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Effects of pirenzepine on vonoprazan-induced gastric acid inhibition and hypergastrinemia

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Abbreviations: pH 4 HTR, pH > 4 holding time ratio; PPI, proton pump inhibitor

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ABSTRACT

Backgrounds: Compared to proton pump inhibitors, vonoprazan exerts a greater inhibitory effect on gastric acid secretion and is useful for treating acid-related diseases, such as gastro-esophageal reflux disease. However, there is a problem that vonoprazan causes hypergastrinemia, which confers a risk of carcinoid tumor. A previous report demonstrated that pirenzepine, an M1 muscarinic receptor antagonist, enhances the acid inhibitory effects while suppressing hypergastrinemia induced by omeprazole. Here, we examined whether pirenzepine enhances the gastric acid inhibitory effects of vonoprazan without further increasing serum gastrin levels.

Methods: Eleven healthy volunteers were subjected to 24-hour intragastric pH monitoring and serum gastrin measurements on day 7 of three different regimens: pirenzepine 75 mg alone, vonoprazan 10 mg alone, and vonoprazan 10 mg plus pirenzepine 75 mg administered in a randomized crossover fashion.

Results: Median pH 4 holding time ratios (range) achieved with pirenzepine 75 mg, vonoprazan 10 mg and vonoprazan 10 mg plus pirenzepine 75 mg were 6.9% (2.4–32.8%), 88.4% (54.6–100%), and 84.2% (40.3–100%), respectively. Respective serum gastrin levels were 79 (75–210) pg/ml, 310 (110–870) pg/ml, and 170 (140–930) pg/ml. In cases with hypergastrinemia (gastrin \geq 200 pg/ml) induced by vonoprazan 10 mg alone, concomitant treatment with pirenzepine significantly reduced serum gastrin levels from 370 pg/ml to 180 pg/ml ($P = 0.028$).

Conclusion: Although pirenzepine does not enhance acid inhibition, it does improve hypergastrinemia induced by vonoprazan to some extent.

(233 words)

Introduction

Sufficient gastric acid inhibition enables proper healing in acid-related diseases such as gastro-esophageal reflux disease (GERD)^{1,2}. Proton pump inhibitors (PPIs) (e.g., esomeprazole, rabeprazole, pantoprazole, and dexlansoprazole) potently inhibit gastric acid secretion, and are thus considered effective treatments for such disorders^{3,4}. The strength of gastric acid inhibition is correlated with the cure rate of GERD⁵. A previous study showed that the intragastric pH should be > 4 for more than 83% of a 24-hour period to completely cure GERD⁶. However, PPIs are not always able to provide sufficient inhibition throughout a 24-hour period and thus cannot completely cure or control GERD. Nocturnal acid breakthrough (NAB), defined as an intragastric pH < 4.0 for longer than 1 hour in the nighttime, is associated with a poor response to PPIs in the treatment of GERD^{7,8}.

Vonoprazan, a novel potassium-competitive acid blocker, is now available for the treatment of acid-related disorders in Japan. Vonoprazan at a dose of 20 mg inhibits gastric acid secretion more potently than PPIs such as esomeprazole 20 mg and rabeprazole 10 mg throughout a 24-hour period^{9,10}. The pH 4 holding time ratio (pH 4 HTR) of vonoprazan 20 mg is reported to be 95%⁹, which is sufficient to almost completely cure GERD. In fact, vonoprazan is more effective than PPIs for curing severe erosive esophagitis¹¹. Further, vonoprazan 10 mg has been shown to inhibit gastric acid secretion more potently than a PPI¹². However, vonoprazan is more strongly correlated with hypergastrinemia than PPIs, and extended use of vonoprazan confers a risk of carcinoid tumors¹³⁻¹⁸. In Japan, the recommended maintenance dose of vonoprazan is 10 mg, which is sometimes insufficient to completely prevent NAB¹⁹.

Histamine 2 receptor antagonists (H2RAs) (e.g., cimetidine, ranitidine, famotidine, and lafutidine) prescribed for the nighttime are useful for preventing NAB when co-administered with a PPI^{8,20-22}. Addition of an H2RA is occasionally more effective than increasing the dose of a PPI²⁰. However, further gastric acid inhibition by addition of an H2RA increases serum gastrin levels, presenting a therapeutic dilemma for treating acid-related disorders. Lafutidine is a second-generation H2RA with unique anti-secretory actions^{23,24} and is more useful than other common antacids for treating intestinal mucositis during cancer chemotherapy because it increases mucus production via activation of sensory afferent neurons²⁵. Uniquely, lafutidine inhibits gastric acid secretion without increasing serum gastrin levels²⁶. While treatment with lafutidine reportedly increases serum somatostatin levels, the drug also inhibits gastric acid secretion^{23,26}. We previously reported that addition of lafutidine 10 mg to vonoprazan 10 mg achieved sufficient acid inhibition without further induction of hypergastrinemia²⁷.

