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Mini Review

# Potassium-Competitive Acid Blocker: Novel Class of Anti-Acid Drug

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## Abstract

Over the past several decades, great progress has been made on understanding mechanisms of gastric acid secretion for developing new anti-acid drugs. Until now most commonly used anti-acid drugs are histamine-2 receptor antagonists and proton pump inhibitors (PPIs) for patients to control acid related disease. However, several clinical limitations of these drugs had been reported. Recently, a new generation of potassium-competitive acid blockers (P-CABs) were launched for clinical use. It has been shown that these new drugs are more convenient and powerful to treat gastric acid-related diseases. In this article, we briefly reviewed the clinical use of this new anti-acid drug P-CAB.

**Keywords:** Potassium-competitive Acid Blocker; Potassium channel; H+/K+-ATPase

## Introduction

H+/K+-ATPase (or proton pump), which is expressed in gastric parietal cells, is one of the potassium transporters acting in the last stage involved in gastric acid production and secretion [1]. It functions in the parietal cells that pump out protons into the luminal space of gastric glands to reach a level of one million-fold enrichment of H+ in the gastric juice. At the same time the K+ is absorbed into the cell, which is coupled with K+ recycling by potassium channels [2,3]. The gastric H+/K+-ATPase has a half-life of 50h, hence about 25% of proton pumps are newly synthesized per day, at a rate of about 1% per hour [4]. The importance of K+ in the production of gastric acid makes its regulation a potential target for treatment [5].

## Discussion

### Clinical Limitation of PPIS

Since proton pump inhibitors (PPI) were first discovered in 1981, several types of PPIs have been used in the treatment of acid–related diseases such as peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD) for the past 30 years [6,7]. PPIs bind irreversibly to the gastric H+/K+-ATPase and inhibit potassium recycling, thus this inhibition is long-lasting and dose not show rapid tolerance which allows acid rebound following withdrawal that had also appeared in histamine-2 receptor antagonists. However, they have short plasma half-life of about 2hrs and are rapidly degraded in vivo and bind only to activated proton pump. Therefore, these drugs require daily dosing of 4 to 5 days to achieve the maximum efficacy [8]. There were many cases in which they were unable to demonstrate sufficient effect when the medication time was not properly maintained before a meal. PPIs binding only to active form of proton pump have been known clinically to be limited to increase the pH to only around 4.0. Meanwhile, it has been reported that increasing the pH to 6.0 instead of to 4.0 for Helicobacter pylori eradication is more effective [9].

### Novel P-CAB Class Drugs

Potassium-competitive acid blocker (P-CAB) reversibly inhibits acid secretion by competing with the potassium ion on the luminal surface of the gastric wall H+/K+-ATPase. The first developed

compound was SCH28080 in 1982 [10]. Animal and early clinical studies have shown that P-CAB is highly selective for gastric H+/K+-ATPase and inhibits gastric acid secretion with fast onset of action [11]. SCH28080 has been used extensively to reveal the mechanism of proton pump inhibition. However, the first-generation drugs did not come out due to its brief action time and hepatotoxicity [12]. The new generation of P-CAB drugs, Vonoprazan (TAK-438) and Tegoprazan (CJ-12420) that overcome these shortcomings were recently launched [13,14]. These drugs block not only the proton pump in the active form but also the inactive form proton pump, thereby effectively increasing intraluminal pH to 6.0. In the case of vonoprazan, 98% of H. pylori eradication treatment results were reported [15]. The comparisons between PPI and P-CAB products are shown below in the Table 1.

**Table 1:** The differences between PPIs and P-CABs.

| PPIs | P-CABs |
|---|---|
| Prodrug and unstable in acid | No need for conversion and stable in acid |
| Irreversible binding to the external surface of proton pump | Reversible binding to K+ binding domain of proton pump |
| Need to stimulate proton pump | No food effect |
| Inhibit activated proton pump only | Block both resting and stimulated proton pump |
| Take 4~5days to maximal effect | On demand control due to Fast onset |

## Conclusion

Advantages of P-CAB versus PPI include the rapidly and more potent acid suppression, stable in acid condition, meal independent, able to elevate pH to 6.0 and better treatment of PUD, GERD, and H. pylori eradication. It is predicted that P-CAB drugs will be widely used as next generation drugs overcoming the shortcomings of existing PPI drugs.

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