Evaluation of gastric acid suppression with vonoprazan using calcium carbonate breath test

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Vonoprazan, a potassium-competitive acid blocker, is a new class of acid-suppressing agent. The acid-inhibitory effect of vonoprazan has been well-documented. However, there is no report on the extent to which the amount of gastric acid secretion is suppressed, not pH measurement, by the use of vonoprazan. The aim of this study was to evaluate this suppression effect. This was a single-arm, interventional pilot study involving 7 healthy Japanese men. The subjects were administered 20 mg vonoprazan for 6 days. The amount of gastric acid secretion was determined using the calcium carbonate breath test. The acid outputs were defined as the maximum (ΔC max) and area under the curve (AUC) during the 30 min sampling period. The ΔC max and AUC values significantly decreased on the administration of 20 mg vonoprazan. The AUC dropped by approximately 78% on day 1 and by 84% on day 6 and subsequently returned to the control level after cessation of vonoprazan therapy (reduction by 68% on day 7 and by 42% on day 8). In conclusion, the amount of gastric acid secretion rapidly decreased by the administration of vonoprazan; this inhibitory effect was found to be potent and long-lasting. (UMIN ID: UMIN000025469)

Key Words: vonoprazan, gastric acid, calcium carbonate breath test, potassium-competitive acid blocker, proton-pump inhibitors

The histamine H₂ (H₂) receptor antagonists and proton-pump inhibitors (PPIs) are clinically used as gastric acid suppressants worldwide. PPIs strongly inhibit the function of H⁺/K⁺-ATPase in gastric parietal cells and suppress the secretion of gastric acid.¹ The drugs are widely employed for acid-related disorders such as gastric ulcers, duodenal ulcers, and gastroesophageal reflux disease. They are also effective in preventing gastric mucosal injuries resulting from the use of low-dose aspirin and non-steroidal anti-inflammatory drugs as well as in eradicating Helicobacter pylori (H. Pylori) infection.²⁻⁵ Owing to the well-known and widespread benefits of PPIs, their long-term application has been increasing.⁶ However, the use of PPIs could cause the following complications, which need to be looked into: (i) PPIs are acid-activated pro-drugs that convert to gastric acid; therefore, they should be administered before meals to achieve their full efficacy.¹⁵ (ii) The action of PPI is slow and 3–5 days of treatment is usually needed to experience its full efficacy.⁶ (iii) PPIs have a short plasma half-life of about 90 min; hence, they are not capable of inhibiting all gastric acid pumps.¹⁵ (iv) Patient’s response to PPIs varies to a great extent because of CYP2C19 metabolism.¹⁵ In addition, adverse effects related to long-term use of PPIs, such as fractures,¹¹ enteric infections,¹² and development of gastric polyps¹³ have been reported. Recently, Takagi et al.¹⁴ reported a probable association between PPI use and the alternation of microbiota. Vonoprazan is a potassium-competitive acid blocker (P-CAB) that was recently approved for use in Japan (Takeda Pharmaceutical Company Ltd., Tokyo, Japan). P-CAB—a new class of acid-suppressing agents—inhibits gastric H⁺/K⁺-ATPase activity through reversible K⁺-competitive ionic binding to the enzyme. In addition, it does not require acid activation within the parietal cell secretary canaliculus.¹⁵,¹⁶ It has been reported that P-CAB is effective in the eradication of H. pylori infection¹⁷ and ulcer healing after endoscopic submucosal resection.¹⁸⁻¹⁹ Nishizawa et al.²⁰ reported that the eradication rate of the first-line clarithromycin-based triple therapy with PPIs was significantly lower than that with P-CAB and P-CAB was a better choice of antisecretory agent than PPIs especially in young to middle-aged patients (age ≤50 years). Sakurai et al.²¹ demonstrated that plasma vonoprazan concentrations peaked at 2 h after dosing. Furthermore, 20 mg vonoprazan has been proven to exhibit a more rapid and sustained acid-inhibitory effect than 20 mg esomeprazole or 10 mg rabeprazole.²² Nonetheless, there are no reports that suppression effect on the amount of gastric acid secretion. To evaluate this effect, nasogastric tube or endoscope is required for the collection of gastric juice. However, the drawback is that these methods are invasive and complex. Interestingly, some studies have reported that the calcium carbonate breath test (CBT) is useful for estimating changes in gastric acid secretion.²³⁻²⁴ CBT is a non-invasive test, as the subjects are administered ¹⁳C-labeled calcium carbonate (Ca¹³CO₃) orally; subsequently, the amount of ¹³C-labeled carbon dioxide (¹³CO₂) in the breath (produced upon reaction with the gastric acid) is analyzed.

