EUROPEAN ACADEMIC RESEARCH
Vol. IV, Issue 12/ March 2017

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

A fruitful Discovery of proton pump inhibitors and its future

AHMAD MUHAMMAD MEHBOOB
V. VIKASH
LUO HESHENG[1]
Department of Gastroenterology
Remnin Hospital of Wuhan University
Wuhan, Hubei, P.R. China

Abstract:

Acid related diseases like erosive eosophagitis, GERD and H.Pylori resistance are major future health-care concerns. In the past 50 years despite the dramatic success of pharmacological acid suppression, challenges remains in treatment and management of ARDs. The discovery of histamine receptors, H2RBs, antacids, many other antisecretory drugs and later the PPIs played a memorable role in treating ARDs. PPIs still play and will continue to play a major role in treating hypersecretory states. But some ARDs needs complete inhibition of acid secretion as known to all, PPIs cannot completely inhibit acid secretion. Several new drugs are currently being investigated to provide significant advance over current treatments. PCABs (novoprazan) which are already approved in some countries are among new drugs that promise complete inhibition of acid secretion, safe and well tolerated compared to PPIs. Clinicians will continue to rely on PPIs as first line therapy for ARDs. Taking all the above considerations into account there is room for improvement in treating ARDs, to obtain ideal PCABs to overcome the limitations of PPIs. In this review we compared the efficacy of a PCAB (Vonoprazan) to (Lansoprazole) a well-known PPI. The results proved that Vonoprazan a potassium competitive acid blocker is non-inferior to Lansoprazole in efficacy but safe and well tolerated drug in treating

[1] Corresponding author e-mail: xhnk@163.com.renmin

GERD, healing erosive eosophagitis and eradicating H.Pylori infection.

Key words: proton pump inhibitors, erosive eosophagitis, GERD, H.Pylori resistance

INTRODUCTION

The story begins with the discovery of gastrin by John Edkins (Scarpignato et al. 2006). Gastric acid is important for the sterilization of food and water and for digestion. Parietal cell is the only target that involves hormonal, neuronal and endocrine pathways for secreting concentrated HCL in to the gastric lumen. The realization that ulcer occurs in the presence of acid by (Schwartz, 1900) lead to the dictum of "No acid no ulcer" (Inatomi et al. 2016). In 1972 the discovery of histamine receptors and later the H2-receptor blockers changed the practice of gastroenterology. Gastric acid secretion was inhibited effectively and ulcers could be healed to an extent which was not seen before. They were reliable for the time being and helped patients with ulcer related conditions but were not good enough to heal Patients completely especially patients with erosive eosophagitis (DeVault & Talley 2009). And, than later hydrogen potassium adenosine triphosphatase was identified as the proton pump of parietal cell. Currently Proton pump inhibitors are among the safest class of drugs and widely used across the world.

A research project initiated in late 60s, aim was to synthesize a local anesthetic drug that could be orally administered and therefore have its main action on the gastrin. This concept was soon found to be a blind track and further development of the basic compounds CMN131 by the synthesis of H77/ 67 were found to be active in the gastric acid secretion and then a year later the benzinidazole analog of H77/67 was synthesized after testing they found it with powerful acid

inhibitory effects. Binding studies with the substituted benzimidazoles clarified specific binding to H+/K+/ATPase in the secretory vesicles of the parietal cells. Since weak bases like aminopyrine accumulate in the acid compartment of the parietal cells, the chemists changed the substituents of the heterocyclic ring and obtained a compound with a weak base property with an optimal Pka value, thereby maximizing the accumulation of the compound at the site of action. This compound H168/68 was synthesized in 1979 and was given the generic name Omeprazole, which proved to be a potent inhibitor of the proton pump in vitro and preparation from human stomach tissues. The pharmacological studies found the compound not only showed long lasting effect on acid secretion and specific binding to target site but also found the compound with unique therapeutic effects (Lundell 2015).In 1989 omeprazole came into market with optimal acid suppressive property and became one of widely used and profitable drug in history (Maradey-Romero & Fass 2013).It was fruitful and helped cure hypersecretory states for decades around the world but the question is what is the future of PPIs in hypersecretory states can any drug replace the fruitful discovery and how? .yes I am talking about new acid inhibitory drugs like potassium competitive acid blockers, new histamine 2 receptor antagonists, isomeric PPIs, gastrin and CCk receptor antagonists. Now what are the shortcomings of PPIs that any of the above drug will replace one of best drug of all time. Here are some shortcomings or limitations of PPIs for example PPIs cannot completely inhibit acid secretion which are important in some hypersecretory states especially at night, the inconvenience of requiring mealtime dosing to ensure adequate levels of the drug during periods of H+ K+- ATPase activity, PPIs are slow to achieve steady state inhibition of gastric acid secretion, typically taking 3 to 5 days to achieve maximum inhibition(Piche & Galmiche 2005). A PPI can only inhibit active H+ K+- ATPase that is actively secreting at the surface

