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Review Article

Vonoprazan: A Revolutionary Potassium-Competitive Acid Blocker in Gastroenterology

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ABSTRACT

Vonoprazan, a novel potassium-competitive acid blocker (P-CAB) that is emerging as a new alternative among conventional proton pump inhibitors (PPIs) for treating acid-related gastrointestinal disorders. Review vonoprazan's pharmacological details, its excellent ability to suppress acid secretion, and such clinical aspects as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Helicobacter pylori (H. pylori)-associated conditions. The summaries of comparative studies are worth noting, showing the rapid onset and duration of acid suppression achieved with vonoprazan, as well as the increased efficacy in the treatment of PPI-resistant patients. Vonoprazan is fast gaining interest for its action on preventing ulcers caused by NSAIDs and erosive esophagitis. Vonoprazan has favorable safety but recent studies are also evaluating its long-term effects and adverse event risks. The present review summarizes the current evidence to evaluate vonoprazan's therapeutic potential, casting it as a groundbreaking agent in gastroenterology, probably as first-line treatment for acid-related diseases in the next decade.

INTRODUCTION

Various acid disorders like gastroesophageal reflux disease (GERD), Helicobacter pylori

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infection, and peptic ulcer disease (PUD) have been common benign isolations requiring active acid suppression therapy. The major condition that acid reflux represents is GERD-associated development of erosive esophagitis (EE), Barrett esophagus, and the increased risk for cancer of the esophagus.[1,2] H. pylori is attributed to the majority of peptic ulcers and gastric neoplasms, given that eradication eventually reduces the incidence of reoccurrence of ulcers. However, an increase in antibiotic resistance makes standard triple and quadruple therapies consisting of proton pump inhibitors (PPIs), antibiotics, and bismuth preparations lose their effectiveness.[3,4] Peptic ulcers are commonly associated with NSAIDs or with an H. pylori infection and may be complicated by gastrointestinal bleeding or perforation requiring acid suppression for both treatment and prevention.[5,6]

Vonoprazan is the novel potassium-competitive acid blocker. It emerged as a new candidate for PPIs. Unlike PPIs, which have to be solubilized in an active form by an acidic environment and need days for exerting the full effect, it directly inhibits gastric parietal cell H^+/K^+-ATPase enzyme; thus, rapid, strong, and prolonged acid secretion suppression is possible. In less than four hours, it achieves almost complete inhibition of gastric acid, compared with three to five days with PPIs.[7,8] Therefore, it is far more favourable in pharmacokinetic features. Healing rates for GERD with vonoprazan have been proven to be much better than those with PPIs, especially in erosive esophagitis patients.[2,9] Even studies suggested vonoprazan-based regimens had better outcomes in H. pylori eradication compared to the standard PPI-based regimens.[3,4] It is known to prevent NSAID-induced ulcers with decreased recurrence in patients on long-term NSAID usage.[5,6] Moreover, vonoprazan was highly effective in GERD patients who were refractory to PPI. Such patients usually do not respond to standard therapy.[10,11]

This review, therefore, seeks to elucidate the mechanism of action, clinical efficacy, and safety profile of the medicine from current available evidence as well as to explore its possibility of being a first-line therapy for acid-related diseases in the near future.

Mechanism Of Action

It is a potassium-competitive acid blocker that directly impairs the enzyme involved in gastric acid secretion within the parietal cells, i.e., H+/K+-ATPase. In contrast to the proton pump inhibitors (PPIs), which should be energized using the acidic environment and exhibit multiple days' time to become fully effective, vonoprazan quickly and reversibly inhibits acid secretion by competing with potassium ions at the proton pump.[7,8,12] The fast and complete action of this inhibition yields an acid suppression comparable to PPIs with four hours after administration and results in three to five days for maximum effect.[13,15,34] Additionally, vonoprazan gives a much stronger and longer-lasting suppression of acid and, therefore, reduces nocturnal acid breakthrough, which is a common side effect with the PPIs.[9,16]