No other drug combinations with vonoprazan have been reported as a solution for gastric acid inhibition-associated hypergastrinemia.

Pirenzepine, an M1 muscarinic acetylcholine receptor-selective antagonist, inhibits gastric acid secretion via anticholinergic activity on parietal cells^{28,29}. Pirenzepine is known to inhibit gastrin release and increase somatostatin levels³⁰. In addition to enhancing acid inhibition, pirenzepine has also been reported to improve omeprazole-induced hypergastrinemia in humans³¹. Thus, we hypothesized that pirenzepine may enhance acid inhibition and suppress hypergastrinemia induced by vonoprazan. However, there is currently no report on the effects of combining vonoprazan with pirenzepine.

Here, we examined the effect of pirenzepine on gastric acid inhibition and hypergastrinemia induced by vonoprazan.

Methods

Institutional Review Board approval and monitoring of the study

Approval for the study protocol was obtained from the Ethics Committee of Hamamatsu University School of Medicine (approval no. R17-243). Two monitors (M.I., and E.O.) regularly evaluated whether the study was conducted according to the protocol and reported their findings to the Ethics Committee.

Clinical trial registry

This study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry System (UMIN000031632).

Subjects

From April to October 2018, 13 healthy Japanese adult volunteers were consecutively recruited from among medical and nursing students of Hamamatsu University School of Medicine (Figure 1). After obtaining written informed consent, fasting blood samples were collected from all subjects, and serum antibodies to *Helicobacter pylori* (*H. pylori*) were analyzed.

Exclusion criteria were the presence of any underlying disease, smoking habit, past or present *H. pylori* infection, presence of atrophic gastritis, and regular use of any medications. All of the 13 volunteers were enrolled. We decided in advance that participants who dropped out during the follow-up period would be excluded from the analysis.

Study protocol

The aim was to compare acid inhibition and serum gastrin levels in three different regimens: (i) pirenzepine 25 mg after meals three times daily, (ii) vonoprazan 10 mg once daily after lunch, and (iii) vonoprazan 10 mg once daily plus pirenzepine 25 mg three times daily. Acid inhibition was assessed by monitoring the 24-h intragastric pH. Volunteers first underwent 24-h intragastric pH monitoring prior to administration of the test drugs to exclude individuals with abnormal acid secretion. We then tested the effects of the three different regimens on gastric acid secretion and serum gastrin levels in a crossover manner (Figure 2). Twenty-four-hour intragastric pH monitoring and serum gastrin measurement were performed on day 7 of each regimen. The order of the three regimens was randomized. A clinical research coordinator (N.H.) managed each subject's dosing schedule. The washout period between regimens was at least 2 weeks. Vonoprazan was administered after lunch (at 12:00). A reminder e-mail was sent to participants every evening, and compliance was confirmed by receipt of a response confirming completion of the drug protocol for the day.

The median 24-hour intragastric pH and the percentage of time during which intragastric pH is > 4 are important parameters of gastric acid secretion during GERD treatment. We therefore used median 24-h intragastric pH and pH 4 HTR as indices of gastric acid secretion. We also measured fasting serum gastrin concentration on the morning of day 7 of each regimen.

Serum antibodies to *H. pylori*

The presence of serum antibodies to *H. pylori* was analyzed using a commercially available kit (E-plate Eiken *H. pylori* antibody; Eiken Chemical Co., Ltd., Tokyo, Japan). Volunteers with titers of < 10 U/mL were diagnosed as *H. pylori*-negative.

Serum gastrin concentration

All blood samples were collected from subjects in the fasting state, at least 4 h after the last oral intake of food or drink. Baseline gastrin concentration was measured in the morning in the control study and on day 7 of each regimen. Concentrations of serum gastrin were analyzed by a commercial laboratory (SRL, Inc., Tokyo, Japan.) using commercial kits (Gastrin RIA kit II; Fuji Rebio Inc., Tokyo, Japan). The normal range of serum gastrin in this kit is 42–200 pg/ml.

