



Role of potassium-competitive acid blockers in eradication of *Helicobacter pylori* infection

Tae Ho Kim

Division of Gastroenterology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Korea

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Helicobacter pylori (*H. pylori*) is a gram-negative bacterium. Since its discovery by Barry J. Marshall and J. Robin Warren in 1982, it has been shown through various studies that it can cause various diseases including gastric ulcer, MALT lymphoma, gastric cancer, and gastritis. There was a time when *H. pylori* was considered an innocent bystander because most infected people have no symptoms. But since the Kyoto consensus, it has been regarded as an infectious disease and aggressive *Helicobacter* eradication therapy is recommended [1]. The current standard treatment for *H. pylori* infection is a combination of antibiotics and proton pump inhibitors (PPIs), which suppress gastric acid secretion and increase the efficacy of the antibiotics. However, the eradication rate decreases with increasing resistance to antibiotics. Among these antibiotics resistance, clarithromycin resistance is the most significant. Therefore, in low clarithromycin resistance (< 15%) areas, the empirical standard triple therapy consisting of PPI, amoxicillin, and clarithromycin is still used as first-line therapy, but in high clarithromycin resistance (> 15%) areas, bismuth-containing quadruple therapy (PPI, metronidazole, tetracycline, and bismuth) or non-bismuth quadruple concomitant therapy (PPI, amoxicillin, clarithromycin, and metronidazole) is recommended as first-line therapy [2]. Nevertheless, the eradication rates of clarithromycin-based triple therapy or bismuth-containing quadruple therapy remains between 70% and mid-80%. Non-bismuth quadruple concomitant therapy shows an eradication rate of 80–90%, but concomitant therapy has a problem of exposure to various antibiotics.

In addition to antibiotic resistance, various factors have

complex effects on *Helicobacter* eradication, including drug compliance, differences in the degree of gastric acid suppression depending on the drugs used and CYP2C19 genetic polymorphism, and differences in the characteristics of *Helicobacter* itself. Although *H. pylori* can survive in an acidic environment, it actively proliferates in neutral environments, where antibiotics such as clarithromycin act on cell-wall construction are effective. Increasing pH is a factor that significantly affects effective eradication. However, metronidazole, which acts as a mechanism to inhibit nucleic acid synthesis, is relatively less affected by stomach acidity. Strong suppression of gastric acid not only enhances the bactericidal effect of antibiotics, but also increases the concentration of antibiotics in the stomach, and inhibits *H. pylori* by reducing the degradation of *Helicobacter* specific IgA secreted into the stomach [3].

Many attempts have been made to overcome these various limitations, and one of them is to use a potassium-competitive acid blockers (P-CABs) instead of PPIs for eradication therapy [4,5]. P-CABs are agents that inhibit H⁺,K⁺-adenosine triphosphatase (ATPase) through reversible K⁺-competitive ionic binding that results in inhibition of gastric acid secretion. P-CABs are drugs with a stronger acid-suppressing effect than PPIs, and are less affected by the CYP2C19 genotype than PPIs because they are mainly metabolized through CYP3A4. Moreover, the onset of P-CAB activity is faster than that of PPIs and the duration of acid suppression by P-CABs is longer than that by PPIs. In addition, since P-CABs are active drugs, not in the form of prodrugs like PPIs, P-CABs have the advantage of being convenient to take because they can be taken regardless of meals, so it is thought that gastric acid suppression can be achieved more effectively by improving drug compliance [6].

P-CABs are currently developed, approved, and used mainly in Asian countries, but are also approved and used in the United States, Canada, and Europe. Vonoprazan, which is widely used in Japan, tegoprazan, fexuprazan, revaprazan, and linaprazan are currently available, and some companies are developing additional P-CABs. The effect of P-CABs on *H. pylori* eradication is reportedly superior to that of PPIs. In several studies, a 10–30% improvement in eradication rate was detected when using vonoprazan or tegoprazan compared to PPIs. Murakami et al. reported that P-CABs are superior in eradication treatment of CYP2C19 extensive metabolizers. However, there is a limitation that most of the studies were studies using clarithromycin-based triple as first-line therapy [5,6].

Another factor that must be considered in *H. pylori* eradication using P-CABs is the safety of the drug. Known drug adverse reactions of P-CABs include gastrointestinal reactions such as constipation or diarrhea, dermatologic reactions such as skin rash, and hepatic reactions such as elevated liver enzymes, but such reactions are usually not serious and occur rarely [7]. In addition, since the metabolism of P-CABs is less affected by CYP2C19, there are few concerns about drug-drug interactions with commonly prescribed drugs such as clopidogrel, warfarin, phenytoin, and methotrexate [8]. In addition, compared to PPIs, P-CABs have the advantage of rapid attainment of therapeutically effective pH values from day 1 of treatment, so it can be predicted that a shorter treatment period will be possible [9]. This issue should be considered in further research.

The authors' study has the limitation that it was conducted as a single-arm study comparing the eradication rate of tegoprazan-based concomitant therapy with the results of previous studies on PPI-based nonbismuth quadruple therapy and did not show it was helpful in overcoming clarithromycin resistance of *H. pylori* in Korea [10]. But I think it is meaningful in suggesting the possibility of using tegoprazan-based concomitant regimen as first-line therapy relatively safely in areas with high clarithromycin resistance.

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Received : June 6, 2023

Accepted : June 19, 2023

Correspondence to

Tae Ho Kim, M.D., Ph.D.

Division of Gastroenterology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 327 Sosa-ro, Wonmi-gu, Bucheon 14647, Korea

Tel: +82-32-340-7017, Fax: +82-32-340-7227
E-mail: kimtaeho@catholic.ac.kr
<https://orcid.org/0000-0003-2015-5176>

Conflicts of interest

The author discloses no conflicts.

Funding

None