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Influence of daily vs. alternate-day dosing of vonoprazan on intragastric pH, serum gastrin, and the antiplatelet function of clopidogrel

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Short title: Influence of alternate-day dosing of vonoprazan

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Key words: vonoprazan, alternate-day dosing, clopidogrel, ADP-induced platelet aggregation, gastrin, pH4 holding time ratio

Abbreviations: VPZ = vonoprazan, CLP = clopidogrel, IPA = the inhibition of ADP-induced platelet aggregation, pH4 HTR = pH4 holding time ratio

The manuscript consists of 17 text page including 1 Table and figure legends and 6 figures. The body of the text consists of 2790 words.

Background: Vonoprazan, a potassium-competitive acid blocker, inhibits gastric acid secretion and attenuates the antiplatelet function of clopidogrel more potently than esomeprazole. We investigated whether alternate-day dosing of vonoprazan might avoid this interaction with clopidogrel while providing sufficient gastric acid inhibition.
Methods: Following 24 h of pH monitoring (control regimen), 12 healthy volunteers received three regimens (clopidogrel-only regimen: clopidogrel 75 mg daily (q.d.); vonoprazan alternate-day regimen: vonoprazan 10 mg every other day (q.o.d.) + clopidogrel 75 mg q.d.; vonoprazan daily regimen: vonoprazan 10 mg q.d. + clopidogrel 75 mg q.d. for 14 days in a randomized open-label crossover manner. Intragastric pH monitoring was performed for 24 hours on day 13 in the clopidogrel-only regimen and vonoprazan q.d. regimens and for 48 hours on days 13 and 14 in the vonoprazan q.o.d. regimen. Serum gastrin and inhibition of platelet aggregation (IPA) were measured before the commencement of pH monitoring in each regimen.
Results: Twelve volunteers completed the study. Equivalent median IPA values in the q.o.d. and q.d. regimens were measured (21.8% and 25%, respectively) and were significantly lower than that of the clopidogrel-only regimen (40.8%). Median pH4 holding time ratio on the vonoprazan q.o.d. regimen (49.7%) was superior to that of the clopidogrel-only regimen (18.4%), but was significantly inferior to that of the vonoprazan q.d. regimen (77.0%) ($p < 0.01$).
Conclusion: Alternate-day administration of vonoprazan could not prevent the interaction between vonoprazan and clopidogrel and acid inhibition was inferior to vonoprazan daily administration, and appears to be of questionable clinical utility.
(250 words)

Introduction

Given the superaging status of Japan's population, the number of patients with cerebral infarction and ischemic heart disease is increasing, and is accompanied by rising numbers of citizens taking antithrombotic medications. These drugs carry the risk of gastrointestinal (GI) bleeding, which has a poor prognosis in the elderly.[1] The combined use of proton pump inhibitors (PPI) with antithrombotic drugs is recommended to reduce this risk.[2, 3] In 2008, the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG) and the American Heart Association (AHA) published their statement on antiplatelet therapy, which recommends the prescription of a PPI to patients at risk of peptic ulcer and/or receiving two or more antiplatelet agents. However, previous studies have reported that there is a drug-drug interaction between PPI and clopidogrel via CYP2C19 and CYP3A4 and that the use of a PPI may make clopidogrel less effective, resulting in increased risks of myocardial infarction, stroke, or death. [4, 5]

Vonoprazan (VPZ), a first-in-class potassium-competitive blocker, has been clinically available in Japan since February 2015.[6] VPZ is reported to achieve a more profound suppression of gastric acid secretion in comparison with PPIs and to be highly effective for PPI-resistant GERD. [7-10] VPZ is also effective not only for maintenance therapy for GERD [11] but also for preventing the low-dose aspirin and non-steroidal anti-inflammatory drug-related peptic ulcers.[12, 13] Accordingly, VPZ is increasingly being prescribed in Japan.

VPZ is mainly metabolized by the cytochrome P450 isozymes cytochrome P450 3A4 (CYP3A4) and partially by cytochrome P450 2C19 (CYP2C19), cytochrome P450 CYP2B6 (CYP2B6), cytochrome P450 CYP2D6 (CYP2D6), and human sulfotransferase 2A1 (SULT2A1).[14] Our previous clinical study showed that VPZ attenuated the antiplatelet function of clopidogrel (CLP) and prasugrel more potently than esomeprazole via inhibition of CYP2C19.[15] Funakoshi et al. also reported that VPZ potentially inhibited CYP2C19 in a clinical study.[16] Wang et al.[17] reported that VPZ inhibits the isozymes CYP3A4, CYP2D6, CYP2B5 and CYP2C9. A safe and effective gastric acid inhibitory therapy that minimizes the risk of drug-drug interaction is needed.

VPZ is stable at low pH and is able to remain in the secretory canaliculi of parietal cells for more than 24-h even after the plasma concentration decreases,[14, 18] allowing prolonged inhibition of gastric acid secretion.[19, 20] VPZ has been reported to be effective in on-demand therapy in the treatment of reflux esophagitis.[21]

Based on the data noted above, we investigated whether alternate-day (q.o.d.) dosing of VPZ could avoid the drug-drug interactions with CLP while providing sufficient inhibition of gastric acid secretion. We also evaluated the serum gastrin levels by the VPZ q.o.d. therapy.

