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# The Influence of Pre-Treatment with a Proton Pump Inhibitor / H2 Receptor Antagonists on *Helicobacter pylori* Eradication

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*H. pylori*; Eradication therapy; PPI; H2 receptor antagonist; Triple therapy

## 1. Abstract

Vonoprazan (VPZ) is more useful than proton pump inhibitor (PPI)-based regimen as *H. pylori* eradication therapy. It is controversial whether pretreatment with H2 receptor antagonist (H2RA) or PPI before *H. pylori* eradication treatment increases or decreases the eradication rate. In this retrospective study, 802 patients with *H. pylori* infection were treated. We compared the efficacy of eradication regimen [VPZ (n=202), esomeprazole (EPZ) (n=198), sodium rabeprazole (RPZ) (n=200) or lansoprazole (LPZ)(n=202)/amoxicillin/clarithromycin] in patients with *H. pylori* infection with or without H2RA or PPI pretreatment. Analysis of variance, Tukey-Kramer multiple-comparison test and logistic regression analysis were used. In VPZ group, the eradication rate of non-received pretreatment group (94.7%) was significantly higher than PPI (75.0% $p$ = 0.0085) and H2RA (73.7% $p$ = 0.0116) pretreatment received group in the per protocol (PP) analysis. In EPZ, RPZ and LPZ group, no significant difference in the eradication rate was observed between non-received pretreatment group and PPI / H2RA pretreatment received group. Multivariate analysis showed that non-pretreatment of PPI or H2RA was predicting factor. Pretreatment with PPI and H2RA decreases the probability of *H. pylori* eradication in VPZ-based triple therapy.

## 2. Introduction

Vonoprazan fumarate (VPZ), a first-in-class potassium-competitive blocker, is a new potassium-competitive acid blocker (P-CAB) developed to resolve the limitations of conventional proton pump inhibitors (PPI), and can inhibit the $H^+$, $K^+$-ATPase-mediated gastric acid secretion. VPZ is metabolized mainly by CYP3A4, and partially also by CYP2B6 and CYP2C19, CYP2D6 and SULT2A1, which means that the plasma concentrations and acid inhibition induced by VPZ are less affected by genetic polymorphism in drug metabolizing enzymes, such as CYP2C19, than by polymorphisms in enzymes metabolizing other PPIs [1]. The onset of the acid-inhibitory effect was more rapid with VPZ than with EPZ or RPZ. Compared to EPZ and RPZ, VPZ held pH above 4 for a longer period of time [2]. A report that compared VPZ-based with LPZ-based first-line triple therapy showed significantly higher *H. pylori* eradication rates using VPZ among CYP2C19 extensive metabolizers which metabolize PPIs rapidly [3].

Although rapid onset of the acid-inhibitory effect is important for *H. pylori* eradication, it is controversial whether pretreatment with PPI before *H. pylori* eradication treatment increases or decreases the eradication rate. Most of the studies suggested that pretreatment with PPI before *H. pylori* eradication treatment dose not influence the eradication rate [4-11]. Other study suggested that pretreatment with anti secretory drugs increase gastric pH and make effectiveness of antibiotics [12]. On the other hand, the effect of pretreatment with H2 receptor antagonist (H2RA) is unclear. Only one report suggested that pretreatment with H2RA had no significant influence on the efficacy of *H. pylori* eradication treatment [13]. The present retro-

spective study analyzed whether pretreatment with PPI or H2RA decreases or dose not decrease the probability of *H. pylori* eradication.

