, and 1,859 ng/mL for the 50, 100, and 200 mg tegoprazan groups, respectively. Additionally, the area under the concentration-time curve (AUC last) values were 2,469, 5,385, and 11,512 ng.h/mL for the same groups [54,64,74]. The time it took to reach the maximum plasma concentration ranged between 1.42 and 1.84 h for tegoprazan. Tegoprazan showed a faster onset of pH increase compared to dexlansoprazole. All tegoprazan dose groups reached a mean pH ≥4 within 2 h, while the dexlansoprazole 60 mg group took 7 h to reach the same pH level. This indicates that tegoprazan is more effective in controlling nocturnal acid breakthrough [46,54,64].

Fexuprazan

It is the fourth PRAZAN or PCAB, also known as abeprazan, was approved in South Korea for the treatment of erosive esophagitis in 2021, subsequently in Mexico, Philippines, Chile, and Ecuador, and was recently approved in India in April 2025 [3,65,75] In a Phase 1 clinical study, fexuprazan showed fast absorption, around 1.75-3.5 h and a long elimination half-life (about 9 h). It started inhibiting gastric acid secretion within 2 h, which was faster than esomeprazole. The effects of fexuprazans were also maintained overnight, with intragastric pH above 4 for a significant amount of time [65,75-77]. In a phase 3 clinical trial, fexuprazan 40 mg was non-inferior to esomeprazole 40 mg regarding the healing rate at week 8. Both treatments showed similar erosive esophagitis healing rate at week 4, in addition to symptom responses and quality of life assessments. Furthermore, both treatments did not significantly differ in drug-related side effects and serum gastrin levels at weeks 4 and 8 [78].

Keverprazan

It is the fifth PRAZAN or PCAB named as H008 during the clinical development and was first approved in China in 2023 for reflux esophagitis and duodenal ulcer [66,79]. It provides significant, dose-dependent inhibition of gastric acidity. At a 20 mg dose, it reaches a plateau in efficacy, maintaining an intragastric pH >5 for over 84% of a 24 h period on day 1 and nearly 100% after 7 days of treatment [45,46,66,79]. In a phase 3 clinical study, keverprazan 20 mg and esomeprazole 20 mg showed similar H. pylori eradication rates, 87.8% and 82.52%, respectively, with keverprazan being superior to esomeprazole in terms of eradication rate in the per-protocol set. The eradication rates for patients resistant or non-resistant to clarithromycin were both higher with keverprazan than the esomeprazole (83.45% vs. 76.98% for clarithromycin-resistance; 92.31% vs. 88.16% for clarithromycin-non-resistance). Indeed, the incidence of adverse events was similar in both treatments (76.31% vs. 77.62%) [32,66,79].

Zastaprazan

The sixth PRZAN or PCAB, known as JP-1366 during the clinical development, was first approved recently for use in South Korea in April 2024 for the treatment of erosive GERD [67]. This drug induced dose-dependent suppression of gastric acid secretion, with suppression of 85.19% (20 mg) and 91.84% (40 mg) reported, and this effect was almost similar to or greater than that with esomeprazole 40 mg (72.06%). It

was rapidly absorbed within 2 h and eliminated with a half-life of 6-10 h. Pharmacogenomic analysis showed no genetic variant of drug-metabolizing enzymes, including CYP2C19 or drug transporters, associated with the exposure of zastaprazan. It was safe, well-tolerated, and effective in overall assessments similar to the previous PCABs [3,67,68,81]. An 8-week therapy of zastaprazan 20 mg is noninferior to esomeprazole 40 mg in subjects with predominantly low-grade EE. The healing rate at week 4 appears to be higher for zastaprazan than esomeprazole [3,67,68]. It is undergoing phase 3 clinical trials for gastric ulcers, peptic ulcers, and the prevention of NSAID-induced ulcers and acid release-related diseases.

THERAPEUTIC INDICATIONS

(1) PRAZANs or PCABs for erosive esophagitis:

In a phase 2 clinical trial conducted in Japan, they studied subjects with erosive esophagitis. These subjects were given different doses of vonoprazan or lansoprazole for 8 weeks. The results showed that all doses of vonoprazan were just as effective as lansoprazole in healing the esophageal mucosa. Vonoprazan also had a similar incidence of adverse events and was well-tolerated, even at the highest dose of 40 mg. In a subsequent phase 3 trial, they further confirmed that vonoprazan 20 mg was just as good as lansoprazole 30 mg in healing erosive esophagitis [2-4,20,25,45,46].

(2) PRAZANs or PCABs for peptic ulcer disease:

Randomized control trials in Japan have evaluated vonoprazan and lansoprazole for gastric ulcer, duodenal ulcer and achieved success in 93.5% and 93.8% of patients involved, respectively and approved for the treatment of gastric ulcers and duodenal ulcers. Similar results were achieved by tegoprazan 50 mg or 100 mg, with a healing rate of 95% for tegoprazan 50 mg and 100 mg [2-4,20,25,32,45,46]. The first PCAB that hit the market, YH1885 or revaprazan, is currently available in South Korea and India. It has shown similar healing rates for duodenal and gastric ulcers compared to omeprazole [3,48,57].