Patients and Methods

From December 2018 to March 2021, 20 healthy Japanese volunteers were consecutively recruited. Inclusion criteria for volunteers included: 1) Healthy individuals (either males or females); 2) ≥ 20 years old; 3) No use of any medication in the last month; 4) Negative anti-*H. pylori* IgG antibody. Exclusion criteria were: 1) Pregnant or suspected of being pregnant; 2) Breastfeeding; 3) A history of upper gastrointestinal tract disease; 4) Smoking habit ; 5) A subject who was judged to be otherwise ineligible by the clinical investigators.

Study protocol

The study was conducted under an open-label randomized crossover design. The study protocol is shown in detail in Figure 1. Subjects first underwent control 24-h intragastric pH monitoring prior to administration of any of the test drugs to exclude individuals with abnormal acid secretion. Abnormal acid secretion was defined as the mean 24-h intragastric pH>4 based on our previous studies. [22],[23] Then, they were randomized to one of three different regimens (CLP-only regimen: CLP 75 mg daily (q.d.); VPZ alternate-day regimen: VPZ 10 mg q.o.d. + CLP 75 mg q.d.; VPZ daily regimen: VPZ 10 mg q.d. + CLP 75 mg q.d.) for 14 days (Figure 1). Each dose was self-administered orally at 8:00 am before breakfast. Twenty-four-hour intragastric pH monitoring was performed in the CLP-only regimen and the VPZ daily regimen on day 13. Forty-eight hours of intragastric pH monitoring was performed during the VPZ alternate-day regimen on days 13–14. All intragastric pH monitoring started at 8:00 am. Collection of blood samples for the measurement of serum gastrin and inhibition of platelet aggregation (IPA) were performed at 8:00 am just before taking CLP in the morning on days 13 and 14 in each regimen. The washout period between regimens was at least 2 weeks. A medication diary sheet and an empty blister pack were checked on the last day of each regimen. A reminder e-mail was sent to subjects every evening, and compliance

was confirmed by receipt of a response for confirming completion of the taking the drugs for the day according to the protocol.

Ethics approval

The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine, Hamamatsu, Japan. The protocol of the study was registered at Japan Registry of Clinical Trials (jRCTs041180024). The study was conducted in accordance with the principles of the Declaration of Helsinki. Two monitors (M.I., and E.O.) in the Center for Clinical Research in Hamamatsu University School of Medicine regularly evaluated whether the study was conducted according to the protocol and reported their findings to the Ethics Committee. Written informed consent was obtained from all participants.

Intragastric pH measurement

For 24-hour and 48-hour intragastric pH monitoring tests, one-channel single-use pH catheter (Sandhill Scientific, Highlands Ranch, CO, USA) connected to a catheter-based digital data recorder with a Digitrapper pH400 (Sierra Scientific Instruments, Los Angeles, CA, USA). Before the start of each intragastric pH monitoring, the pH catheter and catheter-based digital data recorder were calibrated using buffer solutions (buffer solution pH 1.07 and buffer solution pH 7.01 at 25℃; Given Imaging, GE, USA) according to manufacturer instructions. We transnasally inserted the pH catheter and were placed 5 cm away from the gastric cardia using fluoroscopic guidance. Twenty-four-hour and 48-hour intragastric pH monitoring were started at 8:00 before breakfast. Subjects were provided standard meals at a fixed time. They were allowed to drink only water as a beverage.

Measurement of percent inhibition of platelet aggregation (IPA%)

To evaluate the antiplatelet function of clopidogrel, we used VerifyNow P2Y12 kit in accordance with the manufacturer's instructions. In this kit, the antiplatelet function of clopidogrel was expressed as percent inhibition of platelet aggregation (IPA%), a representative index of the antiplatelet function of clopidogrel. [15 24 25]

Serum gastrin concentration

Concentrations of serum gastrin were analyzed by a commercial laboratory (BML Inc., Tokyo, Japan; ISO 15189, certification number: RML00010) using commercial kits (Gastrin RIA kit II; Fuji Rebio Inc., Tokyo, Japan).

Serum H. pylori IgG analysis

Serum anti-*H. pylori* IgG was analyzed by a commercial laboratory (BML, Tokyo, Japan: ISO 15189, certification number: RML00010) using a commercially available kit (E-plate Eiken *H. pylori* antibody; Eiken Chemical, Tokyo, Japan). Subjects with titers of < 3 U/mL and no history of *H. pylori* eradication were diagnosed as *H. pylori*-negative.

Statistical analysis

Differences among the three regimens plus a control in median pH4 HTR, median serum gastrin levels, and IPA were determined using the Freidman test followed by the Wilcoxon signed-rank test using commercial software (SPSS version 27, IBM Japan, Tokyo). All P values were two-tailed and $p < 0.05$ was considered statistically significant. [15]

Results:

Study flow outline

The study flow is shown in Figure 2. All 20 subjects met the inclusion criteria and were enrolled in this study and underwent the control study of 24-h pH monitoring without medication. Six subjects declined to continue to participate in the study after the initial pH monitoring. The remaining 14 subjects underwent the crossover study; 24 h/48 h pH monitoring with medication. One subject dropped out due to an adverse event. This subject had complained of small amount of bloody stool before medication intervention. He was finally diagnosed as having suffered from ulcerative colitis, unrelated to the interventions in this study. In other subjects, no severe adverse events occurred during the study period.

One subject was judged to be ineligible due to poor adherence to CLP (0%). Therefore, this subject was excluded from analysis. The other 12 were 100% compliant in the administration period of each regimen and were analyzed.