## 3. Methods

### 3.1. Patients

We retrospectively investigated the *H. pylori* eradication rate over time in 802 patients who visited the outpatient clinic of Horii Clinic (Osaka, Japan) from February 2013 until August 2016, diagnosed by endoscopy as gastric ulcer, duodenal ulcer or gastritis and had been diagnosed as *H. pylori*-infected by at least one positive result for the following tests: [13C]-labeled urea breath test ($^{13}$C-UBT; Ubit, Otsuka Pharmaceuticals, Tokyo, Japan), histology, rapid urease test (Helicocheck Otsuka Pharmaceuticals, Tokyo, Japan), measurement of IgG serology (E plate *H. pylori* antibody II Eiken Chemical, Osaka, Japan), or measurement of *H. pylori* antigen in feces, as recommended by the Japanese Society for Helicobacter Research were selected. 202 patients received eradication therapy including VPZ 20 mg twice as day, AMPC 750 mg twice as day, and CAM 200 mg twice a day (VAC group), 198 patients received eradication therapy including EPZ 20 mg twice as day, AMPC 750 mg twice as day, CAM 200 mg twice a day (EAC group), 200 patients received eradication therapy including RPZ 10 mg twice as day, AMPC 750 mg twice as day, and CAM 200 mg twice a day (RAC group), 202 patients received eradication therapy including LPZ 30 mg twice as day, AMPC 750 mg twice as day, and CAM 200 mg twice a day (LAC group) for seven days, in order to determine the eradication efficacy of the PPIs and P-CAB. VPZ 20 mg tablets (Takeda Pharmaceutical Co. Ltd., Osaka, Japan), EPZ 20 mg capsules (AstraZeneca, Osaka, Japan), RPZ 10 mg tablets (Eisai Co. Ltd., Tokyo, Japan), LPZ 30 mg tablets (Takeda Pharmaceutical Co. Ltd., Osaka, Japan), AMPC 250 mg tablets (Astellas Pharma, Tokyo Japan) and CAM 200 mg tablets (Taisho Pharmaceutical, Tokyo, Japan) were used.

The exclusion criteria were: gastrotomy or vagotomy, previous *H. pylori* eradication treatment using AMPC, CAM or metronidazole (MNZ), past history of drug allergy to PPIs, P-CAB, AMPC or CAM, poor compliance, concomitant liver or kidney disease, severe cardiac or pulmonary disease, suspected or known malignancy.

Successful eradication was determined by performing a UBT following 8 weeks or longer after eradication, and a cut-off value of 2.5‰ was defined as successful eradication. During the observation period, use of bismuth preparations, PPIs, P-CAB were prohibited or restricted.

Analysis of variance, Tukey-Kramer multiple-comparison test and logistic regression analysis were used for the statistical analysis. $p < 0.05$ was considered statistically significant.

This study was approved for implementation by the Medical Ethics Review Committee at Kyoto Prefectural University (reception number ERB-C-908), and was conducted in accordance with the Japanese ethical guidelines for epidemiological research as well as the related laws and regulations in Japan. Information about this study was displayed online and distributed at the study site, and patients were given the opportunity to opt out prior to the results being published. The opt-out method prespecified in the study protocol has been approved by the Medical Ethics Review Committee.

## 4. Results

In this retrospective study, 802 patients with *H. pylori* infection were treated. 202 patients received VAC (vonoprazan + amoxicillin + clarithromycin) therapy, 198 patients received EAC (esomeprazole + amoxicillin + clarithromycin) therapy, 200 patients received RAC (rabeprazole + amoxicillin + clarithromycin) therapy and 202 patients received LAC (lansoprazole + amoxicillin + clarithromycin) therapy. Patients were diagnosed with gastric ulcers ($n$ = 71), duodenal ulcers ($n$ = 94), both gastric and duodenal ulcers ($n$ = 28) or atrophic gastritis ($n$ = 609) with *H.pylori* infection. The demographic and clinical characteristics of the patients in the four groups were comparable (Table 1). Mean age ± SD was 60.4 ± 13.0 years. There were 343 males (42.8%). The rate of males in VAC group was significantly lower than other three groups, but there were no significant differences found in age or diseases between the four groups. For the initial determination of *H. pylori* infection status, a rapid urease test was performed in 281 patients (35.0%), serum antibody test in 431 patients (53.7%), UBT in 25 patients (3.1%), histopathology of biopsy specimens in 45 patients (5.6%), stool antigen test in 18 patients (2.3%) and urine antibody test in 2 patients (0.2%). 24 patients in the VAC group, 18 patients in the EAC group, 19 patients in the RAC group and 21 patients in the LAC group were lost to follow up. No patient in all groups was excluded due to adverse events.

