New pharmacological treatments for gastroesophageal reflux: Potassium-competitive acid blockers and bile acid sequestrants

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RESUMEN

La enfermedad por refluo gastroesofágico (ERGE) es un trastorno representativo de las enfermedades relacionadas con la acidez gastrointestinal. Para tratar estos trastornos se usan principalmente agentes antiserretores, como los inhibidores de la bomba de protones (IBP). Además de los IBP convencionales, recientemente se han desarrollado una nueva clase de agentes antiácidos, los bloqueadores de ácido competitivos de potasio (BAC-P), que actúan inhibiendo la H⁺/K⁺-ATPasa gástrica compitiendo con el K⁺. Por otro lado, el reflujo duodenogastroesofágico del ácido biliar es otro promotor de ERGE y sus complicaciones asociadas, como el esófago de Barrett y el adenocarcinoma esofágico inferior. Por lo tanto, los secuestradores de ácidos biliares pueden desempeñar un papel en este tipo de reflujo. En este documento se revisan las funciones de los BAC-P y los secuestradores de ácidos biliares en el tratamiento de la ERGE. Hay tres tipos de BAC-P, uno de los cuales es el vonoprazán, que tiene un potente efecto antisecretor de larga duración sobre la H⁺/K⁺-ATPasa debido a su alta acumulación y lenta eliminación en el estómago. El vonoprazán se usa actualmente en Japón para el tratamiento de la esofagitis por reflujo, induciendo un alto índice de cicatrización de la mucosa en pacientes con esofagitis por reflujo refractaria resistente a PPI, y en la protección del epitelio esofágico. Los secuestradores de ácidos biliares, como la colestiramina, se unen a los ácidos biliares y pueden ser fisiológicamente eficaces para reducir la exposición al ácido biliar de la superficie del epitelio esofágico. Mientras que actualmente los tres BAC-P tienen diferentes grados de eficacia en la terapia de la ERGE, la de los secuestradores de ácidos biliares no ha sido plenamente probada. (NeuroGastroLatam Rev. 2018;2:18-27)

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a representative disorder of acid-related diseases. Antisecretory agents such as proton-pump inhibitors (PPIs) are mainly used to treat these disorders. Recently, in addition to conventional PPIs, potassium-competitive acid blockers (P-CABs) have been developed as a new class of agents for acid suppression that acts by inhibiting the gastric H⁺/K⁺-ATPase in a K⁺-competitive manner. On the other hand, duodenogastroesophageal reflux of bile acid is another promoter of GERD and their associated complications, such as Barrett’s esophagus and lower esophageal adenocarcinoma. Therefore, bile acid sequestrants may play a role in this type of reflux. Herein, the roles of PCABs and bile acid sequestrants in the treatment of GERD are reviewed. There are three types of P-CABs, one of which is vonoprazan (VPZ), which has a potent and long-lasting antisecretory effect on H⁺/K⁺-ATPase due to its high accumulation and slow clearance from the stomach. VPZ is now used in Japan for the treatment of reflux esophagitis, inducing high mucosal healing rate in patients with PPI-resistant refractory reflux esophagitis and in protecting esophageal epithelia. Bile acid sequestrants, such as cholestyramine, bind to bile acids and may be physiologically effective in reducing the exposure of bile acid to the esophageal epithelial surface. While currently, three available P-CABs have different degrees of effectiveness in the therapy of GERD, that of bile acid sequestrants has not been fully proven.

Key words: Vonoprazan. Tegoprazan. Revaprazan. Cholestyramine.