Clinical characteristics of subjects

Clinical characteristics of the 12 subjects are summarized in Table 1. The median age was 20.5 years; and 8 subjects were male and 4 were female. Median BMI was 19.1 (18.0-24.6), consisting of three underweight (≤ 18.5) and 9 normal weight (18.5–24.9). All of them were seronegative for *H. pylori* infection.

24-hour intragastric pH-time curves

The pH profiles of the 12 subjects on day 13 or day14 in each of the three regimens and the control regimen are shown in Figure 3. The q.d. regimen had the highest pH-time curve, followed in order by the first half (0 h–24 h) and then the latter half (24 h–48 h) of the q.o.d. regimen. Both the control and CLP-only regimens had the lowest pH-time curves.

Comparison of pH 4 holding time ratio by each regimen and control

Median pH 4 holding time ratio (pH4 HTR) with the three regimens plus control are shown in Figure 4. The median of pH4 HTR in the q.d. regimen was 77.0%, which was significantly higher than those in the 0 h–24 h (57.1%, $p < 0.01$) and 24 h–48 h (41.8%, $p < 0.01$) time points of the q.o.d. regimen, while those in both the control (19.4%) and CLP-only regimens (18.4%) were significantly lower than the other regimens ($p < 0.01$). There was no difference in pH4 HTRs between the q.o.d. regimen over 0–24 h and over 24 h–48 h ($p = 0.26$).

Comparison of median serum gastrin levels on each regimen and control

The medians of serum gastrin levels with the three regimens and the control are shown in Figure 5. Medians of serum gastrin levels in the q.o.d. regimen (139 pg/mL) and q.d. regimen (208 pg/mL) were significantly higher than that of the CLP-only regimen (60 pg/mL), while the median serum gastrin levels did not significantly differ between the two regimens ($p = 0.58$).

Comparison of the median of the percent inhibition of ADP-induced platelet aggregation values on each regimen and control

The medians of IPA with the three regimens and control are demonstrated in Figure 6. The medians of IPA of the q.o.d. (21.8%) and q.d. regimen (24.5%) did not differ significantly ($p = 0.06$) and were both significantly lower than that of the CLP-only regimen (40.8%, $p < 0.01$). The medians of IPA of each regimen were both significantly higher than that of the control ($p = 0.01$).

Discussion:

In this study, we demonstrated that the gastric acid inhibitory effect (pH4 HTR) of q.o.d. administration of VPZ 10 mg was significantly inferior to that of q.d. administration of VPZ 10 mg. In addition, the interaction between VPZ and CLP could not be avoided by the q.o.d. regimen. Serum levels gastrin in the q.o.d. and q.d. were not significantly different. Therefore, we suggest that there is no clinical utility of q.o.d. dosing of VPZ in patients treated with CLP.

Intragastric pH 4 HTR is a critical threshold, above which neither tissue damage nor symptoms are likely to be elicited by refluxate reaching the distal esophagus. [26, 27] It has been demonstrated that an intragastric pH > 4 promotes ulcer healing in acid peptic disease. [28] In this study, the pH4 HTR with VPZ 10 mg q.d. was 77.0%, similar to the 88.4% with VPZ 10 mg q.d. measured in our previous study.[22] Thus, we hypothesized that q.o.d. dosing of VPZ 10 mg could maintain sufficient acid inhibition. In the present study, the median pH4 HTR in q.o.d. dosing of VPZ were 57.1% over 0 h–24 h and 41.8% over 24 h–48 h, respectively. There were no significant difference ($p = 0.255$). Previous reports demonstrated that the pH4 HTR using lansoprazole 15 mg and 30 mg was 35.6% and 46.0%, respectively. [28] and that the pH4 HTR using esomeprazole 20 mg was 68%.[23] Therefore, the acid inhibitory effect of the q.o.d. administration of VPZ 10 mg would be considered to be almost the same as those of standard doses of PPIs, suggesting that the effect of q.o.d. administration of VPZ 10 mg would be as useful as that of PPIs at the standard doses. In other words, when VPZ 10 mg is administered q.o.d., the superiority of VPZ over PPI is lost.

Concerns about possible adverse effects related to long-term use of PPIs have been raised in terms of infections, impaired absorption of nutrients, dementia, kidney disease, drug-drug interaction and hypergastrinemia-related side effects.[23, 2930] These are also considered to be linked to VPZ. Adverse effects other than drug-drug interactions were the results of potent acid inhibition and subsequent hypergastrinemia.[31] Past studies reported that hypergastrinemia due to long-term use of PPIs might be related to the risk of development of neuroendocrine tumors, gastric cancer, colon cancer, pancreatic cancer, esophageal cancer, and hematologic cancers.[32-35] In this study, the median of serum gastrin levels after VPZ 10 mg daily was 207.5 pg/ml. That in our

previous study using the same dose was 310 pg/ml.[22] Therefore, hypergastrinemia is induced by VPZ 10 mg. The gastrin levels achieved with the q.o.d. regimen were 193.0 pg and 129.0 pg/ml at 24 h and 48 h after the last dose. Although the difference was not statistically significant, the serum levels of gastrin seemed decreased by alternate-day dosing in comparison with daily dosing of VPZ 10 mg. However, the acid inhibitory effect was also decreased by the q.o.d. regimen.

