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Original Article

# The Effect of Tegoprazan on Serum Gastrin Levels and the Development of Hypergastrinemia in the Maintenance Treatment for Gastroesophageal Reflux Disease: Comparison to Lansoprazole

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## Background/Aims
Safety data on potassium-competitive acid blockers are limited. We aim to evaluate the effect of tegoprazan on serum gastrin levels during maintenance treatment for gastroesophageal reflux disease compared to lansoprazole.

## Methods
In a prospective, randomized trial, patients who underwent initial treatment with a standard dose of a proton pump inhibitor (n = 121) or tegoprazan (n = 226) were randomized to receive a half-dose of tegoprazan (n = 173) or lansoprazole (n = 174) as maintenance treatment for up to 24 weeks. Serum gastrin levels were measured immediately after initial treatment and monitored throughout the maintenance treatment period.

## Results
Baseline gastrin levels were similar between the tegoprazan and lansoprazole groups ($P$ = 0.335). During maintenance treatment, gastrin levels were significantly lower in the tegoprazan group at week 16 ($P$ = 0.001) and week 24 ($P$ = 0.012) compared to the lansoprazole group. Although the proportion of hypergastrinemia (> 115 pg/mL) was similar at baseline between the tegoprazan and lansoprazole groups ($P$ = 0.114), it was significantly lower in the tegoprazan group during maintenance treatment ($P$ = 0.003, 0.033, and 0.039 at weeks 8, 16, and 24, respectively) than in the lansoprazole group. Multivariate analysis revealed that age, sex, baseline gastrin levels, *Helicobacter pylori* infection, and the drug group were independently associated with final gastrin levels.

## Conclusion
Tegoprazan has a smaller impact on increasing serum gastrin levels and the development of hypergastrinemia than lansoprazole, suggesting that tegoprazan may reduce safety concerns related to hypergastrinemia, particularly at half doses.
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## Key Words
Gastrins; Hypergastrinemia; Proton pump inhibitors

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## Introduction

Acid secretion inhibitory agents are commonly prescribed for acid-related disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease.[1] Proton pump inhibitors (PPIs) have been used as the first-line treatment for GERD. Although PPIs effectively maintain the intragastric pH level above 4, they have several limitations, including slow onset of action, short plasma half-life, efficacy influenced by cytochrome P450 CYP2C19 genetic polymorphism, and the need for mealtime dosing.[2,3] Furthermore, while evidence establishing causal relationships is limited, studies have raised concerns about the adverse effects of long-term PPI use, including alterations in the gut microbiome, enteric infections, pneumonia, micronutrient deficiencies, chronic kidney disease, bone fractures, fundic gland polyps, and gastrointestinal malignancy.[4,5] Population-based studies suggest that PPIs may increase the risk of gastric cancer, particularly in individuals with *Helicobacter pylori*-associated chronic gastritis and atrophy.[5] Gastrin, a hormone secreted by antral G cells, acts as a potent cell growth factor with proliferative and trophic effects on the gastrointestinal mucosa.[6-8] Persistent hypergastrinemia is thought to be involved in the development of gastric neoplasms or malignancy during long-term use of PPIs.

Potassium-competitive acid blockers (PCABs) are a novel class of acid-suppressive drugs recently introduced as an alternative to PPIs. PCABs offer several advantages over conventional PPIs.[9-11] Tegoprazan, a PCAB available in South Korea, exhibits a more potent and longer-lasting acid-inhibitory effect than conventional PPIs.[12,13] Serum gastrin levels are believed to be increased by a condition of low acidity in the stomach through the acid secretion feedback system.[14,15] Accordingly, it is concerned that serum gastrin levels may be more elevated with PCAB use compared to PPI use.

However, the effect of PCABs on serum gastrin levels appears to be variable and inconsistent. A phase III randomized study comparing vonoprazan to lansoprazole in the maintenance treatment for healed erosive esophagitis found that vonoprazan significantly increased serum gastrin levels more than lansoprazole.[16] In contrast, a phase III randomized trial comparing tegoprazan to lansoprazole in the maintenance treatment for healed erosive esophagitis showed no significant difference in serum gastrin levels between the 2 groups.[17] Recent studies have suggested that other factors, such as *H. pylori* infection and atrophic gastritis, may be more important in causing hypergastrinemia than the acid-secretory agent itself.[15,18-20]

The present study aims to evaluate the effect of a half-dose of tegoprazan on serum gastrin levels and the development of hypergastrinemia during 6-month maintenance treatment for GERD, compared with a half-dose of lansoprazole.

