A Novel Potassium-Competitive Acid Blocker Improves the Efficacy of Clarithromycin-containing 7-day Triple Therapy against Helicobacter pylori

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INTRODUCTION

Helicobacter pylori is one of the most prevalent bacterial pathogens and is associated with upper gastrointestinal disorders such as gastritis, peptic ulcer, functional dyspepsia, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer [1-3]. Eradication of H. pylori infection is reported to provide an effective approach to curing or preventing these H. pylori-associated diseases [4, 5].

In the USA, the American College of Gastroenterology guidelines recommend first-line clarithromycin (CAM)-based triple therapy for H. pylori infection; this comprises a proton pump inhibitor (PPI) (standard dose, twice daily), CAM (500 mg, twice daily), and amoxicillin (1 g, twice daily) or metronidazole (400 or 500 mg, twice daily) [6]. As the prevalence of CAM resistance had increased to 29% by 2009 in the USA, the current triple therapy has an H. pylori eradication rate of 70–85% in patients who have not been previously treated with a macrolide antibiotic.

In Europe, the Maastricht IV/Florence Consensus Report recommended that the anti-H. pylori regimen should consider the local CAM resistance rate, with regions of high or low resistance identified using a threshold of 15–20%. In areas with low CAM resistance, CAM-based triple therapy including a PPI, CAM, and amoxicillin or metronidazole is recommended for first-line empirical treatment [7]. The efficacy of this standard triple therapy has significantly decreased to < 80% in many European countries because of the increasing H. pylori resistance to CAM.

In Japan, the Japanese Society for Helicobacter Research recommends a 7-day triple therapy using a PPI (standard dose of omeprazole, lansoprazole, rabeprazole, or esomeprazole;
twice daily), amoxicillin (750 mg, twice daily), and CAM (200 or 400 mg, twice daily); this is the only regimen currently covered by the Japanese national health insurance system. Triple therapy with amoxicillin, CAM, and lansoprazole or rabeprazole is available as a one-sheet tablet; this was prepared to improve drug compliance. Metronidazole-containing salvage therapy for patients where CAM-containing triple therapy has failed to eradicate *H. pylori* consists of a 7-day triple therapy with a PPI (standard dose, twice daily), amoxicillin (750 mg, twice daily), and metronidazole (250 mg, twice daily) [8].

In Japan, CAM-containing 7-day triple therapy was approved for gastric and duodenal ulcers in 2000, when the initial eradication rate was approximately 90% [8]. However, this rate subsequently decreased significantly to 70% [9]. A large-scale nationwide multicenter prospective study of rabeprazole, amoxicillin, and CAM conducted between 2007 and 2009 recorded a successful eradication rate of 80.7% [10]. The effectiveness of this triple therapy has been limited by the increase in CAM resistance, as demonstrated by a 0–33% eradication rate of CAM-resistant bacteria, as compared with 90% of CAM-sensitive bacteria [11, 12]. A working group of the Japanese Society of Helicobacter Research undertook a surveillance study to determine the temporal antimicrobial susceptibility profiles of *H. pylori* isolated during 2002–2006 and 2010–2011 in 67 institutions; this resulted in the analysis of 7,735 isolates. Primary resistance to CAM increased from 19% to 31% as CAM use increased [13]. Furthermore, in the 1990s, the primary resistance rate of CAM was 7.3%. This increased dramatically to 31% in the 2010s, while the primary eradication rate decreased gradually from 89%. Generally, primary resistance to antibiotics arises due to the wider use of these antibiotics in the community as a monotherapy for other indications [8].

Vonoprazan, a potassium-competitive acid blocker (P-CAB) was approved by the Japanese Ministry of Health, Labour and Welfare for the treatment of adult patients with acid-related disease, including gastric ulcer, duodenal ulcer, and reflux esophagitis. This compound is also used to prevent the recurrence of gastric or duodenal ulcers in patients receiving low-dose aspirin or non-steroidal anti-inflammatory drugs, as well as an adjunct to *H. pylori* eradication in patients with gastritis, gastric or duodenal ulcers, gastric mucosa-associated lymphatic tissue lymphoma, idiopathic thrombocytopenic purpura, and after endoscopic resection of early-stage gastric cancer (since December 2014; Takeda media release). The non-inferiority and superiority of vonoprazan to lansoprazole as a component of first-line triple therapy (with amoxicillin and CAM) to eradicate *H. pylori* infection was established in a randomized, double-blind phase III study [14, 15]. Eradication (evaluated by the 13C-urea breath test) was recorded in 92.6% of vonoprazan and 75.9% of lansoprazole recipients (95% confidence interval, CI 11.2–22.1; p < 0.0001) [14]. In patients with CAM-resistant bacteria, the eradication rate was also significantly higher for those treated with vonoprazan, as compared with lansoprazole (82.0 vs. 40.0%; p < 0.0001) [14].