We also looked at the effect of q.d. vs. q.o.d. VPZ administration on CLP's antiplatelet effects.[15,16] We previously reported that VPZ 10 mg q.d. attenuated the antiplatelet functions of CLP and prasugrel more potently than esomeprazole 20 mg.[15] We also previously tried to avoid the interaction between clopidogrel and PPIs by separate administration of clopidogrel in the morning and PPIs in the evening and found that the half a day of separate administration could not avoid this interaction.[36] In this study, we investigated the effect of VPZ q.o.d. administration on the antiplatelet effect of CLP. When CLP was dosed q.d. and VPZ was dosed q.o.d., we hypothesized that the influence of VPZ on CLP would be greatly reduced and that the antiplatelet effect of CLP would be fully restored. However, the influence of VPZ dosed q.o.d. on CLP was almost the same as that of q.d. dosing. The mean half-life of VPZ ranged from 5.1–8.7 h in the Japanese study and from 7.3–9.0 h in a UK study.[37] Therefore, we expected that CLP dosed without VPZ could fully exert its antiplatelet function. However, the antiplatelet effect of CLP was significantly attenuated by VPZ dosed both q.o.d. and q.d. We cannot offer the appropriate explanation for the long-term influence of VPZ on the antiplatelet function of CLP. We suggest that the inhibitory effect of VPZ on the metabolic enzymes of CLP might be sustained for a longer time, independent of the plasma concentration of VPZ. Further studies on the drug-drug interaction of VPZ with other drugs are needed.

Our results must be interpreted within the study limitations as follows: First, the study subjects were young healthy volunteers, not patients requiring acid inhibition and/or anti-platelet therapy. Second, the duration of drug administration was short. Although the period of 2 weeks is longer than our previous studies, clinical patients are taking medicine for a much longer period. Third, we did not test for the CYP2C19 genotype although the antiplatelet function of CLP is influenced by this genotype. Fourth, the research was conducted on a small number of subjects. Therefore, our study results must be considered as preliminary and should not be extrapolated to clinical patients until larger studies have been completed.

In conclusion, compared with q.d. administration, q.o.d. administration of VPZ could not avoid the interaction with CLP. However, acid inhibition attained by q.o.d. administration of VPZ as assessed by pH 4 HTR was inferior to that by q.d. administration.

Conflict of interest

All authors declare that there is no conflict of interest related to this study.

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Authors' Contributions:

Tomohiro Higuchi: Acquisition of pH monitoring data, help with statistical analysis and interpretation of data, drafting of the manuscript
Mihoko Yamade: Acquisition of pH monitoring data
Satoru Takahashi: Acquisition of pH monitoring data
Satoshi Tamura: Measurement of platelet coagulability by VerifyNow
Shinya Tani: Acquisition of pH monitoring data
Takuma Kagami: Acquisition of pH monitoring data
Takahiro Uotani: Acquisition of pH monitoring data
Yasushi Hamaya: Acquisition of pH monitoring data
Moriya Iwaizumi: Acquisition of pH monitoring data
Satoshi Osawa: Acquisition of pH monitoring data
Ken Sugimoto: Acquisition of pH monitoring data
Takahisa Furuta: Study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

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Table 1. Demographic and clinical characteristics of 12 healthy volunteers who completed the study

Parameters	N = 12
Age; Median (median with range)	20.5 (20–23)
Gender (male/female)	8/4
Height (median with range)	167.5 (150–177)
Weight (median with range)	53.5 (42–69)
Body Mass Index (median with range)	19.1 (18.0–24.6)
H. pylori status (negative / positive)	12/0
Pepsinogen I (median with range)	40.8 (29.1–55.6)
Pepsinogen II (median with range)	7.1 (4.6–11.5)
Pepsinogen I / II (median with range)	5.85 (4.1–9.1)
Baseline serum gastrin (pg/ml) (median with range)	83 (42–281)
Baseline IPA (%) (median with range)	3.25 (0–25.0)
Baseline pH 4 holding time ratio (%) (median with range)	19.4 (2.7–42.8)

Figure legends

Figure 1. Study protocol. Following 24 h gastric pH monitoring as a control, subjects underwent three regimens in a randomized crossover manner: (1) Clopidogrel (CLP)-only regimen: CLP 75 mg once daily (q.d.) for 13 days, (2) Alternate-day regimen: vonoprazan (VPZ) 10 mg alternate day administration (q.o.d.) plus CLP 75 mg q.d. for 14 days, and (3) Daily regimen: VPZ 10 mg q.d. plus CLP 75 mg q.d. for 13 days. The time of each dose was at 8:00 before breakfast. 24-hour intragastric pH monitoring was performed in the CLP-only regimen and VPZ q.d. regimen on the 13th day and 24-hour intragastric pH monitoring was performed in the VPZ q.o.d. regimen on days13–14. Each intragastric pH monitoring started at 8:00. Collection of blood samples for the measurement of serum gastrin and IPA (the inhibition of ADP-induced platelet aggregation) was performed at 8:00 on day 13 and 14 in each regimen. The washout period between regimens was at least 2 weeks.

Figure 2. Study flow outline. A total of 20 subjects met the inclusion criteria. The 12 subjects who completed the study were analyzed.