INTRODUCTION

Although proton-pump inhibitors (PPIs) have been the mainstay of gastroesophageal reflux diseases (GERD) treatment for the last two decades, approximately 20-40% of GERD patients are refractory to the standard doses of PPI taken more than 8 weeks, which is referred to as PPI-resistant GERD. PPIs such as omeprazole, lansoprazole (LPZ), rabeprazole, and esomeprazole that are available in Japan are of irreversible inhibition of H⁺/K⁺-ATPase, which form a covalent complex with the protein at specific cysteine residues. Although recognized as the most potent drugs for the treatment of acid-related diseases, PPIs exhibit a delayed onset and achieve full effect only slowly (needs several days). Recently, as an alternative to PPIs, potassium-competitive acid blockers (P-CABs) which reversibly inhibit gastric parietal cell H⁺/K⁺-ATPase by competing with the K⁺ on the luminal surface have been developed. These P-CABs rapidly achieve high plasma concentrations with a fast onset of action. On the other hand, not only acid reflux but also duodenogastroesophageal bile reflux is another important inducer of GERD as well as a promoter of its complications, such as Barrett’s esophagus (BE) and Barrett’s esophageal adenocarcinoma (EAC). In this comprehensive review, we present an update on the state of P-CABs and bile acid sequestrants in the treatment of GERD and in the prevention of GERD complications.
We start describing the details of the three recently developed P-CABs currently available or in the pipeline, especially in East Asia (Table 1).

Vonoprazan (VPZ) is a novel P-CAB, which may provide clinical benefits in acid-related disorders, including GERDs. Non-clinical studies have shown that VPZ exerts more potent and sustained suppression of acid secretion than previously used PPIs, LPZ, or a prototype P-CAB (SCH28080). The therapeutic potential of VPZ might be derived from its ability to accumulate at high concentrations in the canaliculi of gastric fundic parietal cells, its slow clearance from the gastric fundic glands, and its acid-independent effects3,4. Unlike earlier P-CAB derivatives, VPZ has no imidazopyridine ring, which has been associated with a reversible increase in liver transaminases5. VPZ may thus offer a favorable safety profile with additional clinical advantages over conventional acid suppressants. After clearing clinical trials, VPZ became available in Japan for the treatment of patients with GERD. The ability of VPZ to strongly suppress acid secretion with rapid onset (< 3 h) is also highly effective in eradicating *Helicobacter pylori*6,7.

Revaprazan (YH1885) is another P-CAB available in South Korea. According to the study in healthy volunteers by Yu et al.8, the plasma concentration of revaprazan reached peak levels 1.3-2.5 h after a single-dose administration and then declined monoexponentially. In contrast, revaprazan showed linear pharmacokinetic characteristics and a low accumulation in a multiple-dose administration study. Dose-dependent pharmacological effects were obvious at doses of 150 mg and higher in the single-dose study. On the other hand, the onset of drug effect in the multiple-dose study was rapid, with maximum effects observed on the 1st day of administration, in line with two other P-CABs. Serum gastrin levels also showed rapid increases during the dosing period but with a weak
dose-effect relationship. These results suggest that revaprazan is safe and well-tolerated and effectively induced the inhibition in acid secretion and the dose-dependent increase in intragastric pH. According to a double-blind, three-way crossover study with 30 healthy male volunteers randomly allocated to 100, 150, or 200 mg of oral administration of revaprazan daily for 7 days, the median intragastric pH over 24 h and the mean percentage time of intragastric pH > 4 were increased in a dose-dependent manner and were significantly higher on days 1 and 7 compared with baseline in all groups. The antisecretory effect of revaprazan was rapid and nearly maximum on day 1 in all groups. These findings suggested that revaprazan would also be effective broadly for the treatment of acid-related disorders. Choi et al. compared the bioavailability and tolerability of revaprazan–itopride combination therapy to those of equally dosed monotherapies to acquire information about the basic drug-drug interaction of revaprazan in a multiple-dose, randomized crossover study conducted in healthy male Korean subjects, showing the bioequivalence of revaprazan monotherapy and revaprazan–itopride combination, with no clinically significant drug to drug interaction. These results further suggested the possible application of revaprazan in combination with prokinetics drugs for the treatment of not only GERD but also functional dyspepsia (FD), especially in patients with postprandial distress syndrome. Furthermore, similar to the additional pharmacological actions of PPIs, revaprazan imposed direct anti-inflammatory actions against the diverse etiologic factors of gastritis, including *H. pylori* infection and nonsteroidal anti-inflammatory drugs challenge.

