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MINIREVIEWS

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MINIREVIEWS

Potassium-competitive acid blockers - are they the next generation of proton pump inhibitors?

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Abstract

The modern lifestyle caters to an increase in the incidence of peptic ulcer disease, gastroesophageal reflux disease and several other acid-related conditions of the gut. The drugs to prevent these conditions work either through H2 receptor blockade or inhibition of the H^+, K^+ ATPase enzyme. Although proton pump inhibitors have been proven to be efficacious, they have a slow onset of action with limited resolution of symptoms in most patients. Potassium-competitive acid blockers (P-CABs) are novel drugs that bind reversibly to K^+ ions and block the H^+, K^+ ATPase enzyme, thus preventing acid production. P-CABs have a fast onset of action and have dose-dependent effects on acid production. Animal studies exist that differentiate the better results of P-CABs from proton pump inhibitors; further human trials will give a comprehensive picture of the results and will help to elucidate the therapeutic benefits of this new group of drugs.

Key words: Potassium-competitive acid blockers; Gastroesophageal reflux disease; Proton pump inhibitors; Peptic ulcer disease; Vonoprazan

Core tip: There have been tremendous changes in the treatment of acid-related diseases. In this rapidly evolving field, novel drugs such as potassium-competitive acid blockers (P-CABs) show promising potential. This review aims to provide a perspective on this new class of drugs by summarizing the mechanism of action, therapeutic benefits, adverse effects and approval status of various P-CABs in the market.

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INTRODUCTION

A principal and vital component aiding in digestion is gastric acid. Gastric acid is secreted by the parietal cells into the lumen of the stomach. However, gastric acid is also responsible for the pathogenesis of gastric ulcers, gastroesophageal reflux disease (GERD), nonsteroidal anti-inflammatory drug-induced gastrointestinal damage and ulcers in Zollinger Ellison Syndrome. The identification of the bacterium *Helicobacter pylori* (*H. pylori*) as the cause for peptic ulcer was a breakthrough approximately 30 years ago, and *H. pylori* eradication could prevent or cure these conditions. The cure is directly related to the decrease in acid secretion by parietal cells[1].

Gastric acid is secreted by the parietal cells of the gastric glands. This secretion is related to food intake, although it can also occur due to the taste, smell or thought of food. The stimulation of the parietal cell occurs through 3 kinds of receptors namely, H2 (histamine) receptors, M3 (cholinergic muscarinic) receptors and CCK2R (gastrin receptors)[1,2].

HISTORY OF POTASSIUM-COMPETITIVE ACID BLOCKERS - VARIOUS DRUG TYPES

Potassium-competitive acid blockers (P-CABs) are a group of drugs developed in the early 1980s. The first drug developed was SCH28080, an antisecretory drug that inhibited H^+, K^+ ATPase via a competitive interaction with K^+ site of the enzyme. However, further development of the drug was stopped due to its toxic effects on the liver[2]. Another drug was developed, AZD0865, which was potent but a reversible inhibitor of H^+, K^+ ATPase with a rapid onset of action. In phase II and III trials, this drug displayed similar efficacy to esomeprazole for treating esophagitis and for symptomatic relief of nonerosive reflux disease (NERD); however further trials could not be conducted on this drug, as it was not superior to esomeprazole, and there was an adverse drug reaction: hepatotoxicity with reversible elevation of hepatic transaminases[3]. The first P-CAB used in clinical practice was revaprazan (YH-1885, Revanex), marketed in South Korea. Like other P-CABs, it had a quick action onset, however, was not superior to the existing proton pump inhibitors (PPIs)[4]. The second P-CAB introduced in clinical practice was vonoprazan fumarate (TAK-438), marketed in Japan in early 2015; it became popular because of its superior properties such as rapid onset of action, long duration of action, and consistent and potent acid suppression compared to the traditional PPIs[4].

Phase III trials were conducted in South Korea for reflux esophagitis for comparing the safety and efficacy of a new P-CAB, tegoprazan (RQ-00000004/CJ-12420) 50 mg and 100 mg along with esomeprazole. The complete and final results of this study are not yet published[4]. Tegoprazan was approved for the treatment of erosive esophagitis (EE) and NERD in South Korea in July 2018.