Figure 3. Intragastric pH profiles with three regimens and control. The intragastric pH profiles of the control, CLP-only regimen, and q.d. regimen were for 24 h. Intragastric profiles of q.o.d. regimens were demonstrated separately by the first half (0 h–24 h) and latter half (24 h–48 h).
CLP = Clopidogrel, VPZ = vonoprazan

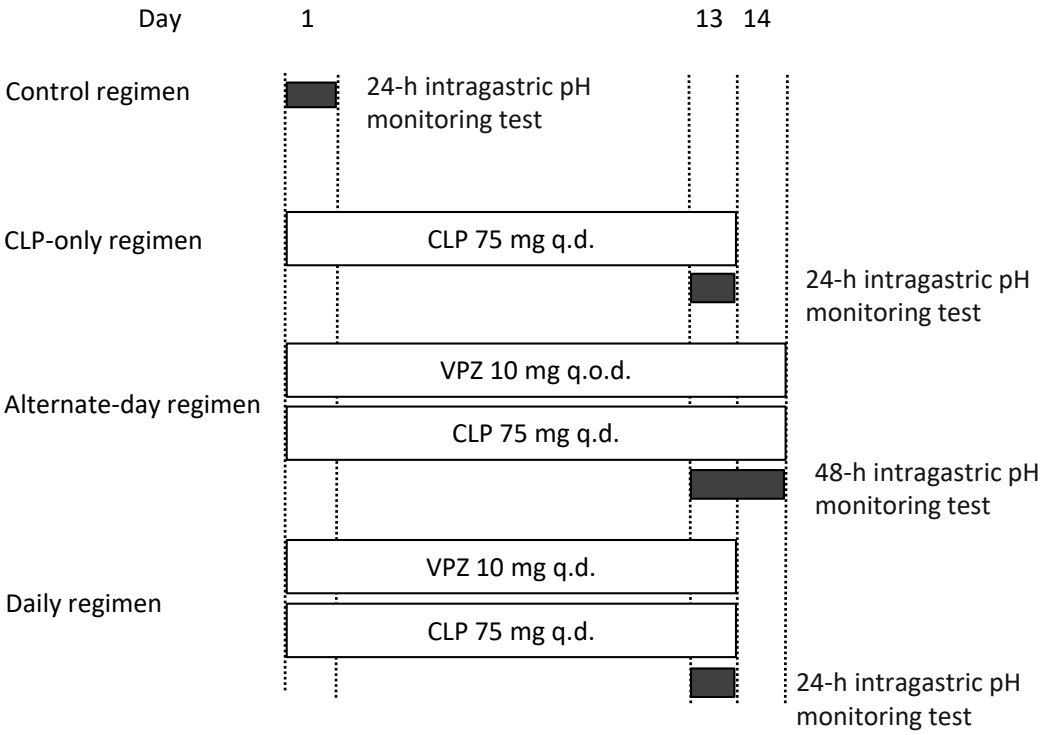
Figure 4. Whisker box plots of median pH 4 holding time ratio for 24-h (control, CLP-only regimen, and q.d. regimen) and 48-h (q.o.d. regimen).
CLP = Clopidogrel, VPZ = vonoprazan

Figure 5. Whisker box plots of serum gastrin values with the three different regimens and Control.
CLP = Clopidogrel, VPZ = vonoprazan

Figure 6. Whisker box plots of IPA with the three different regimens and Control.

CLP = Clopidogrel, VPZ = vonoprazan, IPA = the inhibition of ADP-induced platelet aggregation

Figure 1.



q.d. = daily; q.o.d. = every other day

Figure 2.

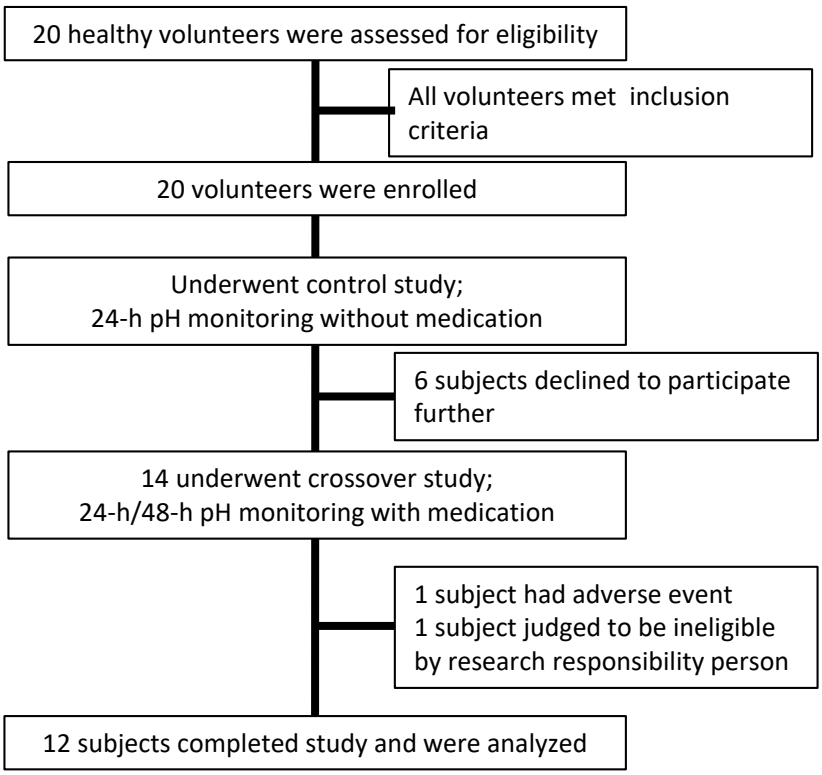

20 healthy volunteers were assessed for eligibility
All volunteers met inclusion criteria
20 volunteers were enrolled
Underwent control study;
24-h pH monitoring without medication
6 subjects declined to participate further
14 underwent crossover study;
24-h/48-h pH monitoring with medication
1 subject had adverse event
1 subject judged to be ineligible by research responsibility person
12 subjects completed study and were analyzed

Figure 3.