**Table 1:** Clinical characteristics of the patients in the present study

ITT, intention-to-treat; PP, per protocol; VAC, VPZ + AMPC + CAM; EAC, EPZ + AMPC + CAM; RAC, RPZ + AMPC + CAM; LAC, LPZ + AMPC + CAM; RUT, rapid urease test; IgGAb, IgG antibody; UBT, urea breathtest; Ab, antibody *P < 0.05

| Characteristics | Total patients | VAC | EAC | RAC | LAC | P |
|---|---|---|---|---|---|---|
| **ITT analysis (n)** | 802 | 202 | 198 | 200 | 202 | |
| **PP analysis (n)** | 720 | 178 | 180 | 181 | 181 | |
| **Age(yr)(mean±SD)** | 60.4 ± 13.0 | 60.6 ± 13.8 | 60.1 ± 12.6 | 60.1 ± 13.3 | 60.9 ± 12.6 | 0.9093 |
| **range** | 15-93 | 15-90 | 28-85 | 23-85 | 30-93 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Sex, male, %** | 343, 42.8% | **67, 33.2% *** | 90, 45.5% | 91, 45.5% | 95, 47.0% | **0.0160*** |
| **Disease for H. pylori eradication** | | | | | | |
| **Gastric ulcer, n, %** | 71, 8.9% | 21, 10.4% | 23, 11.6% | 11, 5.5% | 16, 7.9% | 0.1405 |
| **Duodenal ulcer, n, %** | 94, 11.7% | 29, 14.4% | 21, 10.6% | 18, 9.0% | 26, 12.9% | 0.351 |
| **Gastroduodenal ulcer, n, %** | 28, 3.5% | 6, 3.0% | 8, 4.0% | 8, 4.0% | 6, 3.0% | 0.884 |
| **Atrophic gastritis, n, %** | 609, 75.9% | 146, 72.3% | 146, 73.7% | 163, 81.5% | 154, 76.2% | 0.145 |
| **Test for H. pylori diagnosis** | | | | | | |
| **RUT/serum IgGAb/UBT** | 281/431/25 | 105/81/4 | 72/104/8 | 51/120/9 | 53/126/4 | |
| **/histopathology** | /45 | /5 | /10 | /15 | /15 | |
| **/stool antigen/urine Ab** | /18/2 | /7/0 | /3/1 | /4/1 | /4/0 | |

### 4.1. Eradication of *H.pylori* Infection

The efficacy of the four eradication therapies is shown in Figure 1. Intention-to-treat (ITT) analysis showed eradication rates 78.7%, 71.2%, 64.5 % and 63.9% in VAC, EAC, RAC and LAC groups, respectively. The per protocol (PP) eradication rate was 89.3%, 78.3%, 71.3 % and 71.3%. Comparisons of the four therapies, the eradication rate of VAC group was significantly higher than RAC group ($p$ = 0.0102) and LAC group ($p$ = 0.0063) in the ITT analysis, and then RAC group ($p$ = 0.0002) and LAC group ($p$ = 0.0002) in the PP analysis, respectively.

We excluded patients who received PPI and/or H2RA pretreatment before *H. pylori* eradication (Table 2) from each groups and also calculate eradication rates (Figure 2). ITT analysis showed eradication rates 83.8%, 76.7%, 69.0% and 63.3% in VAC, EAC, RAC and LAC groups, respectively. The PP eradication rate was 94.7%, 80.3%, 75.7 % and 70.4%. Comparisons of the four therapies, in the ITT analysis the eradication rate of VAC group was significantly higher than RAC group ($p$ =0.0341) and LAC group ($p$ = 0.0006), respectively. In the PP analysis the eradication rate of VAC group was significantly higher than EAC group ($p$ = 0.0151), RAC group ($p$=0.0012) and LAC group ($p$< 0.0001), respectively.