(3) PRAZANs or PCABs for Secondary prevention of low-dose aspirin or NSAID-induced gastric mucosal damage:

Using NSAIDs and having an H. pylori infection can both independently and together increase the risk of gastric and duodenal ulcers and bleeding. The higher the pH in the stomach, the lower the chance of NSAID-related upper GI injury. In studies that compared vonoprazan, a PCAB, to lansoprazole, a PPI, vonoprazan was shown to effectively prevent ulcer recurrence during long-term NSAID therapy, with a low proportion of patients experiencing recurrent ulcers [2-4,20,22,25,32,45,46].

(4) PRAZANs or PCABs for esophagitis:

The study on vonoprazan for PPI-resistant reflux esophagitis showed that 87.5% of patients experienced healing with a 20 mg dose. The frequency of symptoms related to gastroesophageal reflux disease significantly decreased within the first 28 days of starting vonoprazan. In Japan, they approved 10 mg of vonoprazan for maintenance therapy, and if needed, the dose can be increased to 20 mg [2-4,20,25,32,45,46].

(5) PRAZANs or PCABs for GERD:

While proton pump inhibitors (PPIs) remain the first-choice treatment for GERD patients, various studies, including one conducted in 2019 with Korean patients, suggest that there is no significant difference in short-term symptom management among different PPIs. The study revealed that tegoprazan at both 50 mg and 100 mg dosages exhibited comparable efficacy to fexuprazan 40 mg in terms of healing rates for confirmed erosive esophagitis at week 8, with all rates reaching 98.9%. Furthermore, patients tolerated tegoprazan well, indicating its favorable safety profile. Another study focusing on individuals with moderate to

severe heartburn found that fexuprazan provided superior relief of symptoms persisting throughout the night. The medication demonstrated good tolerability, with similar side effect rates across all treatment groups [2-4,20,25,32,45,46].

(6) PRAZANs or PCABs for H. pylori eradication:

The global challenge of declining H. pylori eradication due to rising antibiotic resistance underscores the need for effective management strategies. H. pylori infection, a modifiable risk factor for gastric cancer and a common cause of PUD and upper gastrointestinal bleeding, presents challenges in treatment. While a 14-day course of bismuth-based quadruple therapy is recommended as a reliable first-line therapy, its limitations include complexity and limited availability of generic tetracycline. Concomitant non-bismuth quadruple therapy is an alternative but may lead to poor antibiotic stewardship. The recent approval of omeprazole, rifabutin, and amoxicillin combination regimen offers a potential impact on management, particularly after the US-based clinical trial results [2-4,20,24,25,31,32,45,46].

Antibiotic resistance testing, where available, is recommended after eradication failure with two regimens. Post-treatment testing for confirmation using various methods is crucial. The incorporation of vonoprazan or other PCABs into eradication regimens is of interest, especially with promising results from studies in Japan and other Asian countries [4]. Regional resistance and susceptibility data, along with patient-specific information, should guide empiric eradication therapy in the absence of pre-treatment susceptibility testing. Simplification of treatment regimens and the emergence of combination products aim to improve patient compliance and ultimately enhance eradication rates. Effective management involves appropriate diagnostic testing, avoiding ineffective regimens, and routine confirmation of eradication. vonoprazan demonstrates significant promise as a robust alternative to proton pump inhibitors (PPIs) in H. pylori eradication [46,52,53]. Numerous studies, both randomized controlled trials (RCTs) and non-RCTs, consistently show that vonoprazan-based triple therapy is more efficacious than the standard PPI-based regimen in the first-line treatment of H. pylori. In third-line eradication regimens, combining PPI or vonoprazan with amoxicillin and sitafloxacin yields better results. Studies demonstrate that vonoprazan-based regimens outperform PPI-based ones, particularly in cases of sitafloxacin-resistant H. pylori [2-4,20,24,25,31,32,45,46]. Bismuth-based quadruple therapies pose challenges due to higher pill burden and complex dosing schedules. In contrast, PCAB-based dual therapy, especially with vonoprazan, provides a simplified yet effective option, especially considering evolving antibiotic resistance [2-4,24,32,45,46,66,80].

CONCLUSION

PCABs, also known as PRAZANs, address the limitations of conventional and widely used acid suppression drugs, such as PPIs. PCABs offer rapid onset of action, dose-dependent effects, and reversible binding to the H^+/K^+-ATPase enzyme. They provide efficient acid suppression with fewer drug interactions and are not influenced by genetic polymorphisms. Drug utilization and drug evaluation studies with continuous surveillance of prescription patterns and trends of PCABs, emphasizing their effects on special populations, organ-compromised patients, and patients at risk of osteoporosis, are active. Currently, revaprazan, vonoprazan, tegoprazan, fexuprazan, keverprazan, and zastaprazan are the approved PCABs for clinical use based on the evidence-based research that ensured promising safety and efficacy profiles, making them valuable alternatives for treating acid-related diseases, including PUDs, such as H. pylori-induced ulcers, NSAID-induced ulcers, as well as erosive esophagitis, dyspepsia, and GERD.

Declaration by Authors

Ethical Approval: Not required

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

Authors' Contributions: All authors contributed to the review design and plan. All the authors contributed to the data search, collection, extraction, and quality assessment for this review. SE and HP created the figures, tables, and improved the contents for the manuscript. All authors wrote the text, reviewed and edited the manuscript, and made substantial contributions to discussions of the content.

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How to cite this article: Sowmya Errabaka, Haritha Pasupulati, Satyanarayana SV Padi. PRAZANs or PCABs, potassium competitive acid blockers: a new therapeutic class in acid-related diseases. *Int J Health Sci Res.* 2026; 16(2):109-126. DOI: *10.52403/ijhsr.20260215*

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