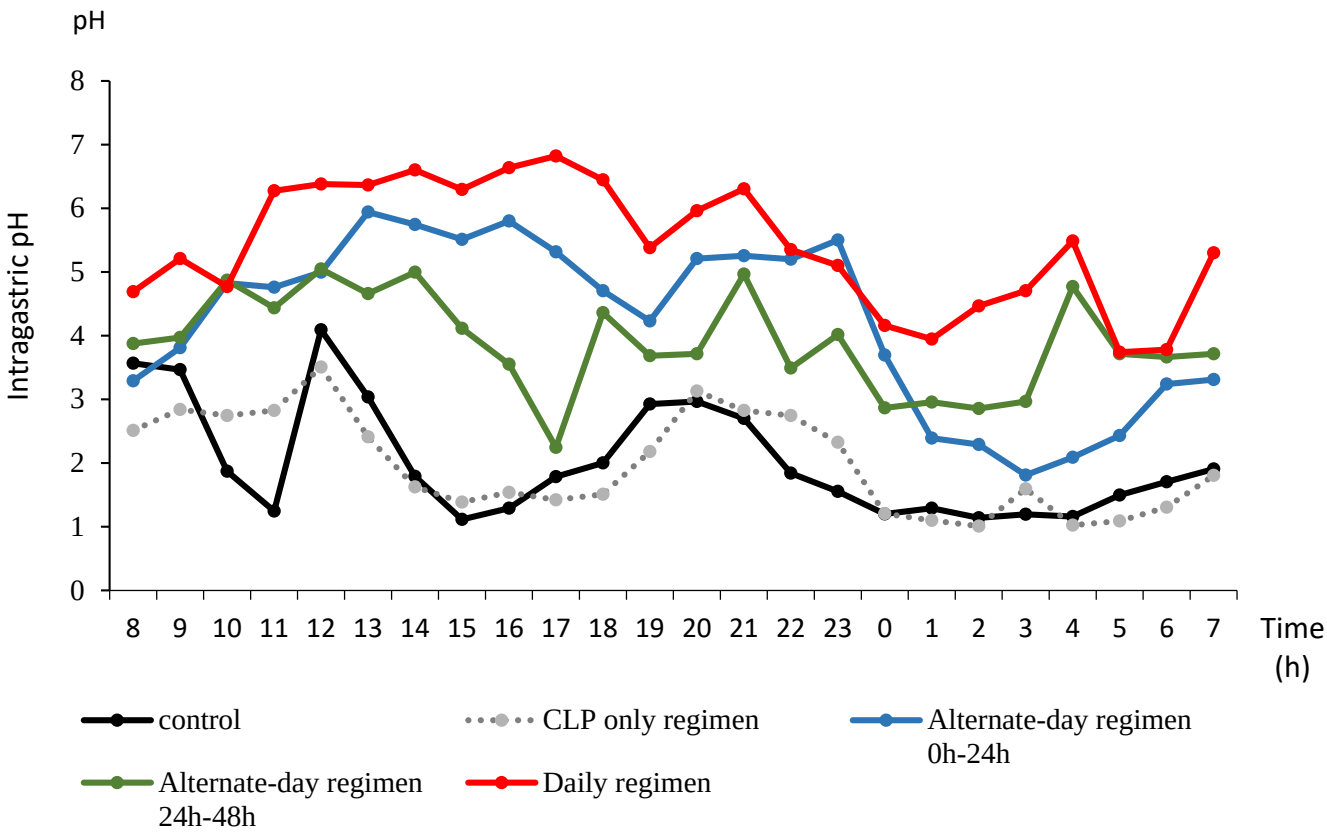
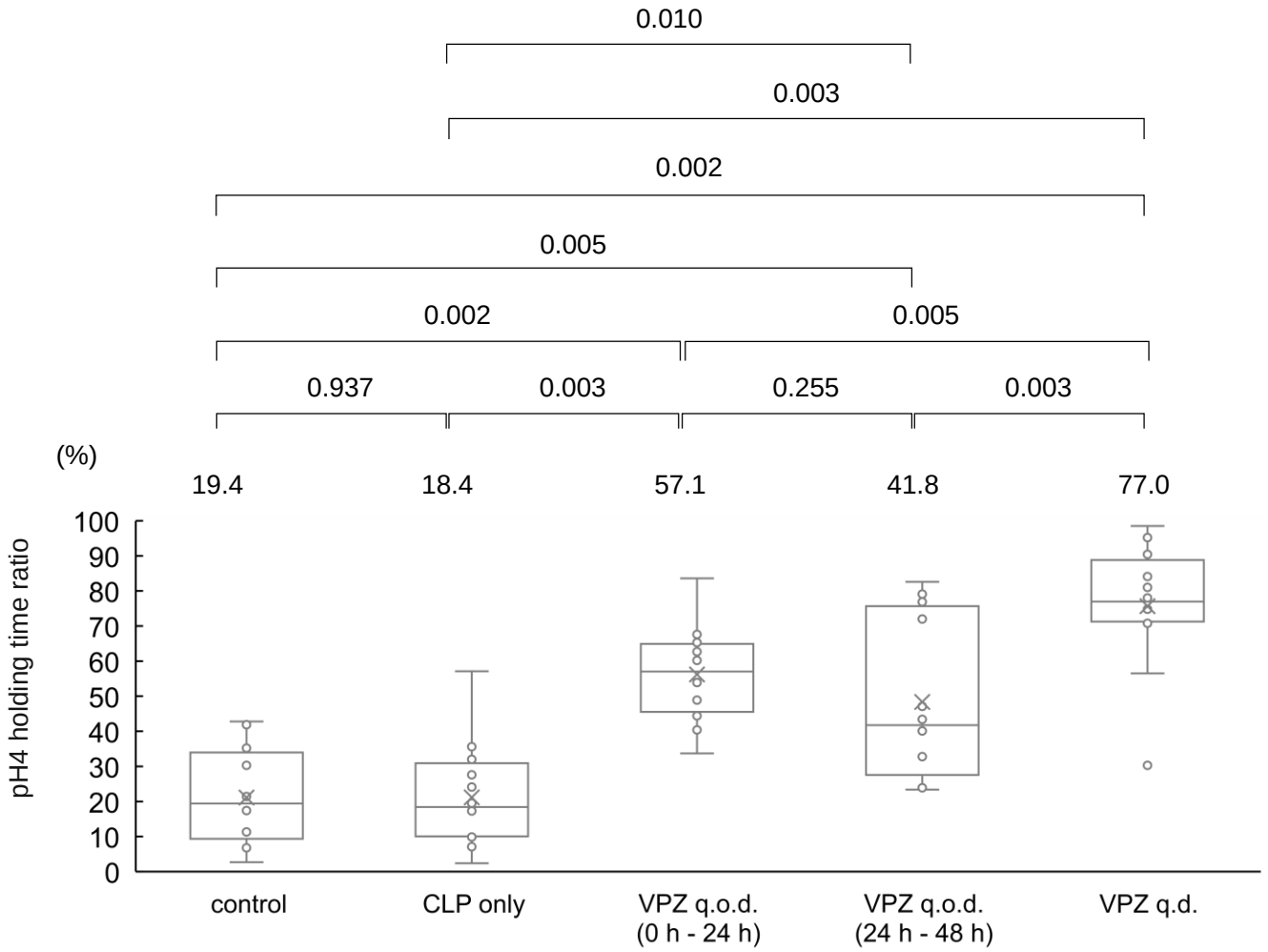