On the other hand, according to Jung et al., there is a possible interaction between revaprazan and warfarin, suggesting that revaprazan can cause the shortening of prothrombin time (PT). Therefore, in cases where revaprazan is prescribed to patients on warfarin therapy, PT should be frequently monitored.

Another P-CAB, called tegoprazan, may provide a new option for the treatment of gastric acid-related and dysmotility diseases. Tegoprazan inhibited the porcine, canine, and human kidney H⁺,K⁺-ATPases in vitro with inhibitory concentration 50 (IC₅₀) values ranging from 0.29 to 0.52 µM and more than 100 µM Na⁺/K⁺-ATPase in canine kidney. A kinetic analysis revealed that tegoprazan inhibited H⁺/K⁺-ATPase in a potassium-competitive and reversible manner. Oral single-dose administrations of tegoprazan ranging from 0.3 to 30 mg/kg in dogs were well-absorbed into the bloodstream and more highly distributed in gastric tissue or fluid higher than in plasma. Tegoprazan strongly inhibited the histamine-induced gastric acid secretion in dogs, with a complete inhibition observed at 1.0 mg/kg starting from 1 h after administration. Moreover, oral administration of tegoprazan at 1 and 3 mg/kg reversed the pentagastrin-induced acidified gastric pH to the neutral pH range. In addition, 3 mg/kg tegoprazan immediately evoked a gastric Phase III contraction of the migrating motor complex (MMC) in the pentagastrin-treated dogs and similar effects were observed with VPZ. Tegoprazan was, therefore, suggested as a new option for the therapy of gastric acid-related and motility-impaired diseases.
P-CAB THERAPY FOR EROSIvE ESOPHAGITIS (EE)

Ashida et al. examined the efficacy and safety of VPZ in patients with EE\textsuperscript{15}. In their multi-center, randomized, double-blind, parallel-group, dose-ranging study, 732 patients with endoscopically confirmed EE received 5, 10, 20, or 40 mg VPZ or 30 mg LPZ once daily for 8 weeks. The proportion of healed EE subjects at week 4 was 92.3%, 92.5%, 94.4%, 97.0%, and 93.2%, respectively. The effects of all VPZ doses were non-inferior to LPZ when adjusted for baseline Los Angeles (LA) grades A/B and C/D EE. Among those with LA grades C/D, the proportions of healed EE subjects were 87.3%, 86.4%, 100%, 96.0%, and 87.0%, with 5, 10, 20, and 40 mg VPZ and 30 mg LPZ, respectively, which showed that VPZ was effective and non-inferior to LPZ in the treatment for EE\textsuperscript{15}. In addition, VPZ 20 mg or higher was highly effective against severe EE (LA grades C/D)\textsuperscript{15} and was associated with no safety concern during this 8-week study, despite a dose-dependent increase in serum gastrin\textsuperscript{15}. A once daily of 20 mg VPZ is reported to be the recommended clinical dose for treating EE\textsuperscript{15}.

Ashida et al.\textsuperscript{16} also verified the non-inferiority of VPZ to LPZ in patients with EE and established the long-term safety and efficacy of VPZ as maintenance therapy. In their multi-center, randomized, double-blind, and parallel-group comparison study, patients with endoscopically confirmed EE (LA Grades A-D) were randomly allocated to receive 20 mg VPZ or 30 mg LPZ once daily after breakfast. Of the 409 eligible subjects randomized, 401 completed the comparison study and 305 entered the following long-term (52 weeks) maintenance study. The proportion of patients with healed EE up to week 8 was 99.0% in the VPZ group and 95.5% in the LPZ group, indicating the non-inferiority of VPZ ($p < 0.0001$)\textsuperscript{16}. VPZ was also effective in patients with more severe EE (LA Grades C/D) and CYP2C19 extensive metabolizers. In the long-term maintenance study, there were a few recurrences during the trial (< 10%) of EE in patients treated with 10 or 20 mg VPZ\textsuperscript{16}. Despite that, VPZ was generally well tolerated by the patients.