We also compared the eradication rates between the groups of patients who pretreatment non-received/received before *H. pylori* eradication in VAC, EAC, RAC and LAC groups. The eradication rates who received PPI pretreatment were 66.7%, 61.3%, 63.2% and 66.7% in the ITT analysis, 75.0%, 76.0%, 64.9% and 78.3% in the PP analysis in VAC, EAC, RAC and LAC groups, respectively. The eradication rate of non-received pretreatment group was significantly higher than PPI pretreatment received group in VAC group ($p$ = 0.0085) in the PP analysis (Figure 3). The eradication rates who received H2RA pretreatment were 60.9%, 58.8%, 55.1% and 63.8% in the ITT analysis, 73.7%, 71.4%, 65.9% and 69.8% in the PP analysis in VAC, EAC, RAC and LAC groups, respectively. The eradication rate of non-received pretreatment group was significantly higher than H2RA pretreatment received group in VAC group ($p$ = 0.0317) in the ITT analysis, ($p$ =0.0116) in the PP analysis (Figure 3). There were no significant differences found between pretreatment non-received group and received groups in EAC, RAC and LAC groups.

Multivariate analysis showed that eradication using VPZ and non-pretreatment of PPI or H2RA were predicting factors (Table 3).

**Table 2:** Duration of PPI pretreatment and H2RA pretreatment in VAC, EAC, RAC and LAC groups

PPI / H2RA pretreatment were performed at our clinic, or other clinics / hospitals.

PPI pretreatment; Lansoprazole 15mg or 30mg per day, rabeprazole 10mg per day, esomeprazole 10mg or 20mg per day, omeprazole 10mg or 20mg per day

H2RA pretreatment; Famotidine 20mg or 40mg per day, Ranitidine Hydrochloride 150mg or 300mg per day, Cimetidine 400mg or 800mg per day, Roxatidine Acetate Hydrochloride 75mg or 150mg per day, Nizatidine 150mg or 300mg per day, Lafutidine 10mg or 20mg per day

PPI, proton pump inhibitor; H2RA, H2 receptor antagonist; VAC, VPZ + AMPC + CAM; EAC, EPZ + AMPC + CAM; RAC, RPZ + AMPC + CAM; LAC, LPZ + AMPC + CA

| **PPI pretreatment** | **VAC** | **EAC** | **RAC** | **LAC** |
|---|---|---|---|---|
| n | 27 | 31 | 38 | 27 |
| Pretreatment duration (week) | 1 ～ 520 | 1 ～ 624 | 1 ～ 296 | 1 ～ 403 |
| Average | 125.9 | 65.7 | 33.1 | 49 |
| **H2RA pretreatment** | **VAC** | **EAC** | **RAC** | **LAC** |
| n | 23 | 34 | 49 | 47 |
| Pretreatment duration (week) | 1 ～ 520 | 1 ～ 260 | 1 ～ 428 | 1 ～ 520 |
| Average | 41.7 | 17.1 | 44.9 | 60.2 |

**Table 3:** logistic regression analysis results VAC, VPZ + AMPC + CAM; PPI, proton pump inhibitor; $^{**}P < 0.01$, $^{***}P < 0.001$

| **Multivariate analysis** | **OR** | **95%CI** | ***P* value** |
|---|---|---|---|
| PPI | | | |
| VAC | 1.94 | 1.296 – 2.892 | 0.0013 ** |
| Pre-treatment | | | |
| none | 1.77 | 1.287 – 2.442 | 0.0005 *** |