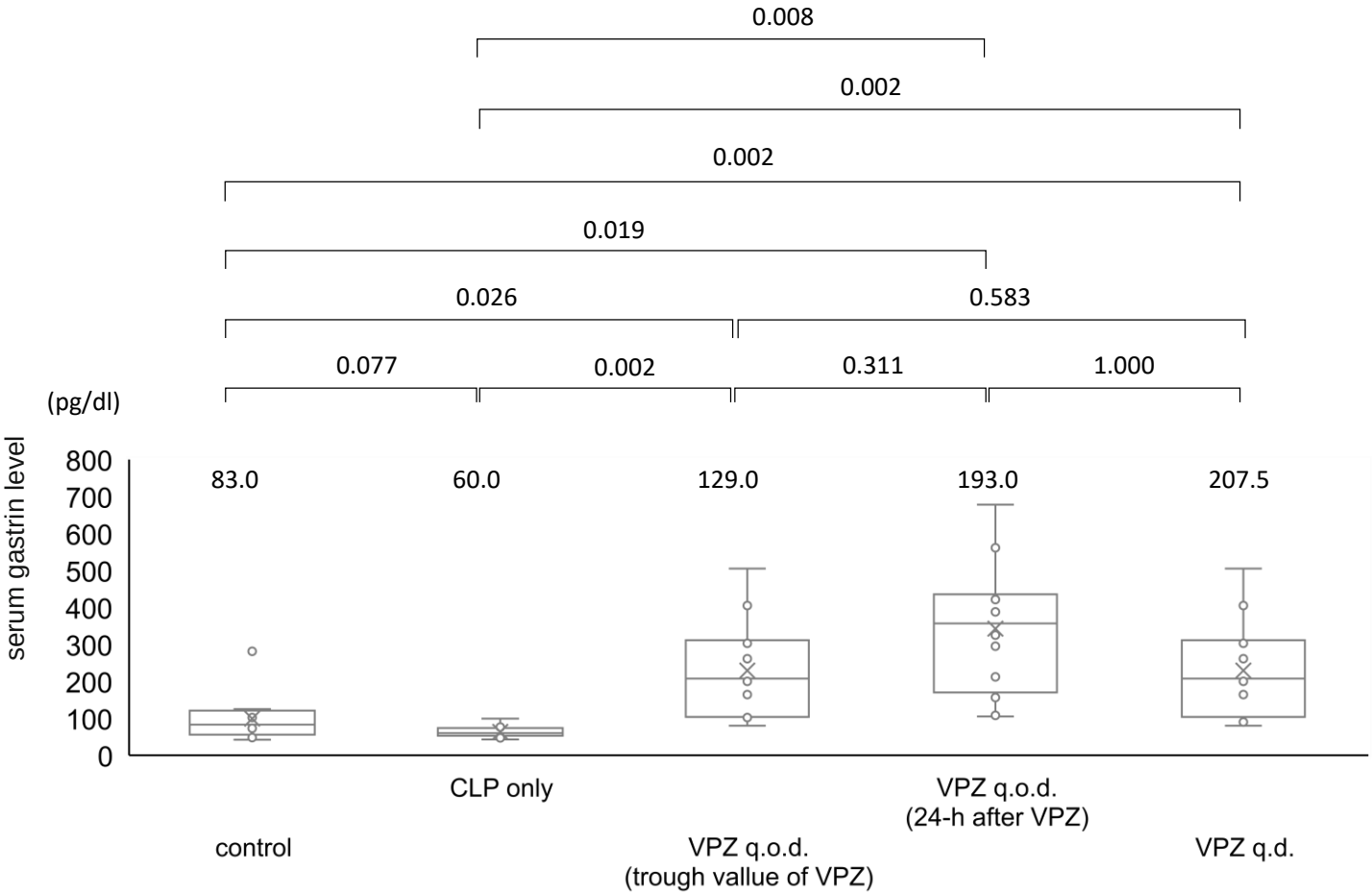