MECHANISM OF ACTION/PHARMACOKINETICS

The P-CABs are weak bases, and the protonated form of these drugs inhibits the H^+ K^+ ATPase enzyme. It is found that linaprazan's potency was high when it was exposed to vesicles that are ion-tight rather than to ion-leaky vesicles. This suggests that the drug gets concentrated under low pH and acts in the gastric lumen. The pKa of these drugs varies: 5.6 (SCH28080), 6.1 (linaprazan) and 9.3 (vonoprazan). Since the pKa of vonoprazan is high at 9.3, most of it gets protonated easily and exerts its inhibitory action. Additionally, since the protonated forms are less prone to cross membranes than the nonionic molecules, these protonated forms of P-CABs concentrate in the acid-secreting canaliculi of parietal calls where they exert the effect of H^+ K^+ ATPase enzyme inhibition[5].

THERAPEUTIC BENEFITS OF P-CABs

GERD is a common condition where reflux of the gastric contents leads to various gastrointestinal symptoms and complications. Most patients have one of 3 types, namely, NERD, EE and Barrett's esophagus.

PPIs and H2 receptor antagonists are the current treatment of choice of this condition, which causes gastric acid suppression. The main goals of the treatment are to give symptomatic relief, heal and maintain remission of EE, prevent complications and improve the quality of life. Presently, there are several unmet needs in this therapy[6].

P-CABs represent a heterogeneous group of drugs which inhibit H^+, K^+ ATPase in a potassium-competitive reversible mechanism. They do not require proton pump activation to achieve their action; further, they have rapid action onset and reduce acid secretion due to a steady rise in their plasma concentration.

Vonoprazan is an acid-stable and fast absorbing drug approved for the treatment of reflux esophagitis for prevention of relapse[7]. In GERD, vonoprazan improves epigastric pain, postprandial distress, constipation, and diarrhea[8]. Linaprazan (AZD8065) has shown similar efficacy as esomeprazole in healing and preventing symptoms of GERD with EE; however, it has not shown any benefit in patients with NERD. Soraprazan showed immediate acid suppression in *in vitro* studies. It was also found to be superior to esomeprazole in rapid action onset and the duration of maintaining gastric pH > 4 in animal models. However, no clinical studies are available for this drug. Revaprazan was found to be similar to PPIs in acid suppression[6].

Peptic ulcer disease

Vonoprazan has been approved in Japan for the treatment of gastric and duodenal ulcers[7]. Two randomized controlled trials were conducted to evaluate the drugs vonoprazan and lansoprazole for the treatment of gastric ulcer (GU) and duodenal ulcer (DU). For GU, approximately 93.5% of patients treated with vonoprazan and 93.8% of patients treated with lansoprazole achieved a cure. It was then confirmed that vonoprazan is equally effective as lansoprazole with only a difference of 0.3% in cure rate. In the case of DU, 95.5% of patients on vonoprazan and 98.3% on lansoprazole achieved a cure. Here, the difference is 2.8%, and hence, vonoprazan was not confirmed to be superior or equally potent as lansoprazole. However, it was found that the treatment-emergent adverse events were slightly lower in GU than DU with vonoprazan. There was a single death case reported due to subarachnoid hemorrhage in the vonoprazan-treated DU group; the possibility of a causal association between the study drug and the unexpected death could not be ruled out. The study concluded that vonoprazan 20 mg has a tolerability profile similar to that of lansoprazole 30 mg with similar efficacy in DU healing and noninferior with respect to GU healing[9].

H. pylori eradication

A multicenter study was done to assess the safety and efficacy of vonoprazan-based triple treatment. The triple therapy included treatment with vonoprazan and two antibiotics (amoxicillin and clarithromycin or metronidazole). The eradication among 799 patients in the study was 94.4% in the per-protocol analysis for the first-line therapy and 97.1% for the second-line therapy. The first line included vonoprazan 20 mg, amoxicillin 750 mg and clarithromycin 200 or 400 mg, twice a day for one week and the second line included vonoprazan 20 mg, amoxicillin 750 mg, and metronidazole 250 mg, twice a day for one week. The incidence of adverse events was 4.4% with no patients hospitalized. It was thus concluded that vonoprazan-based triple therapy was safe and effective for *H. pylori* eradication[10].