Intragastric pH monitoring

Twenty-four-hour intragastric pH monitoring was performed using pH catheters

(one-channel crystal antimony single-use pH catheter; Synectics Medical, Barcarena, Portugal) and a catheter-based ambulatory pH monitoring system (Digitrapper pH400; Sierra Scientific Instruments, Los Angeles, CA, USA). Before each 24-h intragastric pH monitoring session, the pH catheter and catheter-based ambulatory pH monitoring system were calibrated using standard buffer solutions (Buffer solution pH 1.07 and Buffer solution pH 7.01; Given Imaging, GA, USA). The pH catheter was inserted transnasally and placed about 5 cm below the lower esophageal sphincter under fluoroscopy guidance after collection of blood samples for gastrin measurements. Twenty-four-hour intragastric pH monitoring was started at 12:00. Three standard meals were then provided at 12:00, 18:00, and 8:00. Bottled water was allowed but other beverages were not permitted.

Sample size estimation

We statistically determined the ideal sample size for this study. While we had no reference data on acid inhibition by pirenzepine 75 mg plus vonoprazan 10 mg, previous data indicated that the median (standard deviation: SD) pH 4 HTR was 83.4% (16.7) for vonoprazan 20 mg q.d. and 63.3% (8.7) for vonoprazan 10 mg q.d. on day 7¹⁰. Therefore, we set the population mean difference to 20.0. When alpha = 0.05 and 1-beta = 0.8, the appropriate sample size was determined to be 12 with the paired t-test (two-tailed). At an expected dropout rate due to loss to follow-up or protocol violation of 10%, the sample size increased to 13. Sample power values were calculated using IBM SPSS Sample Power 3.0.1 (IBM, Madison Ave, NC, USA). **In the similar study with vonoprazan by Jenkins, et al³², the number of subjects in each regimen group was 9. Therefore, our sample size estimation is considered to be appropriate.**

Statistical analysis

Statistically significant differences in median pH profile, median pH 4 HTR, and median serum gastrin concentration between the three regimens were determined using the Freidman test followed by the Wilcoxon signed-rank test. Statistical calculations were performed using SPSS ver. 25. All P values were two-tailed, and $P < 0.05$ indicated statistical significance.

Results

Subjects' clinical characteristics

Of the 13 volunteers, 2 dropped out during the study and were excluded from the analysis. Eleven volunteers completed the study, which was conducted from April to October 2018 (Table 1). All volunteers were sero-negative for *H. pylori* infection (anti-*H.*

pylori IgG antibody titers were all less than 3 U/ml). No adverse events occurred during the study period. Drug compliance was 100%, as confirmed by daily receipt of emails during the administration period for each regimen.

Twenty-four-hour intragastric pH-time curves

The pH profiles (median with range) of the 11 volunteers on day 7 of the three drug regimens are shown in Figure 3. The pH profile of vonoprazan 10 mg alone overlapped with that of vonoprazan 10 mg plus pirenzepine. Similarly, the pH profile of pirenzepine alone overlapped with that of the control.

Comparison of median intragastric pH values in the three regimens

Median intragastric pH values measured in a 24-hour period and in the nighttime in the control and three drug regimens are shown in Figure 4. Median 24-h intragastric pH values achieved with vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg were 5.9 and 5.7, respectively, which were significantly higher than the 1.8 with pirenzepine 75 mg ($P = 0.003$) and 1.9 with control ($P = 0.003$) (Figure 4a).

In the nighttime, median pH values achieved with vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg were 5.7 and 5.8, respectively, which were significantly higher than the 1.4 with pirenzepine 75 mg ($P = 0.003$ for both) (Figure 4b).

In contrast, there were no significant differences in median 24-hour pH (1.9 vs 1.8) or nighttime pH (1.0 vs 1.4) between control and pirenzepine alone. Similarly, there were no significant differences between vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg (5.9 vs 5.7 for 24-hour pH and 5.7 vs 5.8 for nighttime pH).

Comparison of median pH 4 HTRs achieved with the three drug regimens

Median (range) pH 4 HTRs in a 24-hour period and in the nighttime achieved with the control and three drug regimens are shown in Figure 5. Median (range) pH 4 HTRs in a 24-hour period achieved with pirenzepine 75mg alone, vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg were 6.9% (2.4–32.8%), 88.4% (54.6–100%), and 84.2% (40.3–100%), respectively (Figure 5a). Median pH 4 HTRs achieved with vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg were both significantly higher than that with pirenzepine 75 mg ($P = 0.003$).