Studies indicate that the mechanism of action of vonoprazan renders it particularly useful for H. pylori eradication, gastroesophageal reflux disease (GERD), and peptic ulcer disease (PUD), with more consistent pH control, enhancing antibiotic effectiveness in H. pylori therapy.[3,4,17] Besides, it can maintain high gastric pH levels, denying chances for NSAID-induced ulcers; thus, an ideal for long-term NSAID users.[5,6]

Pharmacokinetics And Pharmacodynamics

Vonoprazan, conversely, has clearly surpassed the PPIs with respect to bioavailability and stability in acidic conditions since they degrade quite rapidly under low pH conditions. It absorbs irrespective of the time of food intake and does not depend on gastric acid for its activation, making it more efficient for all demographics.[1,7,18] Due to its greater binding affinity with the proton pump, vonoprazan provides prolonged acid suppression using a single daily dose, managing to keep the intragastric pH (>4) above count for more than 24 h, while this can allow for intermittent acid secretion with PPIs.[11,12,19] Vonoprazan pharmacokinetics show it has a longer plasma half-life, which allows for even more consistent acid control when doses are missed.[9,10] It's primarily a valuable property for PPI-recalcitrant GERDs, which require more robust and enduring acid suppression[2,11] Furthermore, the strong acid suppression it induces renders it more effective at increasing the success of H. pylori eradication regimens, most notably in dual therapy with amoxicillin.[20,21,22]

Vonoprazan therefore has rapid onset as well as prolonged acid suppression and better stability making it a stronger, more reliable alternative to PPIs in managing acid-related disorders.

Gerd Management

Vonoprazan has shown superior efficacy in the treatment of gastroesophageal reflux disease (GERD), especially in the case of erosive esophagitis (EE) and proton-pump-inhibitor (PPI)-resistant cases. Several randomized clinical trials and meta-analyses have shown that vonoprazan achieves higher healing rates with faster symptom relief than PPIs ever could.[9,13,16] In contrast to standard PPI regimens, vonoprazan produced rates for healing EE of more than 90% by weeks 4 to 8.[9,2] Additionally, vonoprazan has also been shown to control nocturnal acid breakthrough, which is recurrent in those patients suffering from GERD who are on PPI therapy, enabling a 24-hour continuous control of acid suppression.[10,11] Vonoprazan especially shines in PPI-refractory cases of GERD, namely when the patients do not respond to standard therapy. Long-term studies have demonstrated that patients with persistent GERD symptoms on PPIs would undergo substantial symptom amelioration on switching to vonoprazan.[16,23,24] Vonoprazan-based therapy also promotes better patient compliance because of its early effect and lower meal dependency.[8,18]

Helicobacter Pylori Eradication

In patients with antibiotic-resistant cohort, Vonoprazan-based therapy has been proven to show more superior eradication rates for H. pylori infection. Multiple clinical studies and systematic reviews indicate that triple therapies using vonoprazan have eradication rates much higher than those of PPI-based regimens, being over 90% even in patients whose H. pylori strains are resistant to clarithromycin.[3,4,20,21]

Arguments for comparative effectiveness of vonoprazan over other drugs in treatment of H. pylori infection include the fact that it is very potent and sustained acid suppression, which can keep gastric pH over 4 for more than 24 hours, thus affecting amoxicillin and clarithromycin efficacy.[17,22,25] Studies reveal that the capacity of dual therapy eradication using vonoprazan plus amoxicillin is similar to standard triple therapy; thus, it provides excellent option for these patients who can’t tolerate clarithromycin or metronidazole.[20,21]

Vonoprazan-based regimens also cut down the possibility of treatment failure and, therefore, reduce the emergence of antibiotic resistance,

making them optimal candidate therapy high areas of PPI resistance.[17,26]

Peptic Ulcer Disease

Vonoprazan has been shown to be very effective in treating and preventing peptic ulcer disease (PUD), particularly with regard to NSAID-induced ulcers and repeat gastric bleeds. Vonoprazan has been shown in clinical studies to be superior to PPIs for preventing NSAID-induced ulcers, as it provides a stronger and longer acid suppression, reducing the recurrence of ulcers.[5,6] It has been demonstrated that, in a randomized controlled trial, vonoprazan significantly decreases ulcer recurrence risk in NSAID therapy patients within 12 months. It does so with non-crossing of the threshold for clinically favoured outcomes with lansoprazole, albeit at a faster healing rate.[5,6] Vonoprazan-based therapies have also been shown to be effective in the prevention of gastric bleeding and recurrent peptic ulcer disease in special populations, especially among patients undergoing chronic NSAID therapy.[2,5,6] Moreover, the ability of vonoprazan to elevate gastric pH favours coagulation and mucosal healing and prevents rebleeding.[9,12]