of secretory canaliculus of the parietal cell. Two third of patients suffering from symptomatic GERD ,reflux symptoms are not adequately controlled by initial dose of PPI and 50% still suffering from symptoms after 3 days (Hunt & Scarpignato 2015) and one third of GERD patients treated with PPIs reports persistent symptoms and were not satisfied with PPIs treatment (Chey et al. 2010). So it was logical that other potential approaches would be considered. A more innovative approach has been the development of potassium-competitive acid blockers. We will try to compare the efficacy and safety of potassium competitive acid blocker vonoprazan vs. lansoprazole a PPI.

POTASSIUM-COMPETITIVE ACID BLOCKERS

In the early 1980s, an imidazopyridine compound, SCH28080, was developed by Schering-Plough that inhibited gastric acid secretion in animals and humans (Ene et al. 1982). SCH28080 inhibited the acid response to histamine, high K+, methacholine, and cyclic AMP. Kinetic studies indicated competitive inhibition of H+,K+- ATPase by SCH28080 with respect to K+, suggesting a competitive interaction with the high affinity K+-site of H+,K+-ATPase (Beil et al. 1986). This initiated studies of a series of SCH28080 derivatives. Like Imidazopyridinederivatives (e.g., linaprazan and BY841), imidazonaphthyridine derivatives (e.g., soraprazan), imidazothienopyridines (e.g., SPI-447), quinolone derivatives (e.g., SK&F96067 and SK&F97574), pyrrolopyridazinederivatives (e.g., CS-526), pyrimidine derivatives (e.g., revaprazan) and pyrole derivatives (e.g., vonoprazan) were developed. Such compounds that compete with K+ binding and inhibit gastric acid secretion are called potassium-competitive acid blockers (P-CABs). Only Revaprazan and vonoprazan were developed and approved for clinical use and as therapeutics for the treatment of ARDs. In

1970s revaprazan was introduced in South Korea for the treatment of duodenal ulcer, gastric ulcer and gastritis, and is also available in India. Vonoprazan was first launched in Japan in 2015 by Takeda Pharmaceuticals for the treatment of gastric ulcer, duodenal ulcer, erosive eosophagitis, prevention of low dose aspirin or NSAID induced ulcer recurrence, and as an adjunct for H. pylori eradication. SCH28080, linaprazan and vonoprazan have pKa values of 5.6, 6.1, and 9.3, respectively all above P-CABs are weak bases (Gedda et al. 2007).Linaprazan inhibited K+ stimulated H+,K+-ATPase with an IC50 of 1.0 μM at pH 7.4, but was 8 times more potent at pH 6.4. The theoretical percent of protonated linaprazan is about 33% at pH6.4 and less than 5% at pH 7.4. The inhibitory effect of SCH28080 is also weaker in neutral conditions (IC50= 0.14 μM at pH 6.5 vs. IC50= 2.5 μM at pH 7.4). These results suggest that protonated forms of P-CABs inhibit H+, K+-ATPase. Linaprazan inhibited more potently in ion-tight vesicles than in ion leaky vesicles, suggesting this agent concentrates in regions of low pH and has a luminal site of action (Gedda et al., 2007). As the pKa value of vonoprazan is 9.3, most of this compound should be protonated instantly and exert potent inhibition (IC50= 19 nM at pH 6.5, IC50= 28 nM at pH7.5 (Hori et al. 2011). Linaprazan provided similar efficacy to esomeprazole, but raised liver transaminase in a dose-dependent fashion, the clinical development was stopped because by repeating administration drug was found to be responsible for hepatic toxicity. Because protonated compounds are less membrane permeable than non-ionic compounds, protonated P-CABs are thought to concentrate in the acidic secretory canaliculi of parietal cells where they produce H+,K+-ATPase inhibition. P-CABs are instantly protonated and accumulate at much higher concentrations than PPIs, and inhibit acid secretion by binding with H+, K+-ATPase ionically and by competing with K+, recently demonstrated that [14C]- vonoprazan binds equally to resting and stimulated rabbit gastric glands, while auto