In the nighttime, median (range) pH 4 HTRs achieved with control, pirenzepine 75mg, vonoprazan 10 mg and vonoprazan 10 mg plus pirenzepine 75 mg were 0.0% (0.0–31.8%), 0.3% (0–47.2%), 77.6% (52.1–100%), and 84.4% (57.4–100%), respectively (Figure 5b). Median pH 4 HTRs achieved with vonoprazan 10 mg alone and vonoprazan

10 mg plus pirenzepine 75 mg were significantly higher than that with pirenzepine 75 mg ($P = 0.003$). The incidence of NAB with vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg was 54% (6/11) and 36% (4/11), respectively. There were no significant differences in parameters of gastric acid inhibition between vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg regimens. However, there were no significant differences in pH 4 HTRs or the incidence of NAB between control and pirenzepine 75 mg alone and between vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg.

Comparison of serum gastrin concentrations

Median (range) serum gastrin concentrations in control and on day 7 of the pirenzepine 75 mg, vonoprazan 10 mg, and vonoprazan 10 mg plus pirenzepine 75 mg regimens were 81 pg/ml (53–130 pg/ml), 79 pg/ml (59–130 pg/ml), 310 pg/ml (110–870 pg/ml), and 170 pg/ml (130–930 pg/ml), respectively (Figure 6a). Serum gastrin concentrations measured following administration of vonoprazan 10 mg alone and vonoprazan 10 mg plus pirenzepine 75 mg were both significantly higher than that following pirenzepine 75 mg ($P = 0.003$ for both) and control ($P = 0.005$ and 0.003 , respectively). Interestingly, median serum gastrin levels appeared to decrease rather than increase following administration of vonoprazan 10 mg plus pirenzepine 75 mg compared to vonoprazan 10 mg alone. Treatment with vonoprazan 10 mg increased serum gastrin levels in all subjects, with levels measuring over 200 pg/ml in 7 of 11 subjects. The median serum gastrin level in these 7 subjects was 370 pg/ml (Figure 6b). Additional administration of pirenzepine up to 180 pg/ml improved this hypergastrinemia ($P = 0.028$).

Discussion

Our results demonstrate that pirenzepine exhibited very weak acid inhibition, and addition of pirenzepine did not enhance the acid inhibitory effects of vonoprazan 10 mg. However, addition of pirenzepine showed some suppression of hypergastrinemia induced by vonoprazan 10 mg.

Although pirenzepine was previously used as a gastric acid inhibitor, it has been replaced in recent decades with H₂RAs, PPIs and vonoprazan. In our hypothesis, we overestimated pirenzepine's ability to suppress acid secretion. If pirenzepine had comparable gastric acid inhibitory ability to lafutidine, it might have enhanced vonoprazan-induced gastric acid inhibition when administered with vonoprazan. Instead, we found that combination treatment with pirenzepine and vonoprazan achieved almost equivalent 24-h intragastric pH (5.7) to vonoprazan 10 mg alone (5.9). Therefore,

contrary to our expectation, pirenzepine did not enhance the acid inhibitory effects of vonoprazan. We suspect that the lower inhibition of gastric acid secretion by pirenzepine compared with vonoprazan may explain this result.

As mentioned above, pirenzepine reportedly suppresses omeprazole-induced hypergastrinemia³¹. Thus, we tested the effects of pirenzepine on vonoprazan-induced hypergastrinemia. We found that vonoprazan 10 mg increased median serum gastrin levels. In several cases, vonoprazan 10 mg even induced hypergastrinemia, defined as serum gastrin > 200 pg/ml. Combination treatment with pirenzepine 75 mg significantly improved this hypergastrinemia.

The mechanism by which pirenzepine inhibits vonoprazan-induced hypergastrinemia could be explained as follows: Gastrin release is regulated by gastric pH, meal stimulation, somatostatin and bombesin. Muscarinic receptor stimulation increases bombesin secretion and inhibits somatostatin release^{33 34}. Therefore, blockade of muscarinic receptors by pirenzepine decreases bombesin release and increases somatostatin release, resulting in the decreased gastrin release³⁵. Although pirenzepine does not normalize vonoprazan-induced hypergastrinemia, our results suggest that pirenzepine may be useful for developing countermeasures against potent acid inhibitor-induced hypergastrinemia.