## Materials and Methods

### Study Protocol and Participants

This study was performed by secondary analysis or a substudy using data from a multicenter, prospective, randomized study assessing the non-inferiority of 25 mg tegoprazan to 15 mg lansoprazole as maintenance therapy in Korean patients with healed erosive esophagitis.[17] The study protocol was approved by the Institutional Review Board of Ajou University Hospital (AJOUIRB-CT-2019-095) and registered at ClinicalTrials.gov (identifier number: NCT04022096; Study title: Study to confirm the safety and efficacy of tegoprazan in patients with healed erosive esophagitis).

Figure 1 illustrates the protocol of the original study. Inclusion and exclusion criteria are described in a previously published paper.[17] During the screening period, endoscopy was performed to evaluate erosive esophagitis based on the Los Angeles classification System. After 4 weeks or 8 weeks of initial treatment with a standard dose of a conventional PPI (esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, or rabeprazole) or tegoprazan, a follow-up endoscopy was performed to confirm healing of erosive

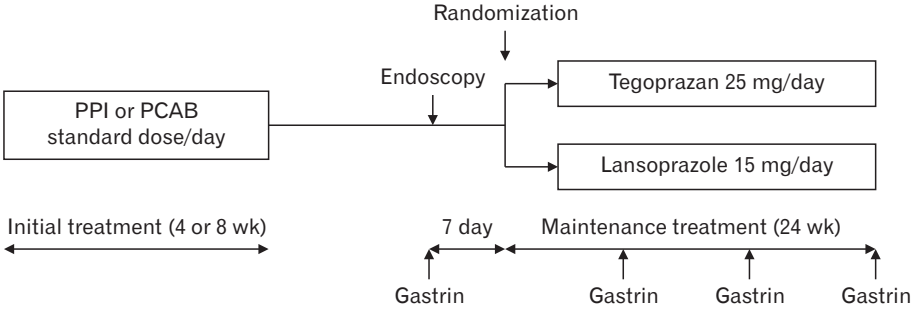


**Figure 1.** Study protocols of the maintenance treatment for patients with healed erosive esophagitis using either tegoprazan or lansoprazole. PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker. Modified from Cho et al.[17]

esophagitis. Patients who showed healing of erosive esophagitis after initial treatment were randomized to receive a half-dose of tegoprazan (25 mg) (n = 174) or lansoprazole (15 mg) (n = 177) as maintenance treatment. Both drugs were administered once daily, 30 minutes before breakfast, for up to 24 weeks. Participants were not permitted to take concomitant medications that could affect study outcomes.

### Measurement of Serum Gastrin, Pepsinogen, and Anti-*Helicobacter pylori* IgG

Serum was obtained in the fasting state and stored at –80 °C until analysis. Serum gastrin levels were measured by electrochemiluminescence immunoassay using a monoclonal antibody specific to gastrin (Immulite 2000; Siemens Healthineers, Forchheim, Germany) and were expressed in picograms per milliliter (pg/mL). Hypergastrinemia was defined as gastrin > 115 pg/mL. The antibodies in the kit recognized both gastrin-17 and gastrin-34. Serum gastrin was measured at baseline before the start of maintenance treatment (week 0) without wash-out period from initial treatment and at 8-week intervals (weeks 8, 16, and 24) during the maintenance treatment period. Serum pepsinogen (PG) I and II levels were measured using a latex-enhanced immunoassay (HiSens; HBI, Anyang, Korea), and the PG I/II ratio was also calculated.

*H. pylori* status was determined by measuring serum *H. pylori* IgG antibodies using electrochemiluminescence immunoassay (Immulite 2000; Siemens), with values ≥ 1.10 U/mL considered positive. Eradication history was not assessed in this study.

### Study Outcomes

The main outcomes included: (1) Final serum gastrin levels, defined as fasting serum gastrin levels measured at the last follow-up during the maintenance treatment, recorded as log-transformed continuous variables to normalize the distribution of gastrin values. (2) Serum gastrin levels measured at each visit during the maintenance treatment period, also recorded as log-transformed continuous variables. (3) Development of hypergastrinemia, defined as a gastrin value > 115 pg/mL at the last follow-up.

PPI or PCAB exposure during the maintenance treatment period was assessed in terms of the total days of drug intake.