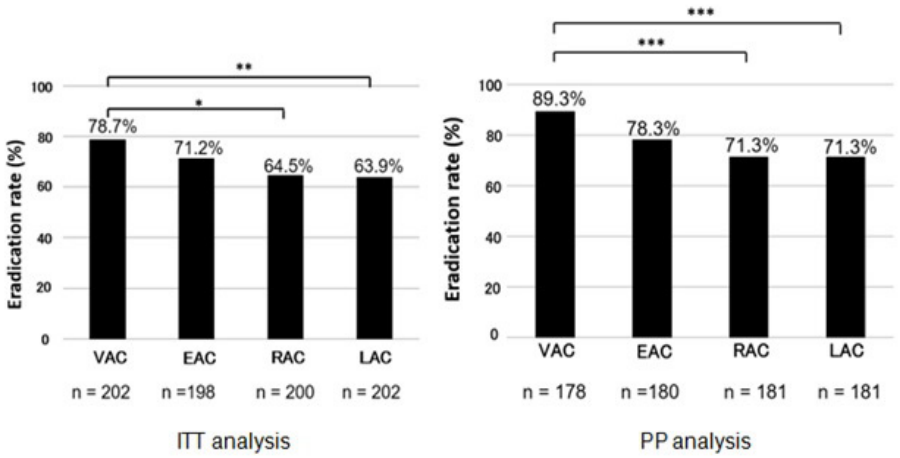


**Figure 1:** The efficacy of VAC, EAC, RAC and LAC eradication therapies. Tukey-Kramer multiple-comparison test was used to detect significant differences between groups.

ITT, intention-to-treat; PP, per protocol; VAC, VPZ + AMPC + CAM; EAC, EPZ + AMPC + CAM; RAC, RPZ + AMPC + CAM; LAC, LPZ + AMPC + CAM *P < 0.05, **P < 0.01, ***P < 0.001

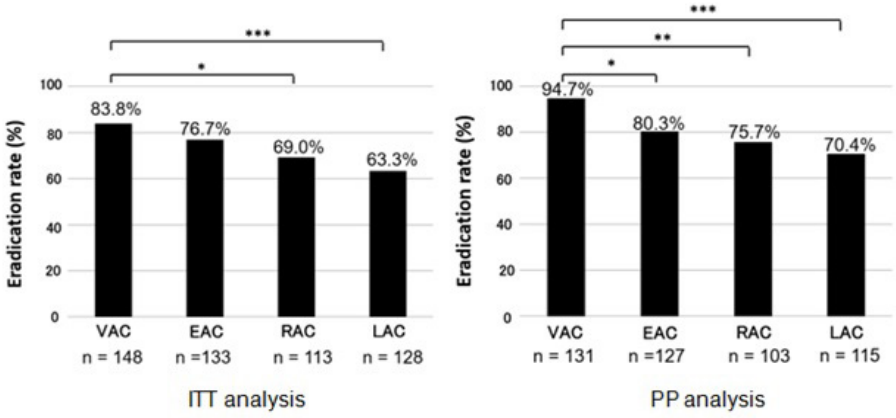


**Figure 2:** The efficacy of VAC, EAC, RAC and LAC eradication therapies in non-pretreatment groups. Tukey-Kramer multiple-comparison test was used to detect significant differences between groups.

ITT, intention-to-treat; PP, per protocol; VAC, VPZ + AMPC + CAM; EAC, EPZ + AMPC + CAM; RAC, RPZ + AMPC + CAM; LAC, LPZ + AMPC + CAM *P < 0.05, **P < 0.01, ***P < 0.001

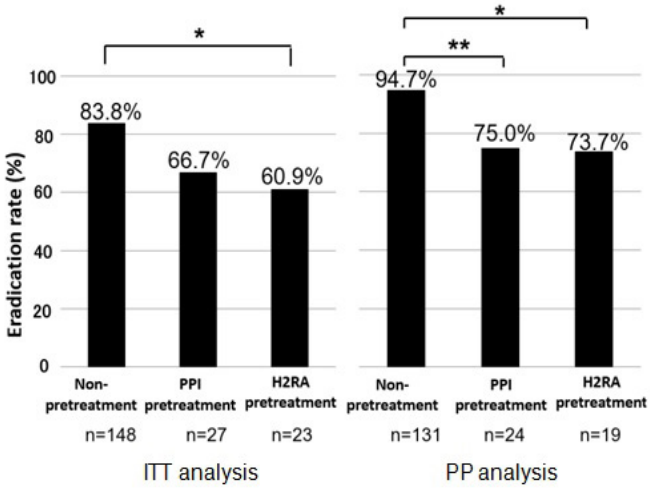


**Figure 3:** The eradication rates between the groups of patients who PPI or H2RA pretreatment non-received/received before *H. pylori* eradication in VAC groups. Tukey-Kramer multiple-comparison test was used to detect significant differences between groups.

ITT, intention-to-treat; PP, per protocol; VAC, VPZ + AMPC + CAM; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist *P < 0.05, **P < 0.01

No one was excluded due to adverse events in the ITT population. Compliance of all patients was good in the PP population and no one in all groups was excluded.