Another countermeasure for hypergastrinemia is to use the gastrin receptor antagonist, such as netazepide. Netazepide has been reported to inhibit the growth of gastric carcinoid in patients with hypergastrinemia³⁶. Because pirenzepine could not sufficiently lower gastrin levels in the present study, the additional use of netazepide on pirenzepine seems very useful for the prevention of development of gastric carcinoid. However, the usefulness combined use of pirenzepine and netazepide should be verified by further clinical study, although the netazepide-available area is limited.

Evidence suggests that potent acid inhibitor-induced hypergastrinemia may be linked to the risk of developing carcinoid, gastric, and colon cancer. It is thus important to be aware of the potential risk of hypergastrinemia during long-term administration of vonoprazan¹⁷. In Japan, the recommended maintenance dose of vonoprazan is 10 mg, indicating that patients treated with vonoprazan likely often experience hypergastrinemia. Although it is important to suppress gastric acid secretion and improve symptoms when treating acid-related disorders, it is also paramount to pay attention to problems associated with hypergastrinemia. Whether pirenzepine can reduce the risk of developing acid inhibitor-induced tumorous lesions is unknown.

Our results should be interpreted with several limitations in mind. First, all participants were young *H. pylori*-negative healthy volunteers without GERD. Second,

the observation period was 1 week. It is unknown whether the pH profiles observed in this study are applicable to patients receiving long-term treatment with the study drugs. Finally, our subjects were all Japanese. Despite these limitations, our study showed that pirenzepine is useful for suppressing vonoprazan-induced hypergastrinemia. The clinical usefulness of this regimen should be verified in appropriate clinical studies.

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Authors' Contributions:

Takahiro Suzuki: Acquisition of pH monitoring data, statistical analysis and interpretation of data, drafting of the manuscript

Tomohiro Higuchi: Acquisition of pH monitoring data, help with statistical analysis and interpretation of data, drafting of the manuscript

Takuma Kagami: Acquisition of pH monitoring data

Takahiro Uotani: Acquisition of pH monitoring data

Mihoko Yamade: Acquisition of pH monitoring data

Satoshi Tamura: Acquisition of pH monitoring data

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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

Hiroaki Miyajima: Study supervision

Takahisa Furuta: Study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtaining funding.

Table 1. Demographic data and clinical characteristics of 11 *Helicobacter pylori*-negative healthy volunteers who completed the study.

Sex (F/M)	4/7
Age, y (median with range)	21 (20-23)
Height, cm (median with range)	162 (152-173)
Weight, kg (median with range)	55 (47-80)
Control median intragastric pH (median with range)	1.9 (1.2-2.7)
Baseline serum gastrin (pg/ml) (median with range)	81 (50-130)

Figure legends

Figure 1. Study flow outline. Includes the number of participants enrolled and the number of participants who completed the study.

Figure 2. Schematic of the study protocol. In addition to control, subjects received three regimens in a randomized crossover manner: (1) pirenzepine (PRZ) 25 mg three times daily (t.i.d.) for 7 days; (2) vonoprazan (VPZ) 10 mg once daily (q.d.) for 7 days; (3) VPZ 10 mg q.d. plus PRZ 25 mg t.i.d. for 7 days. Each dose was given at 12:00 (30 minutes after lunch). Monitoring of 24-h intragastric pH started at 12:00. Blood samples for serum gastrin measurement were collected at 11:30 on day 7 in each regimen. The washout period between regimens was at least 2 weeks.

Figure 3. Intragastric pH profiles of volunteers in the three regimens (\square : pirenzepine (PRZ) 75mg, Δ : vonoprazan (VPZ) 10 mg, \diamond : VPZ 10 mg + PRZ 75 mg) and \circ : control. The plots show median intragastric pH values.

Figure 4. Comparison of median intragastric pH values measured over 24 hours (a) and at nighttime (b) in control and on day 7 of the three regimens.

VPZ: vonoprazan, PRZ: pirenzepine.

Figure 5. Comparison of the median pH > 4 holding time ratio (PH 4 HTR) across 24 hours (a) and at nighttime (b) in control and on day 7 of the three regimens.

VPZ: vonoprazan, PRZ: pirenzepine.

Figure 6. Serum gastrin levels of all (a) and 7 cases with vonoprazan-induced hypergastrinemia (gastrin \geq 200 pg/ml) (b) in control and on day 7 of the three regimens.