Ca¹³CO₃ + 2HCl → CaCl₂ + H₂O + ¹³CO₂

Inada et al.²⁵ reported that a high correlation (r = 0.994) between the ¹³C concentration (Cmax) and the total amount of gastric acid in rats with or without PPI. In addition, Shinikai et al.²³ established that the maximum Cmax is correlated with the amount of pooled gastric acid in human (r = 0.95). The aim of this study was thus to evaluate the suppressed amount of gastric acid secretion using CBT.

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Subjects and Methods

Study design. This study was a single-arm, non-randomized, uncontrolled, and interventional pilot study. The research was conducted in accordance with the rules and regulations of the Institutional Review Board at the National Hospital Organization Hakodate Hospital and was registered at the University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: UMIN000025469). Moreover, this study complied with the Good Clinical Practice and the Declaration of Helsinki and Japanese regulatory requirements. All subjects provided a written informed consent to participate in the investigation.

Subjects. Healthy Japanese men aged 20–45 years, weighing ≥50.0 kg, with a body mass index (BMI) of ≥18.5 and <30.0 kg/m², who tested negative for *H. pylori* and did not exhibit any gastric atrophic changes (as confirmed by endoscopy), were found eligible for inclusion in the study.

Blood samples. The fasting blood samples were collected from the subjects on day 0 and on day 6. These samples were immediately centrifuged at 4°C, and the serum was stored at −20°C. The serum gastrin levels were determined using a radioimmunoassay kit (Gastrin RIA Kit II, Fujirebio Inc., Tokyo, Japan), the pepsinogen (PG) I and II levels were quantified by chemiluminescence assay kit (EIA Pepsinogen I and II kit, Fujirebio Inc., Tokyo, Japan), and the serum was stored at −20°C. The amount of gastric acid secretion was examined by CBT on days 0, 1, 6, 7, 8, and 9 (5 h after vonoprazan administration or at 12:00 AM). The blood samples were obtained on days 0 and 6. The subjects were not permitted to take prescription medications, vitamin supplements, nutrient supplements, or over-the-counter drugs for 28 days before day 0 as well as throughout the duration of the study until day 9. All the subjects consumed an identical diet comprising of a rice ball at 07:00 AM and refrained from eating after 09:00 PM during the entire study period.

Statistical analyses. The results were entered into a database for statistical analysis using Prism software (ver. 6; GraphPad Software, Inc., La Jolla, CA). The data were expressed as mean ± SD. The parameters were compared by Student’s *t* test, and the differences were considered to be statistically significant at *p*<0.05.

Results

Subjects. A total of 7 male volunteers were enrolled in this study. None of them displayed gastric atrophic change or active *H. pylori* infection. The median age of the subjects was 33 and the median BMI was 22.7 kg/m² (Table 1).

Assessment of gastric atrophy. Endoscopic atrophy was defined according to the Kimura–Takemoto classification system, in which the atrophic patterns are divided into either closed type (C-0, C-1, C-2, and C-3) or open type (O-1, O-2, and O-3) based on the endoscopically recognized differences in the color and height of the gastric mucosa. The lack of endoscopic atrophy was referred to as type C-0 in the Kimura–Takemoto classification.

Calcium carbonate breath test. The subjects were administered with a single oral dose of 125 mg Ca{sup 13}CO{sub 3} (Cambridge Isotope Laboratories, Inc, MA) suspended in 200 ml water and were maintained in an upright position during the breath test. The breath samples were collected in breath collection bags before receiving the dose as well as at 5, 10, 15, 20, and 30 min after the dosing. At each instance, the {sup 13}CO{sub 2} levels in the expired breath were measured using an infrared spectral analyzer (POCone; Otsuka Electronics Co., Ltd., Hirakata, Osaka, Japan), and the change (Δ{sup 13}C‰) from the baseline level was calculated.

Assessment of acid output. The orally administered Ca{sup 13}CO{sub 3} reacted with gastric acid in the stomach and produced {sup 13}CO{sub 2}. The {sup 13}CO{sub 2} levels in the expired breath were determined at each breath-sampling time, before and after the administration of Ca{sup 13}CO{sub 3}. The {sup 13}CO{sub 2}/{sup 12}CO{sub 2} ratio was calculated each time, and the change (Δ{sup 13}C‰) from the baseline level was also determined. The Δ{sup 13}C‰ in each breath test was plotted as a time curve. The acid outputs were defined as the maximum Δ{sup 13}C‰ (Δ{sup 13}C max) and area under the curve (AUC) during the 30-min sampling period.