## 5. Discussion

The aim of this study was to investigate the influence of pretreatment with PPI or H2RA on *H. pylori* eradication. Our present retrospective study indicated that pretreatment with PPI and H2RA decreases the probability of *H. pylori* eradication in VPZ-based triple therapy.

Some studies suggest that pretreatment with a PPI before the administration of *H. pylori* eradication therapy might decrease the efficacy of the treatment. But some of them treated using dual therapy (OPZ plus AMPC) [14-17], another of them treated using quadruple therapy (LPZ, colloidal bismuth subcitrate, tetracycline and metronidazole) in two-day short term [18]. Most of the studies treating by triple or quadruple therapy suggest that pretreatment with PPI before eradication dose not influence the eradication rate [4-12, 19, 20]. A meta-analysis investigating the influence of PPI pretreatment on the efficacy of triple and quadruple *H. pylori* eradication therapies did not reveal any difference in the eradication rates between patients with and without PPI pretreatment [21]. But most of them used the first-generation PPIs such as OPZ or LPZ at the *H. pylori* eradication therapy. No data was found about the influence of PPIs pretreatment using *H. pylori* eradication regimen containing second-generation PPIs (RPZ, EPZ) or P-CAB.

To achieve cure by a first-line *H. pylori* eradication treatment, the 24-hour intragastric pH value (e.g., higher than 6.0) and the percentage of time that pH is < 4.0 during the post dose 24-hour period (e.g., less than 10%) could be predictive indicators [22]. To increase eradication efficacy, it is important to inhibit acid secretion because AMPC and CAM are stable in a less acidic gastric environment (pH > 6.0) and the bacteria become more sensitive [23]. At a low pH, AMPC is unstable, but its half-life is over 15 hours at pH 2. CAM is even more unstable in acid, and its half-life is less than 1 hour at pH 2. AMPC is effective against bacteria over a pH range ca. 5.5–7.5. Using CAM with PPIs for eradication therapy, CAM accumulates in the gastric mucosa and the mucus layer. The reduction in the amount of gastric juice by the co-administration of a PPI is also enhanced by pH independent factors and results in concentration of the antibiotics in the lumen of the stomach [24]. Meta-analysis showed that high-dose PPI raised cure rates of *H. pylori* infection with CAM-AMPC based triple therapy [25].

Over the pH range 4–8, *H. pylori* survive and grow [26]. At 37°C and at pH 6, the motility of *H. pylori* increases maximally [27]. When the intragastric pH increases to > 5.0, bacteria enter the replicative state and become more susceptible to killing by both AMPC and CAM. Acid inhibition using PPI raises the intragastric pH to between 5.0 and 7.0, stimulates the growth of *H.pylori*, and increases the bactericidal effect of AMPC [28, 29]. These findings suggest the positive probability of *H. pylori* eradication with PPI or H2RA pretreatment. But most of the studies suggested that pretreatment with PPI before *H. pylori* eradication treatment dose not influence the eradication rate [4-11]. Our present retrospective study indicated that pretreatment with PPI and H2RA does not influence the eradication rate in PPI-based triple therapy, and decreases the probability of *H. pylori* eradication in VPZ-based triple therapy.

As a retrospective analysis, this study had several limitations. In particular, CAM resistance, which increases the risk of eradication failure [30-32], was not investigated in the present study. Additionally, the rate of males in VAC group was significantly lower than other three groups. Such inconsistencies were a weak point in our study. We tried to overcome these limitations by performing multivariate analysis, and showed that non-pretreatment of PPI or H2RA were predicting factors.

In summary, this retrospective study indicated that VPZ-based triple therapy verified its superiority to conventional PPI-based therapy as first-line *H. pylori* eradication and also indicated that pretreatment with PPI and H2RA decreases the probability of *H. pylori* eradication in VPZ-based triple therapy. Further prospective cohort studies investigating CAM resistance are needed to confirm this finding. Also pathological study about *H. pylori* which received pretreatment with PPI and H2RA is needed.

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