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Fig. 1

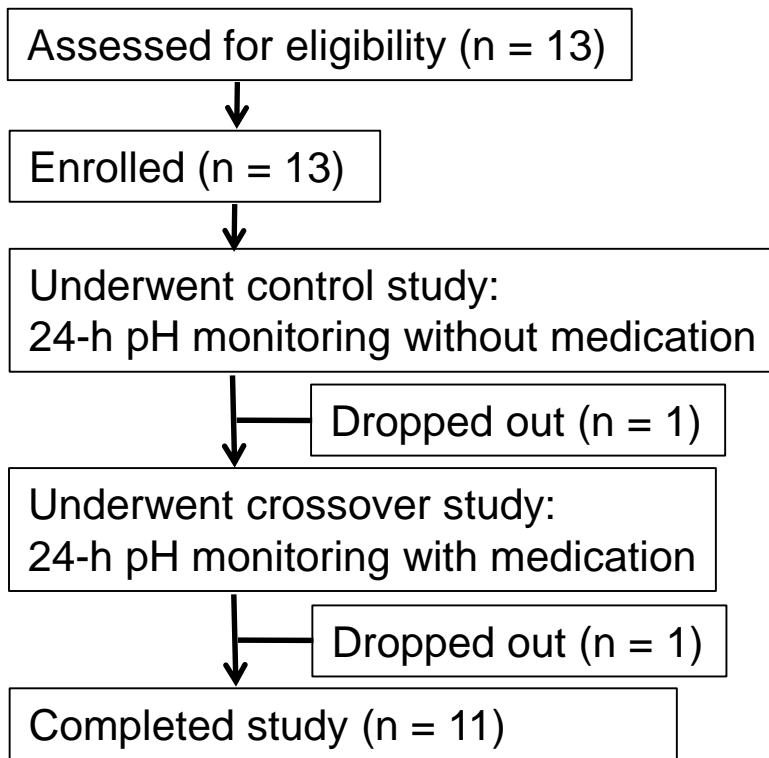


Fig. 2

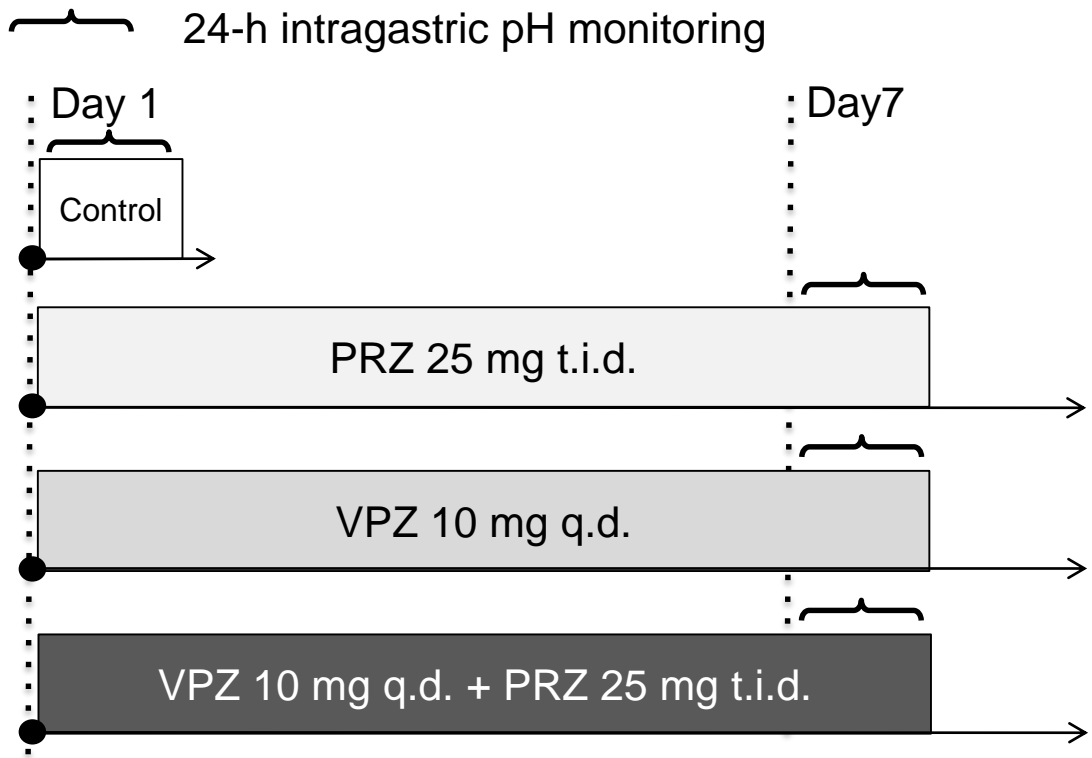


Fig. 3