Study protocol. The subjects were administered 20 mg vonoprazan after breakfast (07:00 AM) from day 1 to day 6 (Fig. 1). The amount of gastric acid secretion was examined by CBT on days 0, 1, 6, 7, 8, and 9 (5 h after vonoprazan administration or at 12:00 AM). The blood samples were obtained on days 0 and 6.

Fig. 1. Study protocol. Subjects administered with 20 mg vonoprazan after breakfast (07:00 AM) from day 1 to day 6. The gastric acid secretion amount was examined by the calcium carbonate breath test (CBT) on days 0, 1, 6, 7, 8, and 9 (that is, 5 h after vonoprazan administration or at 12:00 AM). The blood samples were obtained on days 0 and 6.
The relative AUC is depicted in Fig. 4. The AUC dropped by approximately 78% on day 1 and by approximately 84% on day 6 compared with day 0. Later, AUC gradually returned to the control level after the cessation of vonoprazan administration (reduction of 68% on day 7 and 42% on day 8). The respective AUCs are indicated in Table 2. Half of the control AUC on day 8 (2 days after cessation of vonoprazan) was not achieved by 3 of the 7 cases. In addition, one of the subjects did not reach the control AUC level even on day 9 (3 days after cessation of vonoprazan).

Table 1. Subjects

| Case | Age | BMI | UBT | Atrophy | RAC | H. pylori infection |
|------|-----|-----|-----|---------|-----|-------------------|
| 1    | 33  | 19.6| 0.1 | (-)     | (+) | (-)               |
| 2    | 40  | 23.5| 0.1 | (-)     | (+) | (-)               |
| 3    | 32  | 23.5| 0.3 | (-)     | (+) | (-)               |
| 4    | 34  | 22.7| 0.8 | (-)     | (+) | (-)               |
| 5    | 27  | 20.2| 0.7 | (-)     | (+) | (-)               |
| 6    | 31  | 20.5| 0.7 | (-)     | (+) | (-)               |
| 7    | 44  | 28.7| 0.2 | (-)     | (+) | (-)               |

BMI, body mass index (kg/m²); UBT, urea breath test; RAC, regular arrangement of collecting venule; H. pylori, Helicobacter pylori.
Serum gastrin and pepsinogen levels. The results of serum gastrin level examination are given in Fig. 5. The median level of control serum gastrin was 86 pg/ml on day 0. The median level was significantly increased on day 6 ($p<0.01$), and the median level was 540 pg/ml. However, in 2 of the 6 cases, the levels were only slightly increased. The results of serum PG I and PG II levels are given in Fig. 6. The median levels of serum PG I on day 6 was significantly increased ($p<0.01$). However, a subject who showed a slight increase in the level. Similarly, the median level of serum PG II on day 6 was significantly increased ($p<0.01$).

Discussion

This is the first study to evaluate the suppression and recovery of gastric acid secretion during administration and withdrawal of vonoprazan using CBT. We confirmed that vonoprazan suppressed approximately 80% gastric acid secretion starting from 5 h after the dosing up to 6 days of continuous dosing. In addition, the effect of vonoprazan was continuous, with the reduction of 68% on day 7 (that is 1 day and 5 h after cessation of dosing) and 42% on day 8 (that is 2 days and 5 h after cessation of dosing).

In this study, we evaluated the gastric acid secretion 5 h after the dosing of 20 mg vonoprazan. It has been previously reported that the plasma vonoprazan concentration peaks at 2 h after dosing$^{(21,28)}$ and that the intragastric pH peaks at 4–5 h after dosing.$^{(22)}$ We found that the amount of gastric acid secretion reduced by approximately 80% at 5 h after dosing with 20 mg vonoprazan. Sakurai et al.$^{(22)}$ revealed that the intragastric pH level within 24 h tended to be higher after vonoprazan administration than that after esomeprazole or rabeprazole administration. The amount of gastric acid secretion decreased rapidly on the administration of vonoprazan. This study thus ascertained that the gastric acid suppression by the use of vonoprazan continued for at least 2 days after cessation of the dosing, with 68% reduction at 29 h after cessation of dosing and 42% reduction at 53 h after cessation of dosing. The elimination half-life of vonoprazan was up to 9 h.$^{(21)}$ In previous reports, the acid secretion inhibitory effect (pH>6) was sustained for almost 24 h by vonoprazan.$^{(29)}$ Therefore, these results showed that the gastric acid secretion inhibitory effect of vonoprazan is potent and long-lasting. The reason behind this phenomenon, however, remains unknown. The binding of vonoprazan to the proton pump is reversible and competitive, unlike the irreversible binding of PPI. There is a possibility that the acid resistance of activated vonoprazan and its accumulation in