In other words, the wonderful therapeutic promise vonoprazan holds for GERD, H. pylori eradication, and the treatment of PUD makes it a strong contender for treatment of all acid-related disorders as a first-line therapeutic agent.

Adverse Effects

More or less acceptable among patients, vonoprazan's side-effect profile seems comparable, if not; better than that of PPIs. Among the most common adverse events are mild to moderate diarrhoea, constipation, nausea, abdominal pain, and dyspeptic symptoms.[12,19,29] Meta-analyses concluded that the adverse event rates with vonoprazan were comparable to those found with PPIs, but other reports stated gastrointestinal adverse events to be less.[18,30] However, vonoprazan is suggested to have a higher incidence of hypergastrinemia than PPIs because of its far better acid-inhibiting effects, which last significantly longer.[4,7,8] Hypergastrinemia is, in general, benign but it may induce some alteration over time in the gastric mucosa.[21,31]

Long – Term Safety

Vonoprazan, when used in the long term, raises concerns about hypergastrinemia, infection risks, and changes to the microbiome. The long-term antisecretory treatment leads to the possible hypersecretion of gastrin, which may in turn lead to gastric mucosal hyperplasia and hyperplasia of ECL cells, much like it operates in chronic PPI therapies.[4,7,8] However, vonoprazan poses no appreciable suspicion for causing neoplasia in the stomach in humans.[19,33]

Similar to PPI agents, vonoprazan can increase the risk for GI infections by prolonged alteration of gastric pH.[21,29,31] Such infections include Clostridium difficile and small intestinal bacterial overgrowth (SIBO). Patients receiving long-term vonoprazan therapies have experienced microbiome changes, but their clinical significance remains uncertain.[8,26]

Drug Interactions

Compared to PPIs, vonoprazan has fewer interactions because it undergoes less metabolism through cytochrome P450 enzymes (CYP2C19 and CYP3A4).[4,7,12] In contrast, PPIs are very large substrates of CYP2C19. This leads to inconsistent metabolism of this drug and decreased efficacy for these patients, that is, for CYP2C19 rapid-metabolizers.[8,19]

More evidence is hinted that vonoprazan would have no further major alteration in bioavailability of antiplatelets including clopidogrel thereby making it a better option because they are under double antiplatelet therapy.[24,31] Vonoprazan otherwise greatly interferes much less in the course of drug absorption as compared with PPIs that occasionally tend to reduce some chemotherapeutic and antifungal agents' activity.[8,18]

In this regard, vonoprazan is noted to have a remarkably favourable safety profile for the equal or less adverse reactions compared to PPIs, a lower occurrence of drug interactions, and tolerable potential long-term adverse effects.

Comparison With Proton Pump Inhibitors [PPIs]

Vonoprazan has revealed a multitude of advantages with respect to its effectiveness against proton pump inhibitors (PPIs) regarding the onset of action, the strength of acid suppression, clinical efficacy, and drug interactions.

Faster onset and superior efficacy in acid suppression

There is speed and strength difference in acid suppression between vonoprazan and PPIs. Being a potassium-competitive acid blocker (P-CAB), it directly inhibits the H^+/K^+-ATPase in gastric parietal cells without activation in acidic conditions, this differs from PPIs.[7,8] With a clearly close-to-complete acid suppression within 4 hours, vonoprazan contrasts with standard PPIs that take three to five days for full effect.[13,15,34]

By maintaining these gastric pH levels above 4 for more than 24 hours, vonoprazan helps, whereas due to their shorter half-lives, PPIs allow for intermittent acid secretion.[8,22]. This strong acid suppression will favour patients showing nocturnal acid breakthrough and GERD resistant to PPI treatment.[10,11]