MONITORING OF ACID REFUX: MULTICHANNEL INTRALUMINAL IMPEDANCE-PH (MII-PH)

Yamashita et al. evaluated the effects of VPZ and PPIs in patients with EE using the MII-PH (17). In their study, a total of 8 patients with persistent gastric mucosal injury, despite completing an 8-week standard PPI therapy, were enrolled\textsuperscript{17}. The baseline values of reflux parameters and holding time ratio (HTR) of gastric pH > 4 and esophageal pH < 4 were obtained using 24 h MII-pH monitoring from the patients while still on standard PPI therapy. The patients were reevaluated after the discontinuation of the therapy and 4 weeks of subsequent treatment with 20 mg/day VPZ. The patients were found positive for CYP2C19 (extensive metabolizers) and negative for \textit{H. pylori} infection. In 7 patients (87.5%), the mucosal lesions had healed completely after VPZ therapy. A significant increase in gastric pH > 4 HTR was observed from 26.5% to 78.0% ($p < 0.05$)\textsuperscript{17}. The acid clearance time and total number of reflux effects, including acid and proximal reflux events, were significantly reduced\textsuperscript{17}. 
P-CAB THERAPY FOR NON-EROSIve REFUX DISEASES (NERDS)

Kinoshita et al.\(^{18}\) compared the effect of VPZ with that of placebo on the frequency and severity of heartburn in patients with NERD. This prospective Phase III, double-blind, placebo-controlled, parallel-group, multicenter study included patients in Japan aged ≥ 20 years with Grade N or M NERD and recurrent acid reflux symptoms. In this study, Grade M was defined as minimal changes to the mucosa, such as erythema without sharp demarcation, whitish turbidity, and/or invisibility of vessels due to these findings; Grade N was defined as normal mucosa based on the modified LA classification by endoscopy\(^{19}\). In their study, 827 patients were randomized (placebo: \(n = 278\), VPZ 10 mg: \(n = 278\), and VPZ 20 mg: \(n = 271\)). The median proportion of days without heartburn was 7.4% (placebo), 10.3% (VPZ 10 mg), and 12.0% (VPZ 20 mg). The proportion of days without heartburn between the VPZ and placebo groups (\(p = 0.2310\) [10 mg] and \(p = 0.0504\) [20 mg]) was not statistically significant. The mean severity of heartburn of the placebo group was significantly higher than that of VPZ 10 mg group. Compared with patients treated with placebo, patients treated with VPZ experienced significantly increased proportion of days without heartburn and reduced mean severity of heartburn at 2 weeks and 4 weeks, respectively. A significant decrease in the median proportion of days without heartburn was observed in the Grade M NERD patients treated with VPZ 20 mg\(^{18}\). However, there are some limitations in this study, such as a run-in period with antacid treatment in which participants are excluded from the study when they responded to antacids in this period, a post-observation period with placebo that may have confounded the cumulative heartburn improvement rate, and the inclusion of confounding conditions such as FD and functional heartburn.

In contrast, Asaoka et al.\(^{20}\) investigated the efficacy of VPZ for improving the symptoms of NERD in their hospital-based, retrospective study of outpatients. The rates of symptomatic improvement were 60.0% in 25 NERD patients. The rates of symptomatic improvement were 66.7% and 53.8% in patients who were administered VPZ first and in patients who were resistant to 8 weeks of PPI treatment, respectively. The VPZ treatment for 4 weeks also decreased the reflux symptom (heartburn and acid regurgitation) of NERD patients (\(p < 0.01\)), suggesting the possibility of its use as a novel therapeutic drug for NERD\(^{20}\).

In their retrospective study\(^{20}\), the efficacy of VPZ on the treatment of patients with FD (\(n = 43\)) was also examined. They reported that the rate of symptomatic improvement of FD without VPZ or PPI treatment was 48.8%, whereas the improvements in patients administered first with VPZ and in patients resistant to 8 weeks of PPI treatment were 58.8% and 42.3%, respectively. Although the FD score was decreased after 4 weeks of VPZ therapy (\(p < 0.01\)), the response rate was remarkably lower than that in EE or NERD\(^{20}\).