Clinical studies were done in Japan to determine if P-CABs specifically showed superiority to PPIs for the eradication of *H. pylori*[11]. Approximately 573 patients who underwent *H. pylori* eradication therapy were reviewed retrospectively. The therapy included treatment with clarithromycin 200 mg, amoxicillin 750 mg and an acid-suppressing drug -lansoprazole 30 mg, rabeprazole 10 mg, esomeprazole 20 mg or vonoprazan 20 mg - taken twice daily for 1 wk. The *H. pylori* eradication was successful in approximately 73% of patients using intention-to-treat (ITT) analysis and 76% of patients in per protocol (PP) analysis. The vonoprazan-treated group had a significant and superior eradication rate of 83% in ITT and 85% in PP compared to the results for lansoprazole (66% ITT and 69% PP) and rabeprazole (67% ITT and 70% PP); however, the eradication rate of esomeprazole was similar - 83% ITT and 87% PP. Although the eradication rates with vonoprazan and esomeprazole were not significantly higher than that of the lansoprazole and rabeprazole groups with both ITT and PP analysis in mild gastric atrophy patients, the effects were significantly higher in severe gastric atrophy patients[11]. Further, the group treated with vonoprazan had a significantly higher eradication rate of *H. pylori* than the other

groups with a > 80% eradication rate irrespective of the degree of atrophy[11].

Endoscopic submucosal dissection induced artificial ulcers

Although vonoprazan is found to be superior to PPIs in inhibiting acid secretion, its efficacy in endoscopic submucosal dissection (ESD)-induced artificial ulcers was not found to be superior to any PPIs. A randomized prospective study was done to compare and assess the effects of vonoprazan and lansoprazole for ESD-induced artificial ulcers. This prospective study included 149 patients who had ESD for treatment of early gastric cancers for the period Apr 2015 to May 2017. Treatment was randomly provided with oral vonoprazan 20 mg/d or oral lansoprazole 30 mg/d. The primary endpoint was area and shrinkage ratio of the ulcers at 4 and 8 wk after ESD. Data were analyzed from 129 patients, and it was found that there was no significant difference between the vonoprazan and lansoprazole groups in the area and the shrinkage ratio of the ulcers at 4 and 8 wk respectively. Hence, it was concluded that vonoprazan and lansoprazole are equally effective in the treatment of ESD-induced artificial ulcers[12].

Secondary prevention of low dose aspirin or nonsteroidal anti-inflammatory drug induced gastric mucosal damage

Vonoprazan 10 mg and 20 mg were found to be very well tolerated and effective for the prevention of nonsteroidal anti-inflammatory drug (NSAID) related recurrence of peptic ulcer in Japanese patients, and this preventive action could be maintained with long-term use. A daily dose of vonoprazan 10 mg has been approved in Japan as the recommended clinical dose for the prevention of NSAID induced ulcers. It is foreseen that vonoprazan could become the primary treatment option for NSAID related adverse events in high-risk patients[13].

ADVERSE EVENTS OF P-CABs

Liver toxicity: The earlier P-CABs are not being used clinically worldwide due to their short duration of action and hepatotoxicity. These earlier P-CABs included SCH28080 (imidazopyridine), AZD0865, pyrimidines, imidazonaphthyridines and pyrrolopyridazines[14].

A phase III double-blinded, placebo-controlled, parallel group, multicenter study was conducted in Japan in patients aged ≥ 20 years with Grade N or M NERD and recurrent acid reflux symptoms. The incidence of the treatment-emergent adverse event (TEAE) was 32.7% with placebo, 27.7% with vonoprazan 10 mg and 28% with vonoprazan 20 mg. The most common TEAE with vonoprazan 10 mg and 20 mg in clinical studies was nasopharyngitis. Most of the TEAEs were mild, and no deaths were reported. One serious adverse event, diverticulitis, was reported in the vonoprazan 10 mg group and was considered to be likely due to the drug. Additionally, the mean levels of gastrin, pepsinogen I and pepsinogen II increased after administration of vonoprazan 10 mg and 20 mg[15]. Mild to moderate constipation or diarrhea was reported in certain preapproved clinical studies where vonoprazan was used for treating acid-related disorders[16].