### Statistical Methods

Continuous, normally distributed variables are expressed as mean values with standard deviation, while non-normally distributed values are expressed as median values with 25-75% percentiles. The OR and 95% CIs were calculated using binomial regression analysis. Comparisons for continuous variables were performed using the Student's *t* test, and categorical variables were compared using chi-square or Fisher's exact test. Multiple linear regression was used to evaluate covariates. *P*-values < 0.05 denote statistical significance. Statistical analyses were performed using R-Studio (version 1.1.453) and SPSS (version 25.0 for Windows, IBM Corp., Armonk, NY, USA).

## Results

### Study Subjects

After randomization of a total of 351 patients, safety analysis including serum gastrin levels was performed for 347 patients who received at least one dose of the study drug and underwent at least one safety assessment. In the current study, data of those 347 patients who were randomized into the tegoprazan (n = 173) or lansoprazole (n = 174) maintenance treatment groups were analyzed. Demographics and baseline characteristics are summarized in Table. No significant differences were observed between the groups regarding mean age, sex ratios, the rate of *H. pylori* IgG antibody positivity, baseline serum gastrin levels, and baseline PG I/II ratios measured immediately after initial treatment.

### Serum Gastrin Levels and Hypergastrinemia Development

Baseline serum gastrin levels measured immediately after initial treatment did not differ significantly between the tegoprazan (n = 226) and conventional PPI (n = 121) groups (94.8 ± 100.5 vs 100.4 ± 115.3 pg/mL, $P = 0.637$). Serum gastrin levels decreased at all time points (weeks 8, 16, and 24) during the maintenance treatment period compared to baseline. At week 8, gastrin levels were lower in the tegoprazan group (81.9 ± 77.2 vs 96.8 ± 84.7 pg/mL, $P = 0.099$), and significantly lower at week 16 (70.3 ± 46.7 vs 92.5 ± 71.1 pg/mL, $P = 0.001$) and week 24 (73.2 ± 65.2 vs 97.6 ± 92.2 pg/mL, $P = 0.012$) compared to the lansoprazole group (Fig. 2).

The proportion of patients with hypergastrinemia at baseline did not differ significantly between the tegoprazan (22.6%) and lansoprazole (24.8%) groups ($P = 0.640$). However, during the maintenance period, hypergastrinemia was observed less frequently in the tegoprazan group compared to the lansoprazole group at weeks 8 (14.6% vs 28.2%, $P = 0.003$), 16 (14.7% vs 24.3%, $P = 0.033$), and 24 (16.3% vs 26.5%, $P = 0.039$).

**Table.** Demographics and Baseline Characteristics of 347 Patients Who Were Randomized Into the Tegoprazan or Lansoprazole Maintenance Treatment Groups

| Parameters | Total (N = 347) | Tegoprazan (n = 173) | Lansoprazole (n = 174) | *P* value[a] |
|---|---|---|---|---|
| Age (yr) | 56.1 ± 12.7 | 55.9 ± 12.1 | 56.2 ± 13.3 | 0.800 |
| Sex (M/F) | 248/99 | 126/47 | 122/52 | 0.575 |
| *H. pylori* (+) | 79 (22.8) | 36 (20.8) | 43 (24.9) | 0.370 |
| Baseline gastrin (pg/mL) | 96.8 ± 105.8 | 91.3 ± 98.9 | 102.2 ± 112.2 | 0.335 |
| Hypergastrinemia | 70 (20.2) | 34 (19.7) | 47 (27.0) | 0.105 |
| Baseline pepsinogen I/II | 6.6 ± 1.7 | 6.7 ± 1.8 | 6.6 ± 1.5 | 0.768 |
| Total days of drug intake | 148.7 ± 40.6 | 150.3 ± 39.4 | 145.1 ± 44.2 | 0.605 |

[a]*P*-value for tegoprazan vs lansoprazole.
M, male; F, female; *H. pylori, Helicobacter pylori.*
Data are presented as mean ± SD , n, or n (%).

## Factors Associated With Serum Gastrin Levels Measured at the Last Visit During the Maintenance Treatment Period

Multivariate analysis revealed that age (Beta coefficient 0.004 [95% CI, 0.002-0.006], $P = 0.001$), sex (female) (Beta coefficient 0.103 [95% CI, 0.038-0.169], $P = 0.002$), baseline gastrin levels (Beta coefficient 0.001 [95% CI, 0.001-0.001], $P < 0.001$), *H. pylori* infection (Beta coefficient 0.125 [95% CI, 0.053-0.197], $P = 0.001$), and drug group (lansoprazole) (Beta coefficient 0.063 [95% CI, 0.005-0.122], $P = 0.035$) were independently associated with final gastrin levels measured at the final follow-up during the maintenance treatment period (Fig. 3).