However, there are few reports on the triple therapy for *H. pylori* eradication using a P-CAB. In the present study, we examined the effectiveness of this approach and also investigated the relationship between the eradication rate and the resistance of *H. pylori* to CAM.

**METHODS**

**Patients and study design**

Male or female *H. pylori*-positive patients aged ≥20 years with a history of gastric ulcer, duodenal ulcer, gastro-duodenal ulcer, or gastric tumor were eligible for inclusion in this study. After February 2013, those with a history of gastritis were also eligible for inclusion in the study. The main exclusion criteria comprised previous *H. pylori* eradication therapy, drug allergy, serious cardiovascular, hepatic or renal disorders, a history of gastric surgery, and patients who were judged to be ineligible by their attending physician.

Firstly, we prospectively investigated the *H. pylori* eradication rate from April 2014 to September 2015 in 146 consecutive patients (85 male and 61 female; median age, 66 [52–73] years) who had been diagnosed with *H. pylori* infections using endoscopic biopsy-based tests at Aichi Medical University Hospital. These tests included histopathology and examination of bacterial cultures, including a chemical sensitivity test. This P-CAB group received 7-day triple therapy using vonoprazan (standard dose, twice daily), amoxicillin (750 mg, twice daily), and CAM (400 mg, twice daily). Eradication was determined by performing a 13C-urea breath test 1–2 months after the triple therapy, where ∆ < 2.5‰ was defined as successful.

Secondly, we retrospectively investigated the *H. pylori* eradication rate from January 2011 to September 2015 in 1,305 patients (747 male and 558 female; median age, 64 [55–71] years) who had been diagnosed as *H. pylori*-infected by at least one positive result from a culture test, microscopy or 13C-urea breath test at Aichi Medical University Hospital. This PPI group received a 7-day triple therapy using rabeprazole, CAM, and lansoprazole or esomeprazole twice daily, amoxicillin (750 mg, twice daily), and CAM (200 or 400 mg, twice daily). Successful eradication was determined by performing a 13C-urea breath test 1–2 months after the triple therapy, and ∆ < 2.5‰ was defined as successful.

In both study groups, we investigated whether a number of factors influenced eradication success using univariate and multivariate analysis; these included sex, age, body mass index, smoking and alcohol habits, and CAM-resistance, determined using the flat dilution method and defined as a minimum inhibitory concentration of > 8 μg/ml for *H. pylori*. We also compared the eradication rates of the PPI and P-CAB groups.

This study was approved by the Ethical Committee of the Aichi Medical University (No. 2015-H008).

**Statistical analysis**

The results are presented as medians for quantitative data and as percentages for categorical data. Quantitative data were analyzed using the Mann–Whitney U test and categorical data were analyzed using the χ2 test or Fisher's exact test. Factors found to have a p value of < 0.1 with respect to their effect on eradication success were then evaluated by multiple logistic regression analysis. Factors with a significant effect on *H. pylori* eradication were identified by multiple logistic analysis using
parameters comprising sex, age, and p value of < 0.1 on univariate regression analysis. The odds ratio (OR) and 95% CI values are given for each variable. All statistical analyses were performed by using JMP version 9.02 for Windows software (SAS Institute Inc., Cary, N.C., USA). A p-value < 0.05 was considered significant.

RESULTS

Patient characteristics and H. pylori eradication in the P-CAB and PPI groups

The characteristics of the P-CAB group (n = 146) and the PPI group (n = 1,305) are presented in Table I. More patients in the PPI group had gastric tumors than those in the P-CAB group (p < 0.05). The overall H. pylori eradication rate was significantly higher in the P-CAB group (89.7%; 95% CI, 87.9–91.3) than in the PPI group (73.9%; 95% CI, 66.0–80.8; p < 0.05) (Table I).