radiographic analysis showed no difference in labeling between resting and stimulated gastric parietal cells, indicating that vonoprazan binds selectively to the parietal cell independent of acid secretion and vonoprazan labels both active and inactive H+,K+- ATPase. This is in sharp contrast to the results obtained for omeprazole, where binding of omeprazole to parietal cells in gastric glands increased when acid secretion was stimulated and decreased with inhibition of secretion (Scott et al., 1993). Accumulation and acid activation are required for the action of PPIs, but are not required for the action of vonoprazan. P-CABs bind selectively to the E2-P form of H+,K+-ATPase , a mechanism supported by the finding that SCH28080 binding affinity increased approximately 10 folds in the presence of ATP (Mendlein & Sachs 1990). SCH28080 inhibits K+-stimulated ATPase activity by competing with K+ for binding to E2-P and blocking K+- stimulated dephosphorylation. The binding sites of SCH28080 and vonoprazan have been investigated thoroughly using a H+,K+-ATPase homology model based on the crystallographic structure of Na+K+- ATPase(Shin et al. 2011). Vonoprazan from the lumen get access through TM1/TM2 and TM5/TM6 loops and extracytoplasmic ends of TM8,TM4 AND TM9. Following entry, this space closes and vonoprazan is trapped in the vestibule. The positively charged N-methyl- amino side chain on vonoprazan is located within 2.4 Å of Glu795, producing strong hydrogen bonding and charge interaction with the K+ site at Glu795, which is in contrast with the binding characteristics of SCH28080 and other P-CABs. Another divergence from the predicted binding of vonoprazan to the vestibule in H+,K+-ATPase is the suggested hydrogen bonding between Tyr799 and the sulfone of vonoprazan (Shin et al. 2011). Improved binding site models have recently suggested that vonoprazan is largely occluded by H+, K+-ATPase after binding, and predict that vonoprazan is buried in a greater surface area and occupies a larger percentage of its surface area

than SCH28080. Vonoprazan exit into the lumen is hindered by asp137 and asn138 in the loop between TM1 and TM2, which presents an electrostatic barrier to the movement of the sulfonyl group of vonoprazan (Scott et al., 2015). These binding characteristics could explain the very slow dissociation of vonoprazan from H+, K+-ATPase and its more effective and longer action compared to other P-CABs(Scott et al. 2015).

Efficacy of potassium-competitive acid blockers compared with PPI (lansoprazole) in patients with acid-related diseases

In Japan clinical studies were conducted to investigate the efficacy and safety of vonoprazan in the healing and maintenance of erosive esophagitis, prevention of aspirin or NSAID-induced ulcer recurrence, gastric ulcer, duodenal ulcer, and H. pylori eradication. The clinical results proved that vonoprazan is not inferior in eradicating H.Pylori infection and healing erosive eosophagitis, to clarify the future of potassium competitive acid blockers in hypersecretory states management.

Healing of erosive esophagitis

A total of 732 patients with erosive eosophagitis were administered with vonoprazan and lasoprazole in a phase 2 clinical study. The results showed vonoprazan was not inferior to lansoprazole 30mg ($p<0.004$) (Ashida et al. 2016) In a phase 3 clinical study, a total of 409 patients with LA grades A–D. Eosophagitis were randomized to vonoprazan 20 mg or lansoprazole 30 mg once daily for 8 weeks, and healing of esophagitis was examined by endoscopy at 2, 4 and 8 weeks. The healing rate at 8 weeks, the primary endpoint of the study, was 99.0% in the vonoprazan group and 95.5% in the lansoprazole group. In post-hoc analyses, stratification according to LA grade of eosophagitis at baseline revealed a significant difference in the healing rate between vonoprazan and lansoprazole for grade C/D patients; the healing rates at 8

weeks were 98.7% and 87.5%, respectively. The secondary endpoint was healing rate at 4 weeks, which was 96.6% in the vonoprazan group and 92.5% in the lansoprazole group. The healing rate for vonoprazan 20 mg at 4 weeks was almost identical to that for lansoprazole 30 mg at 8 weeks. The healing rate after 2 weeks treatment in the vonoprazan group (90.7%) was also higher than that observed in the lansoprazole group (81.9%, Pb 0.0132(Ashida et al. 2016).