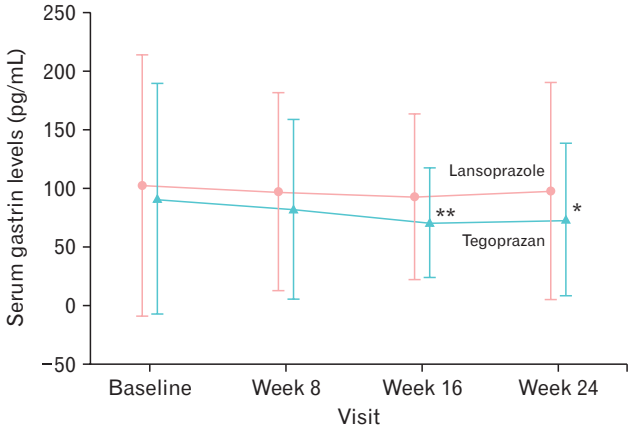


**Figure 2.** Change in serum gastrin levels during the maintenance treatment period (**$P = 0.001$ and *$P < 0.05$ using Student's *t* test).

## Discussion

PCABs have advantages over conventional PPIs, including acid stability, rapid onset of action, longer plasma half-life, efficacy unaffected by cytochrome P450 CYP2C19 genetic polymorphism, more potent acid-inhibitory effects, and no requirement for meal-time dosing.[21-23] Comparative studies between PCABs and PPIs demonstrate that PCABs provide a more potent and longer-lasting acid-inhibitory effect.[12,24,25] However, the stronger inhibitory effect of PCABs on gastric acid secretion raises safety concerns regarding their long-term use, particularly regarding hypergastrinemia and the potential risk of gastric neoplasms. In this study, we found that initial treatment for GERD with a standard dose of tegoprazan did not elevate serum gastrin levels or induce hypergastrinemia more than a standard dose of conventional PPI. Furthermore, a half-dose of tegoprazan had less effect on serum gastrin levels and the development of hypergastrinemia than a half-dose of lansoprazole during 6 months of maintenance treatment for GERD.

Vonoprazan, another PCAB developed by Takeda Pharmaceutical Company, Japan, has been shown to produce more potent and sustained gastric acid suppression than lansoprazole.[26-30] In a phase III randomized trial comparing vonoprazan and lansoprazole over 24 weeks of maintenance treatment, serum gastrin, pepsinogen I, and pepsinogen II levels increased more significantly in the vonoprazan group than the lansoprazole group.[31] However, no notable effects on the histopathology of the gastric mucosa were observed between baseline and week 24.[16] A phase IV 5-year open-label trial comparing vonoprazan and lansoprazole for long-term maintenance treatment of erosive esophagitis reported significantly higher serum gastrin levels in the vonoprazan group at all time points throughout the maintenance treatment period.[31] In this phase IV trial of vonoprazan, patients with healed erosive esophagitis after initial treatment received maintenance treatment (once daily vonoprazan 10 mg or lansoprazole 15 mg) for 260 weeks. Over the maintenance treatment period, parietal cell hyperplasia and foveolar hyperplasia

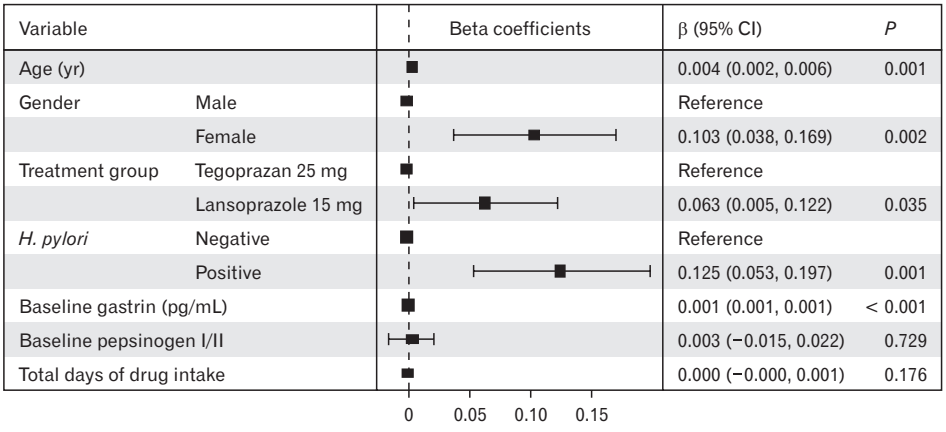


**Figure 3.** Multiple linear regression analysis for factors associated with final serum gastrin levels measured at the last treatment follow-up. *H. pylori, Helicobacter pylori.*

were found to be significantly increased in the vonoprazan group. Despite this, no increased risk of malignant epithelial cell changes or gastric neuroendocrine tumors was observed.[31]

However, this study was limited by a small sample size and by only focusing on Japanese patients who were *H. pylori* negative. Thus, additional data from more diverse populations with risk factors for gastric cancer, such as *H. pylori* infection or advanced atrophic gastritis, are needed to confirm the long-term safety of PCABs, including vonoprazan.