PPI-REFRACTORY GERD

Okuyama et al. investigated the efficacy of VPZ on PPI-refractory GERD and the factors associated with P-CAB non-response by
enrolling 277 patients receiving continuous PPI therapy. Subjects completed a self-report questionnaire, including the frequency scale of the symptoms of GERD (FSSG). After being administered with 20 mg of VPZ once daily for 8 weeks, 28 patients with PPI-refractory GERD were identified as P-CAB responders and 26 were P-CAB non-responders. The VPZ treatment significantly decreased the FSSG scores including nighttime symptoms and Athens insomnia scale. Multivariate analysis demonstrated that the co-existing FD (OR 4.94) and sleep disturbances (OR 4.34) were related with P-CAB non-response, whereas alcohol consumption was inversely related with P-CAB non-response.

Hoshino et al. investigated the efficacy of VPZ therapy at 20 mg for 4 weeks in 24 patients with PPI-resistant EE and at 10 mg as a maintenance therapy for 8 weeks in patients who have been successfully treated. In 21 (87.5%) of 24 patients, esophageal mucosal breaks were successfully treated by 20 mg VPZ, suggesting a good response to VPZ in PPI-resistant GERD. The median FSSG score was significantly lower on days 1-7, 14, and 28 after the administration with VPZ compared with before administration. Meanwhile, the maintenance therapy with 10 mg VPZ prevented the relapse of esophageal mucosal breaks in 16 (76.2%) of 21 patients.

Iwakiri et al. evaluated the acid-inhibitory effects and efficacy of VPZ in patients with PPI-resistant EE, in a randomized, double-blind, multicenter study that analyzed the gastric and esophageal pH over a 24-h period referred to as pH 4 HTR, and also the healing rate of EE. Following a 7-14-day run-in period (LPZ 30 mg), patients with endoscopically confirmed PPI-resistant EE received 20 mg or 40 mg VPZ for 8 weeks. Over a 24-h period, both VPZ 20 mg and 40 mg groups showed significant increases from baseline in the percentage of time in gastric pH 4 HTR, namely, from 73.21% to 96.46% and from 69.97% to 100.00% in the 20 mg and 40 mg groups, respectively. They showed that VPZ effectively inhibited the gastric acid secretion over a 24-h period with significantly increased gastric pH 4 HTR, which resulted in the EE healing rates of 60% and 71.4% at 20 mg and 40 mg, respectively.

SYMPTOMS IN PATIENTS WITH GERD

VPZ treatment was shown to improve gastrointestinal symptoms in patients with GERD. Shinozaki et al. retrospectively analyzed 24 patients with PPI-resistant GERD treated with 10 mg VPZ. The overall rates of improvement and resolution of GERD symptoms assessed by the Izumo scale, which is a validated and widely used questionnaire about quality of life related to various abdominal symptoms, were 88% and 42%, respectively, which are significant. In their study, VPZ achieved 100% (6/6) improvement in EE group and 83% (15/18) in NERD group. Patients in the EE group had a significantly higher rate of symptomatic resolution than in NERD group (83% [5/6] vs. 28% [5/18], p = 0.017). However, in their study, the scores for epigastric pain, postprandial distress, constipation, and diarrhea were unchanged during the treatment period. In addition, VPZ 10 mg was shown to be effective and resolved GERD symptoms in patients with erosions more than in those
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They also retrospectively reviewed 88 *H. pylori*-negative patients with GERD treated with VPZ 10 mg. The rates of symptomatic improvement and resolution of GERD were 86% and 57%, respectively. The improvement and resolution in patients with EE were higher than in those with NERD (91% vs. 83%, \( p = 0.260 \), and 71% vs. 47%, \( p = 0.025 \)). By multivariate analysis, they identified the factors which predict the effects of VPZ at advanced age (≥ 60 years old) (OR 7.281, 95% CI 2.056-25.776, \( p = 0.002 \)), obesity (BMI ≥ 24) (OR 3.342, 95% CI 1.124-9.940, \( p = 0.030 \)), and EE (OR 4.368, 95% CI 1.281-14.895, \( p = 0.018 \)) as positive predictors of symptomatic resolution of GERD by VPZ, while alcohol consumption (OR 0.131, 95% CI 0.027-0.632, \( p = 0.011 \)) and history of *H. pylori* eradication (OR 0.171, 95% CI 0.041-0.718, \( p = 0.015 \)) were identified as negative predictors. The relationship between alcohol consumption and the effect of VPZ in this report is contrary to that by Okuyama et al.21. VPZ also improved the other GI symptoms such as epigastric pain (73%), postprandial distress (60%), constipation (58%), and diarrhea (52%) in patients with GERD.