Helicobacter pylori eradication with vonoprazan and lansoprazole

H.Pylori eradication therapy based on PPIs is still considered first line therapy but PPI-based triple therapy eradication rate has fallen from 90% in 1990s to 70% currently worldwide especially in West and Asian countries like Japan and South Korea. The main reason is antibiotic resistance and inadequate acid inhibition with PPIs demanding new approaches a options in the field of pharmacology. Comparison of PCABs (vonoprazan) and PPIs (lansoprazole) in eradicating H.Pylori infection is below.

To compare first line H. pylori eradication therapies, a total of 650 H. pylori-positive patients with cicatrized gastric or duodenal ulcers were randomized to triple therapy with either vonoprazan (vonoprazan20 mg, amoxicillin 750 mg, clarithromycin 200 mg or 400 mg twice daily for 7 days) or to triple therapy with lansoprazole (lansoprazole 30 mg, amoxicillin 750 mg, clarithromycin 200 mg or 400 mg twice daily for 7 days). Fifty of 101 subjects in whom eradication with a first line therapy failed received a 7-day course of second line therapy (vonoprazan 20 mg, amoxicillin 750 mg, metronidazole 250 mg twice daily). The first line H. pylori eradication rate was 92.6% in the vonoprazan group and 75.9% in the lansoprazole group. Non- inferiority of vonoprazan to lansoprazole was verified. A post-hoc anal- ysis subsequently indicated that vonoprazan performed significantly better than lansoprazole as

a component in the first line therapy. Notably, the H. pylori eradication rate was significantly higher in the vonoprazan group compared with the lansoprazole group in the subjects with clarithromycin resistance (82.0% and 40.0%, respectively; pre-planned grouping and post-hoc statistical test).Second line therapy with vonoprazan resulted in eradication of 98%(Murakami et al. 2016).

Safety of potassium-competitive acid blockers

In clinical phase 3 studies in Japan lansoprazole 30mg and vonoprazan 20mg treatment adverse events were similar 22.3% and 22.2% respectively (Ashida et al. 2016). Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels were not raised because vonoprazan chemical structure differs from other potassium competitive acid blockers. Greater increases in serum gastrin and pepsinogen I and II were observed during treatment with vonoprazan than with lansoprazole, probably as a consequence of greater inhibition of gastric acid secretion by vonoprazan compared with lansoprazole.

CONCLUSIONS

As it's known that in acid related disorders, healing is directly related to degree and duration of acid suppression and the length of treatment. In the past, peptic ulcer diseases were treated empirically, change in diet, milk recommendation, antacids and sometime herbal medicine were used to treat ARD but none of the above helped and satisfied the patients. 40 years back with the discovery of histamine receptors and then H2RB for the first time effectively benefited the hyperacidity states but were relatively weak in efficacy for GERD, H.Pylori eradication and treating erosive esophagitis. A more potent and acceptable treatment with PPIs were introduced which revolutionized the practice of gastroenterology and became the