OTHER P-CABs ON THE MARKET

Tegoprazan (CJ-12420) is a newer P-CAB with a potential to treat GERD. A phase I, randomized, double-blinded, placebo-controlled clinical study was conducted in 56 healthy Korean male volunteers. CJ-12420 was administered to 32 subjects in the doses of 50, 100, 200 and 400 mg in the single ascending dose (SAD) study. Either 100 or 200 mg of the drug was administered every 24 h to 8 subjects for 7 d in a multiple ascending dose (MAD) study. The plasma concentration of CJ-12420 and its metabolite M1 were measured by liquid chromatography-mass spectrometry. There were few adverse events reported in this study, and all were mild in nature. It was concluded that the drug tegoprazan is well tolerated in healthy subjects in the SAD and MAD studies. The study could also successfully elucidate the pharmacokinetics of the drug and its metabolite as well as the pharmacodynamics of gastric pH, thus providing clinical evidence that the drug can be used to treat acid-related disorders[17].

APPROVAL STATUS

Revaprazan was developed in Korea and was the first P-CAB approved. It is also

available in India. Vonoprazan was developed by Takeda; it was approved in Japan in February 2015 for the treatment of acid-related diseases which include reflux esophagitis, GERD, *H. pylori* eradication, EE and peptic ulcer disease (PUD). In the United Kingdom, phase I studies were conducted for GERD, however, no further update was reported[18]. Tegoprazan was approved for the treatment of erosive esophagitis (EE) and NERD in Korea in July 2018. The drugs vonoprazan and revaprazan are currently not available outside Asia, Europe and the United States[19].

CONCLUSION

Over the past 40 years, there have been tremendous changes in the treatment of acid-related diseases from diet and surgery to H2 receptor antagonists and then PPIs. Acid-related disorders are the result of excessive production of acid or decreased mucosal defense. The diseases such as GERD and PUD are important health care problems because of chronicity and high prevalence. Drug-induced gastric acid suppression is the principal component in the treatment of these conditions[20,21]. There has been observed variability in the management of various acid-related disorders, partly due to regional variations in the disease severity and prevalence and partly due to variations in the clinician assessment and application of various published evidence[22]. The first group of drugs identified for inhibition of acid secretion was H2 receptor antagonists in the 1970s. These drugs were not very effective due to a short duration of action, development of drug tolerance after several days of treatment, and finally, it was also found that their effect on meal-stimulated acid secretion was limited compared to their effect on acid secretion in the night. These drugs were then followed by irreversible inhibitors of H^+, K^+ ATPase enzyme - the PPIs, which were more effective in acid suppression[23]. The majority of patients were treated with a once-daily regimen of PPIs. However, there was a subgroup of patients who developed refractoriness to PPI therapy, most likely due to lack of drug effect, reflux patterns, reduced bioavailability of the PPIs, and increased metabolism of the drug and rarely due to mutations in cytochrome P450[24]. Another disadvantage of PPIs was a requirement of acidic parietal cell pH to facilitate the conversion of the prodrug to active form for the pharmacological effect. Considering the various limitations in PPIs, further research was done, and a considerable effort was put in to develop a different kind of inhibitor of H^+, K^+ ATPase without any of the limitations of PPIs. These K^+ competitive acid antagonists or blockers do not depend on acid activation and bind to the enzyme directly with a rapid action onset and better control of acid secretion. However, since they bind reversibly and not covalently, a constant plasma concentration of the drug has to be maintained for the sustained effect. They have a shorter duration of action than the PPIs, but then they are acid stable and are readily formulated into an extended-release tablet for a long duration of action, or they can be given twice daily to inhibit acid secretion during the day and night time[25]. The earlier drugs in this category were discontinued due to liver toxicity and then came TAK-438 (vonoprazan), a novel P-CAB antisecretory agent which had superior efficacy compared to PPIs and less incidence of adverse drug reactions[26]. Various studies were conducted on vonoprazan individually and in comparison with PPIs, and it was found that the drug was well tolerated and produced a rapid, profound and sustained suppression of gastric acid secretion. Because of the tolerability and enhanced effectiveness of P-CABs, it is very likely that they will change the future of treatment of acid-related disorders.