Asaoka et al.20 investigated the efficacy of VPZ for improving symptoms in patients with EE in their hospital-based, retrospective study. The rates of symptomatic improvement in 20 patients with EE were 75.0% in untreated patients, 90.9% in patients administered with VPZ, and 55.6% in PPI-resistant patients. The GERD scores of patients with EE were decreased after 4 weeks of VPZ therapy (\( p < 0.01 \))20. However, since the number of study subjects was small, further and larger prospective studies are required.

**ON-DEMAND THERAPY OF VPZ FOR MILD EE**

Since VPZ exhibits a rapid suppression of acid secretion, it will be useful for an on-demand use. Umezawa et al. evaluated the efficacy of one 20-mg tablet of VPZ taken only when reflux symptoms occurred for 24 weeks on 30 patients with mild EE who were receiving PPIs as maintenance therapy27. They reported that remission was maintained in 25 (86.2%) of the 29 patients (all 10 [100%] LA Grade A cohorts and 15 [78.9%] of the 19 Grade B patients). However, four Grade-B patients exhibited Grade-B relapse. The overall satisfaction, score of symptoms, or the gastrin level in on-demand therapy was not significantly different from those in continuous therapy. In addition, the number of VPZ tablets taken during the observation period of 6 months was only 33 tablets as a median. These findings indicated that the on-demand therapy using 20-mg VPZ is an effective alternative maintenance therapy for mild EE27.

**BILE ACID SEQUESTRANTS**

Duodenogastric-esophageal reflux is the retrograde flow of duodenal contents into the stomach, which then mix with gastric acid and pepsin and subsequently flow into the esophagus. This phenomenon can cause GERD and its complications, including esophageal stricture, BE, and EAC28. Based on a case–control study, we previously suggested a causal association of distal esophageal bile exposure and the development of BE29. In addition, we reported the increased levels of micro-RNAs (MIRs) 221 and 222 in
EAC tissues compared with areas of BE from the same patient and found that the exposure of esophageal epithelial cells to bile acids activates Farnesoid X Receptor (FXR) and increases the levels of MIRs 221 and 222, reducing the levels of p27Kip1 and promoting the degradation of caudal type homeobox transcription factor 2 (CDX2) by the proteasome system. These findings led to targeting bile acid reflux as a therapeutic or preventive strategy for BE and EAC. However, despite having a physiological basis, the efficacy of bile acid-binding agents (bile acid sequestrants) such as cholestyramine is unproven.

**CONCLUSION**

In this study, we outlined the potentials of P-CAB and bile acid sequestrants as novel drug therapies for the treatment of GERD. The P-CAB revaprazan and VPZ have already been used in South Korea and Japan, respectively, whereas tegoprazan is currently being subjected to clinical trials in South Korea. The three P-CABs currently available or in the final stage of the pipeline have different degrees of effectiveness in the treatment of GERD, which should continue to be evaluated to develop a treatment with maximum effectiveness and guaranteed safety. In contrast, bile acid sequestrants are predicted to be effective in suppressing duodenogastic-esophageal reflux, especially reflux of bile acid, which is considered as an underlying mechanism in GERD and its complications. However, their clinical efficacy remains to be examined in further clinical studies.

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