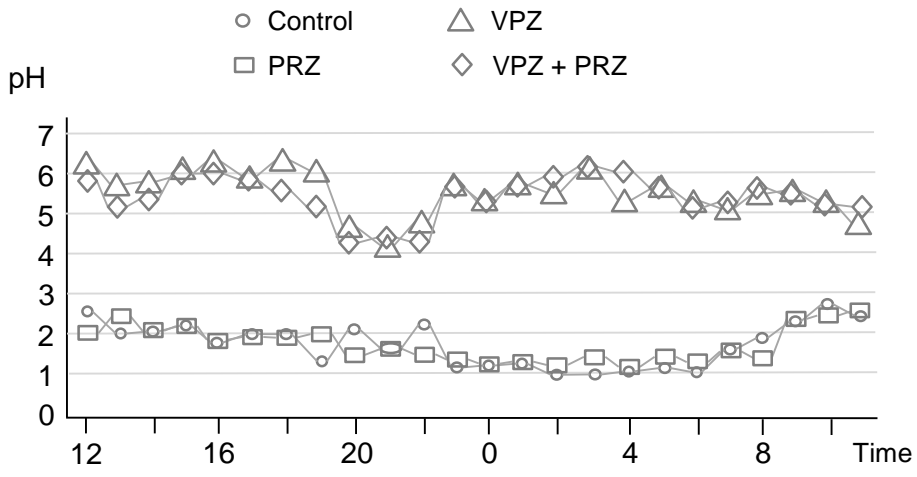
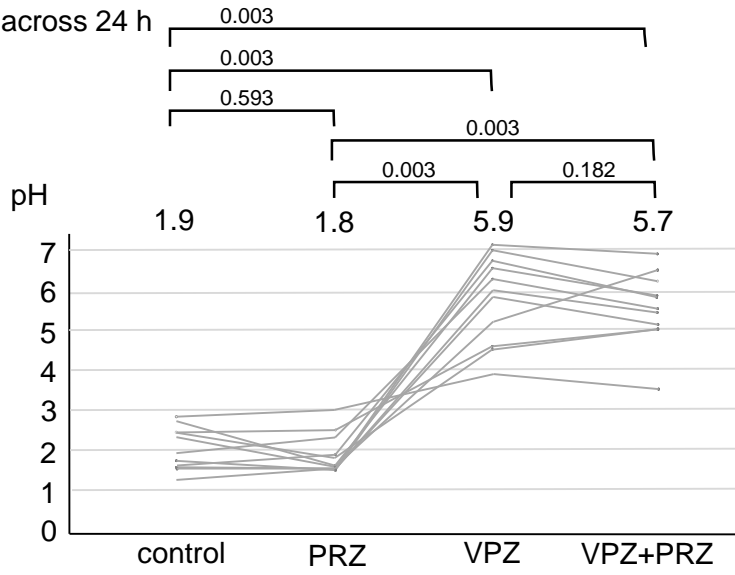


Fig. 4

(a) Median pH across 24 h
(n=11)



(b) Median pH at nighttime
(n=11)