REFERENCES

1 **Inatomi N**, Matsukawa J, Sakurai Y, Otake K. Potassium-competitive acid blockers: Advanced therapeutic option for acid-related diseases. *Pharmacol Ther* 2016; **168**: 12-22 [PMID: 27514776 DOI: 10.1016/j.pharmthera.2016.08.001]

2 **Andersson K**, Carlsson E. Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases. *Pharmacol Ther* 2005; **108**: 294-307 [PMID: 16000224 DOI: 10.1016/j.pharmthera.2005.05.005]

3 **Dent J**, Kahrilas PJ, Hatlebakk J, Vakil N, Denison H, Franzén S, Lundborg P. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol* 2008; **103**: 20-26 [PMID: 18184117 DOI: 10.1111/j.1572-0241.2007.01544.x]

4 **Sugano K**. Vonoprazan fumarate, a novel potassium-competitive acid blocker, in the management of gastroesophageal reflux disease: safety and clinical evidence to date. *Therap Adv Gastroenterol* 2018; **11**: 1756283X17745776 [PMID: 29383028 DOI: 10.1177/1756283X17745776]

5 **Hunt RH**, Scarpignato C. Potassium-Competitive Acid Blockers (P-CABs): Are They Finally Ready for Prime Time in Acid-Related Disease? *Clin Transl Gastroenterol* 2015; **6**: e119 [PMID: 26513137 DOI: 10.1038/ctg.2015.39]

6 **Maradey-Romero C**, Fass R. New and future drug development for gastroesophageal reflux