Table 2. AUC of $\Delta^{13}$CO$_2$ vs time curves

| Case | Day 0     | Day 1     | Day 6     | Day 7     | Day 8     | Day 9     |
|------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1    | 1,493.5   | 358.75    | 89.25     | 172       | 796       | 1,842.75  |
| 2    | 2,841.75  | 623.5     | 456.25    | 885.25    | 2,055.25  | 2,753.75  |
| 3    | 2,565.25  | 254.25    | 679.25    | 1,937     | 3,040.25  | 3,260.75  |
| 4    | 3,932.75  | 2,067.75  | 382.75    | 676.5     | 1,863.75  | 2,161.25  |
| 5    | 2,220.5   | 431.75    | 300.75    | 779       | 1,391.75  | 2,472.5   |
| 6    | 2,360     | 479.75    | 391.5     | 1,605.5   | 2,436.5   | 2,484     |
| 7    | 2,431     | 926.25    | 641.5     | 391.5     | 931.5     | 2,850     |

Fig. 5. Serum gastrin level. This graph shows the level of serum gastrin (pg/ml) on day 0 (control) and day 6 (5 days after continuous dosing of vonoprazan (20 mg/day)) ($n=7$).

Fig. 6. Serum pepsinogen I and pepsinogen II levels. (a) This graph shows the level of serum pepsinogen I (ng/ml) (PG I) on day 0 and day 6 (5 days after continuous dosing of vonoprazan (20 mg/day)) ($n=7$). (b) This graph shows the level of serum pepsinogen II (ng/ml) (PG II) on day 0 and day 6 (5 days after continuous dosing of vonoprazan (20 mg/day)) ($n=7$).
parietal cells and secretory canaliculus is related to remnant acid suppression.\(^{13,29}\) Furthermore, there is a probability of individual differences occurring in the acid secretion inhibitory effect after cessation of dosing. In 2 subjects, the effect was stronger than that in others. Vonoprazan is metabolized mainly by cytochrome CYP3A4.\(^{12,31,32}\) Sata et al.\(^{34}\) documented the existence of a mutant variant of CYP3A4. There are few reports on the clinical effects of vonoprazan by the variant of CYP3A4.\(^{12,33,36}\) In this study, the variant of CYP3A4 was not examined. This is possibly due to the effect exerted by the variant of CYP3A4.

Recently, there were reported that some factors associated with P-CAB non-responder (non-improvement of symptoms) in the patients with PPI-refractory GERD such as sleep disturbances, co-existing functional dyspepsia and alcohol abstinence.\(^{37}\) However, there was not reported that factors of P-CAB non-responder (non-suppression of gastric acid) other than CYP3A4.

There were reported that H\(_2\) receptor antagonists and PPIs had a post-treatment rebound acid hypersecretion.\(^{18,29}\) In this study, the AUC of \(\Delta^{13}\)CO\(_2\) on day 9 (3 days after cessation of vonoprazan) was higher than day 0 (before administration of vonoprazan) in the 5/7 cases, however there was no significant change. Although the rebound phenomena by P-CAB has not been reported, there is a possibility of the rebound phenomena by P-CAB. \(^{38,39}\)

It has been reported that hypergastrinemia induced by vonoprazan was greater than that induced by PPI. In the present study, the mean serum gastrin level was 540 pg/ml on day 6 of 20 mg vonoprazan administration. Suzuki et al.\(^{40}\) reported that the mean serum gastrin level was 504 pg/ml on day 7 of 20 mg vonoprazan administration. Therefore, the serum gastrin levels are rapidly increased with the use of 20 mg vonoprazan. In this study, the serum gastrin levels of 5/7 cases were over 400 pg/ml on Day 6. On the other hand, the serum gastrin levels of case 1 was 140 pg/ml on day 6 and that of case 4 was 210 pg/ml. However, the AUC of \(\Delta^{13}\)CO\(_2\) on day 6 of these 2 cases dropped as with another 5 cases. It has been reported that an elevated gastrin (>100 pg/ml) was associated with gastric acid suppression (gastric pH<4 for 50% of time) in patients with use of PPI.\(^{41}\) In these 2 cases, serum gastrin levels were slightly elevated (>100 pg/ml). The cause of differences of elevated gastrin levels is unclear, however there is possibility of individual differences. An increased risk of carcinoid tumor development has been reported with the long-term use of PPIs for hypergastrinemia.\(^{42,43}\) However, no development of carcinoid tumor with the long-term use of vonoprazan has been reported. There is therefore a need to follow-up esophagogastroduodenoscopy in patients using vonoprazan over a long-term.