pH
Intragastric pH
8
7
6
5
4
3
2
1
0
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 0 1 2 3 4 5 6 7
Time (h)
control
CLP only regimen
Alternate-day regimen 0h-24h
Alternate-day regimen 24h-48h
Daily regimen

Figure 4.



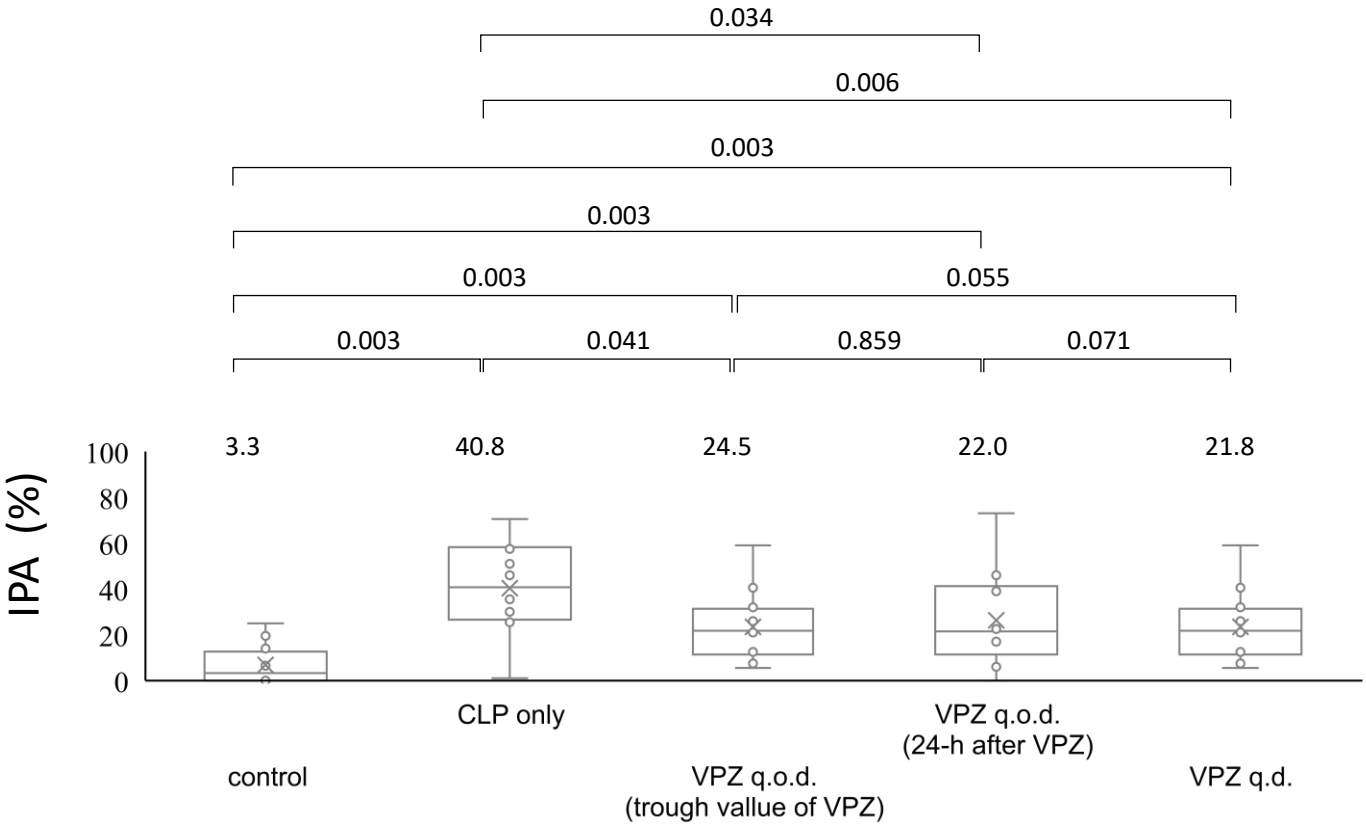
VPZ	—	—	10mg q.a.d.	10mg q.d.
CLP	—	75mg q.d.	75mg q.d.	75mg q.d.

Figure 5



VPZ	—	—	10mg q.a.d.	10mg q.d.
CLP	—	75mg q.d.	75mg q.d.	75mg q.d.

Figure 6



VPZ	—	—	10mg q.o.d.	10mg q.d.
CLP	—	75mg q.d.	75mg q.d.	75mg q.d.