There have been reports of well-differentiated neuroendocrine tumors linked to long-term PPI use.[32,33] In 2 cases, histologic findings showed hyperplasia of enterochromaffin cells, which regressed after cessation of PPI treatment.[33] Although the evidence linking PPI use to gastric cancer remains inconclusive, chronic gastrin elevation and altered gut microbiota caused by prolonged PPI use are believed to play a role in gastric carcinogenesis.[34,35] Population-based studies from several Asian countries have shown that long-term PPI use in patients who underwent *H. pylori* eradication therapy is associated with an increased risk of gastric cancer.[36,37] These studies suggest that PPIs may increase the risk of gastric cancer in individuals with *H. pylori*-associated chronic gastritis and atrophy.[5] More recent studies indicate that background factors such as old age, high baseline serum gastrin levels, low baseline PG ratios, and severe gastric atrophy may be more significant in the development of hypergastrinemia than PPI use itself.[38,39] Larger studies in individuals with these risk factors, who are on long-term maintenance treatment with PPIs or PCABs, are needed to establish the long-term safety of these drugs.

Tegoprazan, which was approved in South Korea in 2018, is available in several countries and has been reported to exhibit a more rapid and stronger acid-inhibitory effect than PPIs.[12,40,41] However, long-term safety data for tegoprazan are lacking, and further studies are needed. Our current findings demonstrate that a half-dose of tegoprazan, recommended for maintenance treatment of mild GERD, has less effect on serum gastrin levels and the development of hypergastrinemia than a half-dose of lansoprazole. Moreover, reducing the standard dose used in initial treatment to a half-dose for maintenance treatment showed a lowering effect on serum gastrin levels. Based on these findings, using the lowest effective dose is recommended for long-term maintenance treatment of GERD with PPIs or PCABs.

Unlike vonoprazan, studies have shown that tegoprazan does not elevate serum gastrin levels more than conventional PPIs.[17,41] However, the reason for this discrepancy between the 2 PCABs remains unclear. Further research is needed to determine whether the differences are related to variations in acid-inhibitory capacity, drug action properties, or the chemical structure of the drugs. Given that serum gastrin levels are lower during the maintenance treatment period in the tegoprazan group than in the lansoprazole group, differences in the properties of drug action or chemical structure might play a larger role than differences in acid-inhibitory capacity. Further investigations are warranted to better understand the variable effects of PCABs on serum gastrin levels. Additionally, long-term safety data extending beyond 6 months are needed for commercially available PCABs, including tegoprazan.

Several limitations in this study should be noted. Serum assays for *H. pylori* antibodies are insufficient for confirming the status of *H. pylori* infection. It is desirable to interpret with endoscopic findings and other *H. pylori* tests. Detailed evaluation of gastric mucosal status (eg, atrophic gastritis) was not considered in this study, even though it can also influence serum gastrin levels. Nevertheless, baseline gastrin levels did not differ significantly between the tegoprazan and lansoprazole groups. Hypergastrinemia was defined as a serum gastrin level > 115 pg/mL based on the assay reference

range, but it remains uncertain whether this cut-off value has clinical significance and represents a risk factor for the development of gastric neoplasia. Additionally, most PCABs, including tegoprazan, lack long-term safety data beyond 6 months, and the present study also did not provide such data.

In conclusion, tegoprazan has a smaller impact on increasing serum gastrin levels and the development of hypergastrinemia compared to lansoprazole, suggesting that tegoprazan may reduce safety concerns related to hypergastrinemia, particularly at half doses.

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**Conflicts of interest:** None.

**Author contributions:** Kwang Jae Lee was involved in conceptualization, study design, data analysis, the drafting of the manuscript, and the editing of the manuscript; Da Hyun Jung contributed to the study design and data analysis; and Oh-Young Lee was involved in the original data of the multicenter randomized trial. All authors approved the final version of the manuscript.

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