Factors affecting eradication success in the P-CAB group

No significant differences were observed in age, sex, body mass index, or smoking and alcohol habits of the P-CAB-treated patients where H. pylori was eradicated, as compared to those where H. pylori was not eradicated. However, the eradicated group comprised significantly more patients who were infected with CAM-sensitive (CAM-S) bacteria, rather than CAM-resistant (CAM-R) bacteria (Table II).

Factors affecting eradication success in the PPI group

No significant differences were observed in age or sex of the PPI-treated patients where H. pylori was eradicated, as compared to those where H. pylori was not eradicated. However, the eradicated group contained significantly more patients who were pretreated with an acid suppressant and who were infected with CAM-S bacteria, as compared with CAM-R. In the PPI group, 25 patients were CAM-S and 13 patients were CAM-R (Table III).

Patient characteristics and H. pylori eradication rates in the CAM sensitivity subgroups

We compared the CAM-S subgroups in the P-CAB and PPI study groups. The eradication rate of CAM-S bacteria in the P-CAB group was 100% (44/44, 95% CI 92.0–100); this was significantly higher than the 88.0% (22/25, 95% CI 68.8–97.5) observed in the PPI group (Fig. 1).

Factors influencing the success of triple therapy

These univariate analyses indicated that CAM resistance was the factor that significantly influenced the success of this therapy and pre-treatment was the factor that significantly influenced success in the PPI group, as evidenced by H. pylori eradication. Multivariate logistic regression analysis indicated that use of PPI and the presence of CAM-R bacteria were predictors of failure to eradicate H. pylori (Table IV).

DISCUSSION

The use of P-CAB, combined with antibiotics, has been demonstrated to protect the stomach and also to increase the H. pylori eradication rate [16]. Antibiotics are more stable in
higher-pH gastric environment; strong gastric acid inhibition therefore increases the efficacy of *H. pylori* eradication. In this study of Japanese patients we demonstrated that a triple therapy that included P-CAB resulted in a greater eradication rate than a triple therapy that included a PPI.

PPIs and P-CABs both inhibit gastric H+/K+ATPase proton pumps, although P-CABs differ from PPIs in that they inhibit this enzyme in a K+-competitive and reversible manner [17]. Vonoprazan is a novel P-CAB that has a potent and long-lasting anti-secretory effect on H+/K+ATPase owing to its high accumulation and slow clearance from gastric tissue [18, 19]. As its inhibitory effect on gastric acid secretion is unaffected by the acid secretory state, the timing of vonoprazan administration is mealtime-independent [19].

The traditional *H. pylori* eradication rate by triple therapy using a PPI, amoxicillin, and CAM is thought to be affected by age, smoking habits, drug compliance, polymorphisms in the cytochrome P450 2C19 (CYP2C19) gene, drug susceptibility, and CAM resistance, which is considered to have a particularly big effect [20–23]. However, it is unclear which of these factors, with the exception of *H. pylori* resistance to antibiotics influences eradication by P-CAB-containing triple therapy.

Smoking has an important effect on eradication failure. A meta-analysis of 22 studies involving 5,538 patients identified an approximately two-fold higher probability of eradication failure in smokers (OR, 1.95; 95% CI 1.55–2.45; p < 0.01) [24]. In our study, however, smoking had no effect on the eradication failure in patients receiving P-CAB-containing triple therapy. Because of the retrospective nature of this study we could not analyze the influence of smoking on eradication in patients receiving the PPI-containing triple therapy.

Proton pump inhibitors are substituted benzimidazole derivatives and are commonly metabolized by hepatic cytochrome P450 enzymes, especially the CYP2C19 subtype. The CYP2C19 genotype can affect therapeutic efficacy by limiting PPI bioavailability and consequently lowering its anti-secretory effect. We did not examine CYP2C19 polymorphisms in the present study and could not determine whether these influenced the eradication observed in the P-CAB and PPI groups. However, previous reports indicated that the efficacy of P-CAB therapy was not influenced by the CYP2C19 genotype [14, 25], because vonoprazan can produce a more sustained elevation of the gastric pH than PPI, regardless of the CYP2C19 genotype [26]. This might partially explain the higher eradication rate of P-CAB-containing triple therapy, as compared with PPI-containing triple therapy, in the present study.