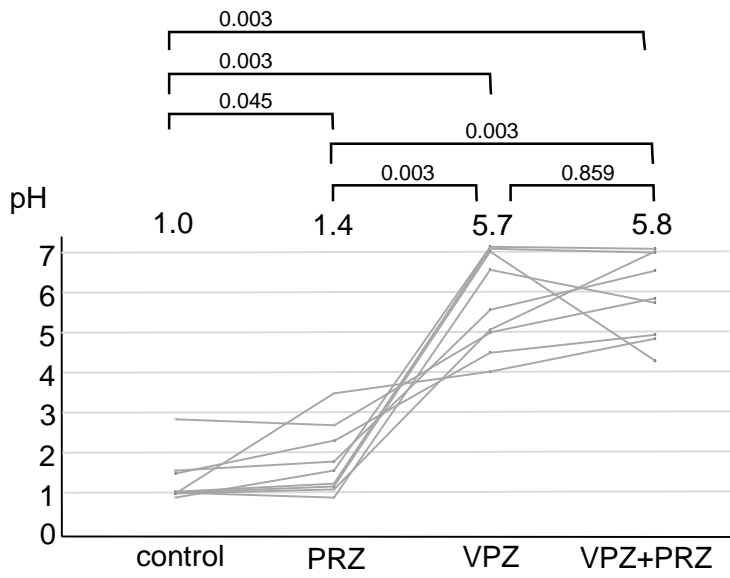
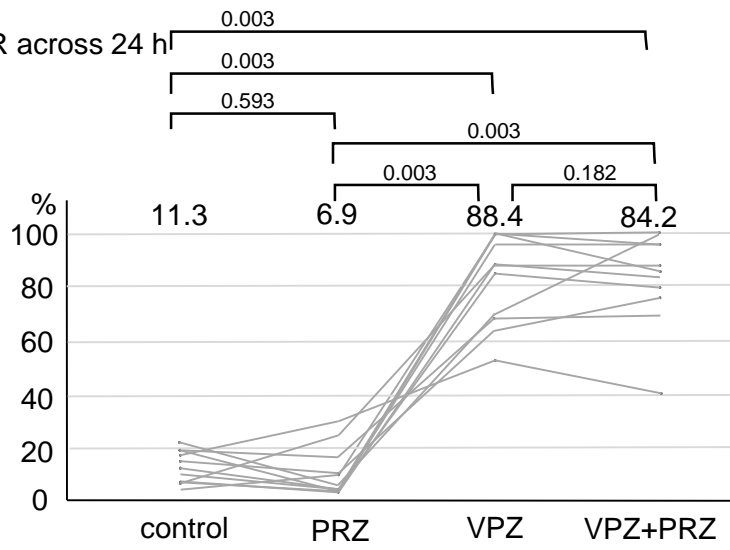


Fig. 5

(a) pH 4 HTR across 24 h
(n=11)



(b) pH 4 HTR
at nighttime
(n=11)

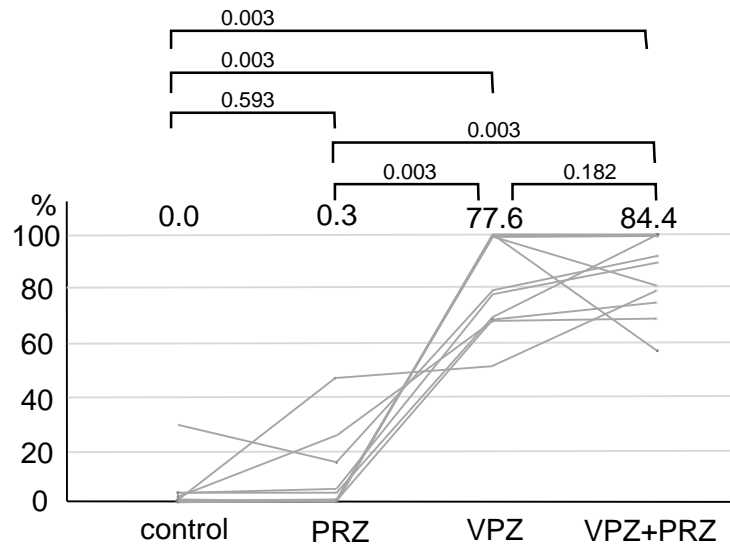
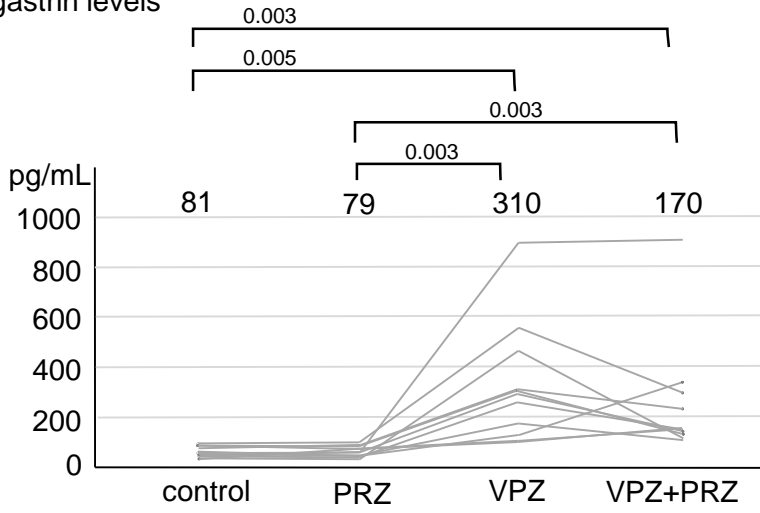


Fig. 6

(a) Serum gastrin levels
(n=11)



(b) Serum gastrin levels
(n=7)