Improved outcomes in GERD and H. pylori eradication

Several clinical trials and meta-analyses have demonstrated that vonoprazan achieves better healing in patients with GERD, especially in those with erosive esophagitis (EE). In grievous cases of EE, therapies with vonoprazan have also surpassed that of PPIs often achieving greater mucosal healing within 4-8 weeks.[2,9,16] Furthermore, it is shown to give a better control of symptoms as well as healing rates in GERD cases, that do not respond to PPI, thus, making it a drug of choice for those suffering from chronic reflux.[11,23,24]

Vonoprazan-based triple therapy eradicates H. pylori much more readily than standard PPI-therapy regimens in patients, especially in patients with clarithromycin-resistant H. pylori stains.[3,4,20,21]. This is because vonoprazan fairly keeps a sufficiently high gastric pH, which is favourable for the effectiveness of the antibiotic.[17,22,25] According to several studies, dual therapy with vonoprazan and amoxicillin results in successful eradication similar to traditional triple therapy, which would be a prospective alternative in cases of suspicion of intolerance to clarithromycin or metronidazole.[20,21]

Reduced food and drug interaction risks

Vonoprazan has fewer interactions with foods and drugs compared to PPIs due to its stability in acidic environments and non-dependence on cytochrome P450 (CYP) metabolism. PPIs are subjected to hepatic metabolism by CYP2C19 and CYP3A4, further leading to their highly variable drug concentrations and consequently, poor response in

rapid metabolizers.[8,19] Vonoprazan, on the other hand, is little affected by any polymorphisms into CYP2C19 and this would ensure activity for the drug among different populations of patients.[4,7,12]

In addition, vonoprazan does not interfere with activation of clopidogrel such that it would be theoretically considered a safer drug for those on dual antiplatelet therapy.[24,31] PPIs sometimes interfere with the absorption of specific antifungals, chemotherapeutic agents, and calcium-based supplements whereas vonoprazan showed a minor effect on the bioavailability of co-administered medicines.[8,18]

Research Gaps and Future Directions

Even if vonoprazan has outshone PPIs in the treatment of GERD, eradication of H. pylori, and peptic ulcer disease, there are research gaps that remain. First, long-term safety data are still limited, especially with regards to chronic hypergastrinemic effects that may influences gastric mucosa modifications, enterochromaffin-like (ECL) cell hyperplasia, and possible neoplastic risks.[4,7,8] While there is no direct evidence connecting vonoprazan to gastric malignancies, prolonged exposure requires assessment via long-term observational studies effectively to prove the safety of extended use.[19,33]

Another area that needs to be researched is the infrequent yet important adverse events that include possibilities of infections such as Clostridium difficile and small intestinal bacterial overgrowth (SIBO) due to prolonged acid suppression.[23,29,31] Changes in the microbiome related to the vonoprazan treatment have not yet been well elucidated and hence studies for the evaluation of possible long-term ramifications are warranted.[8,26] It is still open-ended whether vonoprazan could be utilized in rare acid hypersecretory diseases such as Zollinger-Ellison syndrome (ZES). Given such potent inhibition of acids and a long duration of action, it's certainly of benefit in the treatment of cases with aggressive gastric acid hypersecretion, since usage of PPIs may not do justice. Clinical trials, though, need to confirm this.[7,12]

CONCLUSION

Vonoprazan has an edge over PPI in the rapid onset of action in acid suppression, profound acid inhibition, and clinical end results. Its usefulness above and beyond PPIs in such indications as GERD therapy, H. pylori eradication, and peptic ulcer prevention, coupled with a minimal risk of drug interaction, makes it an attractive alternative to traditional PPI therapy.[13,15,34] Furthermore, it being effective in the treatment of PPI-resistant GERD and clarithromycin-resistant H. pylori infection would suggest its capability of being a first-line agent in treating acid-related disorders.[3,4,20,21]

Nevertheless, long-term studies still need to be performed to assess safety and for potential new therapeutic applications such as Zollinger-Ellison syndrome and other acid hypersecretory disorders. If all goes well, vonoprazan may very well become a game-changer in the management of acid-related diseases, impressively balancing safety with efficacy for patients needing maintenance acid suppression.

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