disease. *J Neurogastroenterol Motil* 2014; **20**: 6-16 [PMID: 24466441 DOI: 10.5056/jnm.2014.20.1.6]
7 **Graham DY**, Dore MP. Update on the Use of Vonoprazan: A Competitive Acid Blocker. *Gastroenterology* 2018; **154**: 462-466 [PMID: 29337157 DOI: 10.1053/j.gastro.2018.01.018]
8 **Shinozaki S**, Osawa H, Hayashi Y, Sakamoto H, Miura Y, Lefor AK, Yamamoto H. Vonoprazan treatment improves gastrointestinal symptoms in patients with gastroesophageal reflux disease. *Kaohsiung J Med Sci* 2017; **33**: 616-622 [PMID: 29132551 DOI: 10.1016/j.kjms.2017.07.004]
9 **Miwa H**, Uedo N, Watari J, Mori Y, Sakurai Y, Takanami Y, Nishimura A, Tatsumi T, Sakaki N. Randomised clinical trial: efficacy and safety of vonoprazan vs. lansoprazole in patients with gastric or duodenal ulcers - results from two phase 3, non-inferiority randomised controlled trials. *Aliment Pharmacol Ther* 2017; **45**: 240-252 [PMID: 27891632 DOI: 10.1111/apt.13876]
10 **Tanabe H**, Ando K, Sato K, Ito T, Goto M, Sato T, Fujinaga A, Kawamoto T, Utsumi T, Yanagawa N. Efficacy of Vonoprazan-Based Triple Therapy for Helicobacter pylori Eradication: A Multicenter Study and a Review of the Literature. *Dig Dis Sci* 2017; **62**: 3069-3076 [PMID: 28664410 DOI: 10.1007/s10620-017-4664-1]
11 **Shinozaki S**, Nomoto H, Kondo Y, Sakamoto H, Hayashi Y, Yamamoto H, Lefor AK, Osawa H. Comparison of vonoprazan and proton pump inhibitors for eradication of Helicobacter pylori. *Kaohsiung J Med Sci* 2016; **32**: 255-260 [PMID: 27316584 DOI: 10.1016/j.kjms.2016.04.009]
12 **Hirai A**, Takeuchi T, Takahashi Y, Kawaguchi S, Ota K, Harada S, Kojima Y, Tominaga K, Tokioka S, Higuchi K. Comparison of the Effects of Vonoprazan and Lansoprazole for Treating Endoscopic Submucosal Dissection-Induced Artificial Ulcers. *Dig Dis Sci* 2018; **63**: 974-981 [PMID: 29464587 DOI: 10.1007/s10620-018-4948-0]
13 **Mizokami Y**, Oda K, Funao N, Nishimura A, Soen S, Kawai T, Ashida K, Sugano K. Vonoprazan prevents ulcer recurrence during long-term NSAID therapy: randomised, lansoprazole-controlled non-inferiority and single-blind extension study. *Gut* 2018; **67**: 1042-1051 [PMID: 28988197 DOI: 10.1136/gutjnl-2017-314010]
14 **Hori Y**, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. *J Pharmacol Exp Ther* 2011; **337**: 797-804 [PMID: 21411494 DOI: 10.1124/jpet.111.179556]
15 **Kinoshita Y**, Sakurai Y, Shiino M, Kudou K, Nishimura A, Miyagi T, Iwakiri K, Umegaki E, Ashida K. Evaluation of the Efficacy and Safety of Vonoprazan in Patients with Nonerosive Gastroesophageal Reflux Disease: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. *Curr Ther Res Clin Exp* 2016; **81-82**: 1-7 [PMID: 28119763 DOI: 10.1016/j.curtheres.2016.12.001]
16 **Echizen H**. The First-in-Class Potassium-Competitive Acid Blocker, Vonoprazan Fumarate: Pharmacokinetic and Pharmacodynamic Considerations. *Clin Pharmacokinet* 2016; **55**: 409-418 [PMID: 26369775 DOI: 10.1007/s40262-015-0326-7]
17 **Han MH**, Park C, Lee DS, Hong SH, Choi IW, Kim GY, Choi SH, Shim JH, Chae JI, Yoo YH. Cytoprotective effects of esculetin against oxidative stress are associated with the upregulation of Nrf2-mediated NQO1 expression via the activation of the ERK pathway. *Int J Mol Med* 2017; **39**: 380-386 [PMID: 28000844 DOI: 10.3892/ijmm.2016.2834]
18 **Garnock-Jones KP**. Vonoprazan: first global approval. *Drugs* 2015; **75**: 439-443 [PMID: 25744862 DOI: 10.1007/s40265-015-0368-z]
19 **Oshima T**, Miwa H. Potent Potassium-competitive Acid Blockers: A New Era for the Treatment of Acid-related Diseases. *J Neurogastroenterol Motil* 2018; **24**: 334-344 [PMID: 29739175 DOI: 10.5056/jnm18029]
20 **Jenkins H**, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, Yoneyama T, Ashida K, Ogama Y, Warrington S. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 2015; **41**: 636-648 [PMID: 25707624 DOI: 10.1111/apt.13121]
21 **Mejia A**, Kraft WK. Acid peptic diseases: pharmacological approach to treatment. *Expert Rev Clin Pharmacol* 2009; **2**: 295-314 [PMID: 21822447 DOI: 10.1586/ecp.09.8]
22 **Boeckxstaens G**, El-Serag HB, Smout AJ, Kahrilas PJ. Symptomatic reflux disease: the present, the past and the future. *Gut* 2014; **63**: 1185-1193 [PMID: 24607936 DOI: 10.1136/gutjnl-2013-306393]
23 **Shin JM**, Vagin O, Munson K, Kidd M, Modlin IM, Sachs G. Molecular mechanisms in therapy of acid-related diseases. *Cell Mol Life Sci* 2008; **65**: 264-281 [PMID: 17928953 DOI: 10.1007/s00018-007-7249-x]
24 **Cicala M**, Emerenziani S, Guarino MP, Ribolsi M. Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease. *World J Gastroenterol* 2013; **19**: 6529-6535 [PMID: 24151377 DOI: 10.3748/wjg.v19.i39.6529]
25 **Sachs G**, Shin JM, Vagin O, Lambrecht N, Yakubov I, Munson K. The gastric H,K ATPase as a drug target: past, present, and future. *J Clin Gastroenterol* 2007; **41** Suppl 2: S226-S242 [PMID: 17575528 DOI: 10.1097/MCG.0b013e31803233b7]
26 **Matsukawa J**, Hori Y, Nishida H, Kajino M, Inatomi N. A comparative study on the modes of action of TAK-438, a novel potassium-competitive acid blocker, and lansoprazole in primary cultured rabbit gastric glands. *Biochem Pharmacol* 2011; **81**: 1145-1151 [PMID: 21371447 DOI: 10.1016/j.bcp.2011.02.009]

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