In this study, we evaluated the changes in gastric acid secretion by CBT, which is a non-invasive test used to calculate gastric acid secretion. The subjects took only oral Ca\(^{44}\)CO\(_3\) and the procedure did not involve the use of nasogastric tubes or endoscopes for collecting the gastric juices. It was reported that CBT well correlated with the total amount of gastric acid calculated by multiplying the gastric acidity by the volume of gastric juice.\(^{45}\) Therefore, CBT is useful for calculating gastric acid secretion.

The limitations of the present study include the fact that it was a single-center study with a small sample size. In addition, the CYP3A4 mutation was not examined.

In conclusion, the gastric acid secretion was rapidly decreased by dosing with vonoprazan, and this gastric acid secretion inhibitory effect of vonoprazan was potent and long-lasting.

### Author Contributions

SM, MT and MK conceived the study, designed and executed experiments, analyzed data, prepared figures and tables, and wrote the manuscript. KM, SM, SO, YS and NS supervised all aspects of the study.

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### Abbreviations

- **AUC**: area under the curve
- **BMI**: body mass index
- **Ca\(^{44}\)CO\(_3\)**: \(1^{3}\)C-labeled calcium carbonate
- **CBT**: calcium carbonate breath test
- **P-CAB**: potassium-competitive acid blocker
- **PPIs**: proton-pump inhibitors

### Conflict of Interest

No potential conflicts of interest were disclosed.

### References

1. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the prescribing physician needs to know. Drugs 2003; 63: 2739–2754.
2. Frazzoni M, De Micheli E, Grisendi A, Savarino V. Effective intra-gastric acid suppression in patients with gastro-oesophageal reflux disease: lansoprazole vs pantoprazole. Aliment Pharmacol Ther 2003; 17: 235–241.
3. Satoh K, Yoshino J, Akamatsu T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2015. J Gastroenterol 2016; 51: 177–194.
4. Miner PB Jr. Review article: physiologic and clinical effects of proton pump inhibitors on non-acidic and acidic gastro-oesophageal reflux. Aliment Pharmacol Ther 2006; 23 Suppl 1: 25–32.
5. Massó González EL, García Rodríguez LA. Proton pump inhibitors reduce histamine-2 receptor antagonists and PPIs had a long-term effect. Aliment Pharmacol Ther 2003; 17: 235–241.
6. Haastrup PF, Paulsen MS, Christensen RD, Sondergaard J, Hansen JM, Jarbøl SM, MT and MK conceived the study, designed and executed experiments, analyzed data, prepared figures and tables, and wrote the manuscript. KM, SM, SO, YS and NS supervised all aspects of the study.