Clarithromycin resistance had a greater effect on triple therapy outcome than metronidazole resistance did, as evident by the decrease in treatment efficacy of 66% versus

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**Fig. 1.** Effects of clarithromycin (CAM) sensitivity and treatment regime on *H. pylori* eradication rates. Patients infected with CAM-sensitive (CAM-S) and CAM-resistant (CAM-R) bacteria in the potassium-competitive acid blocker (P-CAB) and proton pump inhibitor (PPI) groups are compared. There were a significantly higher number of male patients in the CAM-S group than in the CAM-R group. CI, confidence interval; *p < 0.05 for the indicated comparison.

**Table IV.** Multivariate analysis of *H. pylori* eradication success

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1.16</td>
<td>0.2833–4.7559</td>
<td>0.84</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.9733–1.0728</td>
<td>0.38</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>1.45</td>
<td>0.2978–7.0534</td>
<td>0.65</td>
</tr>
<tr>
<td>Acid suppressant</td>
<td>0.11</td>
<td>0.1071–0.0251</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CAM-R (vs. CAM-S)</td>
<td>0.10</td>
<td>0.0233–0.4719</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor; P-CAB: potassium-competitive acid blocker; CAM-S: clarithromycin-sensitive; CAM-R: clarithromycin-resistant; CI: confidence interval.
The present study indicated that the cure rate in resistant infections was unacceptably low. However, vonoprazan would be an appropriate first choice for triple therapy to eradicate H. pylori in Japan.

**Conflicts of interest:** K. Kasugai received research funding and lecture fees from AstraZeneca K.K., Daiichi Sankyo Co. Ltd., and Takeda Pharmaceutical Co. Ltd.

**Author contributions:** H.N., M.S., and K.K. designed the study. H.N., S.N., T.Y., S.G., K.K., S.I., M.E., S.Y., N.O., and K.K. collected data and carried out the study. H.N., M.S., N.O., and K.K. analyzed the data. All authors contributed to the writing and approved the manuscript.

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Un nou blocant al secretei acide gastrice, competitiv cu potasiul, ameliorează eficacitatea triplei terapii de 7 zile conținând claritromicină în infecția cu *Helicobacter pylori*

**ABSTRACT / REZUMAT**

**Premize și Scop:** În Japonia, tripla terapie de 7 zile a infecției cu *Helicobacter pylori*, care include claritromicină (CAM), a fost aprobată în anul 2000. Dar rezistența consecutivă la antibiotice a redus rata de eficiență a acesteia la un nivel inacceptabil (70%). Vonoprazan, un blocant acid competitiv cu potasiul (P-CAB), cu administrare orală, a fost aprobat în Japonia în 2014. Acesta ar putea ameliora rata de eradicare prin creșterea pH-ului intragastric, măriind astfel susceptibilitatea bacteriană la antibiotice. Studiul de față compara eficacitatea triplei terapii de 7 zile care include CAM și fie vonoprazan (P-CAB), fie un inhibitor de pompă de protoni (PPI).

**Pacienți și Metodă:** Am analizat prospectiv ratele de eradicare a *H. pylori* la 146 pacienți care au primit tripla terapie conținând P-CAB (înrolați în perioada aprilie 2015 - septembrie 2015) și retrospectiv la o cohortă de pacienți care au primit tripla terapie de 7 zile conținând PPI (în perioada aprilie 2011 – septembrie 2015).

**Rezultate:** *H. pylori* a fost eradicat la un număr semnificativ mai mare de pacienți tratați cu P-CAB (89.7% [131/146]) decât de pacienți tratați cu PPI (73.9% [965/1305]; p < 0.05). Ratele de eradicare la pacienții tratați cu P-CAB care aveau infecție sensibilă la CAM și la cei cu infecție rezistentă la CAM au fost de 100% (44/44) și, respectiv, 87.5% (28/32). Aceste rate au fost semnificativ mai mari decât cele corespunzătoare la pacienții tratați cu PPI (88.0% [22/25], respectiv 53.8% [7/13], p < 0.05).

**Concluzie:** P-CAB ameliorează eficacitatea triplei terapii de 7 zile conținând CAM, și ar putea reprezenta un tratament eficient de primă linie al infecției cu *H. pylori*. 