first choice of Gastroenterologist for treating ARD worldwide but there are still acid related conditions in which we need complete suppression of gastric acid secretions. PPIs were not able to completely inhibit acid secretion and also takes more time 3 to 5 days to achieve steady state maximum inhibition of acid secretion. Mealtime and multiple dosing were also required to ensure adequate level of the drug during periods of H+,K+-ATPase activation. Inter-individual variations in efficacy were found due to CYP2C19 metabolism and night acid suppression was also not satisfactory. 50% of adult population globally is infected with H. Pylori. H. Pylori eradication rate with PPIs has fallen from >90% in 1990 t0 70% currently. In recent years decrease in H. Pylori eradication, resistance to antibiotics and the H. Pylori role in PUD, gastritis and gastric cancer necessitates the development of more potent acid suppressor, fast acting and a drug with reversible properties. PCABs like vonoprazan have clinical benefits over PPIs in the treatment of erosive esophagitis, GERD and H.Pylori eradication. PCABs completely inhibit acid secretion and rapidly achieve therapeutic plasma levels. Less interindividual variations in efficacy was observed because of minimal involvement of CYP2C19 metabolism. PCABs action is independent of secretory state. PCABs don't need enteric coating because it is acid stable. In Japan, India and South Korea vonoprazan is approved and available in markets has different chemical structure and higher pKa value as compared to other PCABs. Vonoprazan has longer-lasting acid suppression properties and also more effective than lansoprazole in healing reflux esophagitis and H.Pylori eradication. Clinical studies proved now that vonoprazan is safe and well tolerated as compared to lansoprazole and incidence of adverse events is similar to lansoprazole. Vonoprazan-based triple therapy is currently first line and second line therapy effective, well tolerated with better clinical response for H.Pylori eradication sequential, quadruple or long term therapy in the near future vs. PPIs.

REFERENCES

1. Ashida, K. et al., 2016. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Alimentary pharmacology \& therapeutics*, 43(2), pp.240–251.
2. Beil, W., Hackbarth, I. & Sewing, K.-F., 1986. Mechanism of gastric antisecretory effect of SCH 28080. *British journal of pharmacology*, 88(1), pp.19–23.
3. Chey, W.D., Mody, R.R. & Izat, E., 2010. Patient and physician satisfaction with proton pump inhibitors (PPIs): are there opportunities for improvement? *Digestive diseases and sciences*, 55(12), pp.3415–3422.
4. DeVault, K.R. & Talley, N.J., 2009. Insights into the future of gastric acid suppression. *Nature reviews. Gastroenterology & hepatology*, 6(9), pp.524–32.
5. Ene, M., KHAN-DANESHMEND, T. & Roberts, C., 1982. A study of the inhibitory effects of SCH 28080 on gastric secretion in man. *British journal of pharmacology*, 76(3), pp.389–391.
6. Gedda, K. et al., 2007. Mechanism of action of AZD0865, a K+-competitive inhibitor of gastric H+, K+-ATPase. *Biochemical pharmacology*, 73(2), pp.198–205.
7. Hori, Y. et al., 2011. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. *Journal of Pharmacology and Experimental Therapeutics*, 337(3), pp.797–804.
8. Hunt, R.H. & Scarpignato, C., 2015. Potassium-competitive acid blockers (P-CABs): are they finally ready for prime time in acid-related disease?
9. Inatomi, N. et al., 2016. Potassium-competitive acid blockers: Advanced therapeutic option for acid-related diseases. *Pharmacology \& therapeutics*, 168, pp.12–22.

10. Lundell, L., 2015. The physiological background behind and course of development of the first proton pump inhibitor. *Scandinavian journal of gastroenterology*, 50(6), pp.680–684.
11. Maradey-Romero, C. & Fass, R., 2013. New and future drug development for gastroesophageal reflux disease. *Journal of neurogastroenterology and motility*, 20(1), pp.6–16.
12. Mendlein, J. & Sachs, G., 1990. Interaction of a K (+)-competitive inhibitor, a substituted imidazo [1, 2a] pyridine, with the phospho-and dephosphoenzyme forms of H+, K (+)-ATPase. *Journal of Biological Chemistry*, 265(9), pp.5030–5036.
13. Murakami, K. et al., 2016. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study. *Gut*, 65(9), pp.1439–1446.
14. Piche, T. & Galmiche, J.P., 2005. Pharmacological targets in gastro-oesophageal reflux disease. *Basic \& clinical pharmacology \& toxicology*, 97(6), pp.333–341.
15. Scarpignato, C., Pelosini, I. & Di Mario, F., 2006. Acid suppression therapy: where do we go from here? *Digestive Diseases*, 24(1-2), pp.11–46.
16. Scott, D. et al., 2015. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+-ATPase. *Alimentary pharmacology \& therapeutics*, 42(11-12), pp.1315–1326.
17. Shin, J.M. et al., 2011. Characterization of a novel potassium-competitive acid blocker of the gastric H, K-ATPase, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438). *Journal of Pharmacology and Experimental Therapeutics*, 339(2), pp.412–420.