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No potential conflicts of interest were disclosed.
(pyridin-3-ylsulfonyl)-1H-pyrrolo[3,4-](N-methylmethanimine)-monofumarate (TAK-438). J Pharmacol Exp Ther 2011; 339: 412–420.
17 Jung YS, Kim EH, Park CH. Systematic review with meta-analysis: the efficacy of vonoprazan-based triple therapy on Helicobacter pylori eradication. Aliment Pharmacol Ther 2017; 46: 106–114.
18 Horikawa Y, Mizutamari H, Mimori N, et al. Short-term efficacy of potassium-competitive acid blocker following gastric endoscopic submucosal dissection: a propensity score analysis. Scand J Gastroenterol 2018; 53: 243–251.
19 Tsuchiya I, Kato Y, Tanida E, et al. Effect of vonoprazan on the treatment of artificial gastric ulcers after endoscopic submucosal dissection: Prospective randomized controlled trial.Dig Endosc 2017; 29: 576–583.
20 Nishizawa T, Suzuki H, Fujimoto A, et al. Effects of patient age and choice of antisecretory agent on success of eradication therapy for Helicobacter pylori infection. J Clin Biochem Nutr 2017; 60: 208–210.
21 Sakurai Y, Nishimura A, Kennedy G, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Japanese subjects. Clin Transl Gastroenterol 2015; 6: e94.
22 Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment Pharmacol Ther 2015; 42: 719–730.
23 Shinaki H, Iijima K, Koike T, et al. Calcium carbonate breath test for non-invasive estimation of gastric acid secretion. Tohoku J Exp Med 2014; 232: 255–261.
24 Tobita K, Inada M, Sato A, Sudo K, Sato H. Estimation of gastric pH in cynomolgus monkeys, rats, and dogs using [(13)C]-calcium carbonate breath test. Dig Liver Dis 2016; 48: 1035–1040.
25 Inada M, Kunizaki J, Tobita K, Akamatsu S, Sato H. Calcium [(13)C]carbonate breath test for quantitative measurement of total gastric acid in rats. Scand J Gastroenterol 2012; 47: 148–154.
26 Kato T, Yagi N, Kamada T, et al. Diagnosis of Helicobacter pylori infection in gastric mucosa by endoscopic features: a multicenter prospective study. Dig Endosc 2013; 25: 508–518.
27 Kimura K, Satoh K, Ido K, Taniguchi Y, Takimoto T, Takemoto T. Gastritis in the Japanese stomach. Scand J Gastroenterol Suppl 1996; 214: 17–20; discussion 21–3.
28 Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2015; 41: 636–648.
29 Otake K, Sakurai Y, Nishida H, et al. Characteristics of the novel potassium-competitive acid blocker vonoprazan fumarate (TAK-438). Adv Ther 2016; 33: 1140–1157.
30 Hori Y, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. J Pharmacol Exp Ther 2011; 337: 797–804.
31 Matsukawa J, Kogame A, Tagawa Y, Inatomi N. Radiographic localization study of a novel potassium-competitive acid blocker, vonoprazan, in the rat gastric mucosa. Dig Dis Sci 2016; 61: 1888–1894.
32 Sugimoto M, Ban H, Hira D, et al. Letter: CYP3A4/5 genotype status and outcome of vonoprazan-containing Helicobacter pylori eradication therapy in Japan. Aliment Pharmacol Ther 2017; 45: 1009–1010.
33 Yamasaki H, Kawaguchi N, Nonaka M, et al. In vitro metabolism of TAK-438, vonoprazan fumarate, a novel potassium-competitive acid blocker—Xenobiotica 2017; 47: 1027–1034.
34 Sato F, Sapone A, Elizondo G, et al. CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. Clin Pharmacol Ther 2000; 67: 48–56.
35 Kagami T, Yamade M, Suzuki T, et al. Comparative study of effects of vonoprazan and esomeprazole on antiplatelet function of clopidogrel or prasugrel in relation to CYP2C19 genotype. Clin Pharmacol Ther 2018; 103: 906–913.
36 Jenkins H, Jenkins R, Patat A. Effect of multiple oral doses of the potent CYP3A4 inhibitor clarithromycin on the pharmacokinetics of a single oral dose of vonoprazan: a phase I, open-label, sequential design study. Clin Drug Investig 2017; 37: 311–316.
37 Okuyama M, Nakahara K, Iwakura N, et al. Factors associated with potassium-competitive acid blocker non-response in patients with proton pump inhibitor-refractory gastroesophageal reflux disease. Digestion 2017; 95: 281–287.
38 Lodrup AB, Reimer C, Bytzer P. Systematic review: symptoms of rebound hypersecretion following proton pump inhibitor treatment. Scand J Gastroenterol 2013; 48: 515–522.
39 Sandvik AK, Brenna E, Waldum HL. Review article: the pharmacological inhibition of gastric acid secretion–tolerance and rebound. Aliment Pharmacol Ther 1997; 11: 1013–1018.
40 Suzuki T, Kagami T, Uotani T, et al. Comparison of effect of an increased dosage of vonoprazan versus vonoprazan plus lansoprazole on gastric acid inhibition and serum gastrin. Eur J Clin Pharmacol 2018; 74: 45–52.
41 Bonapace ES, Fisher RS, Parkman HP. Does fasting serum gastrin predict gastric acid suppression in patients on proton-pump inhibitors? Dig Dis Sci 2000; 45: 34–39.
42 Nandy N, Hanson JA, Strickland RG, McCarthy DM. Solitary gastric carcinoid tumor associated with long-term use of omeprazole: a case report and review of the literature. Dig Dis Sci 2016; 61: 708–712.
43 Jianu CS, Lange OJ, Viset T, et al. Gastric neuroendocrine carcinoma after long-term use of proton pump inhibitor. Scand J Gastroenterol 2012; 47: 64–67.