Proton Pump Inhibitors Increase Incidence of Nonsteroidal Anti-Inflammatory Drug–Induced Small Bowel Injury: A Randomized, Placebo-Controlled Trial

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BACKGROUND & AIMS: Some studies have reported a high incidence of small bowel injuries in 60%–80% of subjects who take nonselective nonsteroidal anti-inflammatory drugs and PPIs simultaneously. We performed a randomized, double-blind, controlled study to determine whether proton pump inhibitors (PPIs) exacerbate nonsteroidal anti-inflammatory drug–induced small bowel injury.

METHODS: Fifty-seven healthy subjects were randomly assigned groups given the cyclooxygenase (COX) 2 inhibitor celecoxib (200 mg, twice daily) plus placebo for 2 weeks (COX-2 placebo group, n = 30), or celecoxib plus the PPI rabeprazole (20 mg, once daily) for 2 weeks (COX-2 + PPI group, n = 27). The study was performed from October 2012 through September 2013 at a tertiary medical center in Japan. All subjects were evaluated by capsule endoscopy at the start of the study and then after 2 weeks administration of celecoxib with rabeprazole or placebo. The incidence rates and the numbers of small bowel injuries (ulcers and erosions) that were observed under capsule endoscopy were compared between groups. The primary endpoint was the incidence of mucosal injuries at the second capsule endoscopy examination.

RESULTS: A significantly higher proportion of subjects in the COX-2 + PPI group developed small bowel injury (12 of 27 subjects; 44.4%) than in the COX-2 + placebo group (5 of 30 subjects; 16.7%; P = .04). Subjects in the COX-2 + PPI group had a significant increase in risk of small bowel injury compared with the COX-2 + placebo group (relative risk, 2.67; 95% confidence interval, 1.08–6.58). The number of erosions in each member of the COX-2 + PPI group was greater than in each member of the COX-2 + placebo group (P = .02). The number of ulcers did not differ between groups. Twenty-six percent of subjects in the COX-2 + PPI group developed mucosal injury in the jejunum, compared with none of the subjects in the COX-2 + placebo group (P = .003); no such trend was found in the ileum.

CONCLUSIONS: In a randomized, controlled trial, PPIs increased the risk of short-term nonsteroidal anti-inflammatory drug–induced small bowel injury. UMIN clinical trial registry number: UMIN000008883.

Keywords: Intestine; Damage; Cyclooxygenase-2 Inhibitor; COX-2.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently prescribed types of medication worldwide. Despite their favorable analgesic effect, the use of NSAIDs is associated with high incidence of gastrointestinal (GI) toxicity. Gastroduodenal ulcers have been found to occur in 20%–30% of chronic NSAIDs users.¹² Moreover, the applications of capsule endoscopy (CE) and balloon-assisted enteroscopy have revealed that NSAIDs induce small bowel injuries more frequently than had previously been believed.³⁶

Abbreviations used in this paper: CE, capsule endoscopy; COX, cyclooxygenase; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
Antiacid secretory drugs, especially proton pump inhibitors (PPIs), have become the mainstay prophylactic treatment against NSAID-induced GI toxicities. The results of animal studies have suggested PPIs exert prophylactic effects against small bowel injuries. However, recent clinical trials using CE have shown considerably high incidence of small bowel injuries (60%-80%) in subjects who take nonselective NSAIDs and PPIs simultaneously.

We recently carried out a randomized clinical trial to evaluate small bowel toxicity in association with celecoxib, a clinically available cyclooxygenase (COX)-2 selective inhibitor, in healthy subjects and identified small bowel injuries in 43% of the study population. Although the incidence of the mucosal injuries was conspicuously higher in comparison with the previous studies of Goldstein et al., we were not able to arrive at provisional explanation for our discordant results. However, Wallace et al. subsequently demonstrated PPI use exacerbated NSAID-induced small bowel injury in a rodent model. A review of the study protocols revealed a difference: PPI was simultaneously administered in our previous study, but not in the studies of Goldstein et al. These observations strongly suggested that PPIs might be closely associated with the development of NSAIDs-induced small bowel mucosal injuries in humans.

To examine the influence of concomitant use of PPIs on NSAID-induced small bowel injury in humans, we performed a prospective, double-blind, randomized controlled study.

Methods

Study Design

This study was a prospective, double-blind, randomized controlled trial. Before randomization, all subjects underwent laboratory tests (complete blood cell count, serum chemistry, and Helicobacter pylori antibodies), an electrocardiogram, and a baseline CE. Subjects with abnormal laboratory test results or those who had abnormal electrocardiogram findings were excluded from the study. Subjects in whom small bowel bleeding, ulcers, or erosions were detected in baseline CE were also excluded. Under a computer-generated randomization system using a minimization method, the study subjects were allocated into 1 of 2 groups: the COX-2 SI group received COX-2 selective inhibitor and placebo, whereas the COX-2 SI + PPI received COX-2 selective inhibitor plus rabeprazole. The following patient characteristics were chosen as stratification factors: age (<30 years or ≥30 years), sex, and the hemoglobin level (<14.5 g/dL or ≥14.5 g/dL). Subjects in the COX-2 SI group received celecoxib (200 mg, twice daily) plus placebo (lactose 20 mg, once daily); the subjects in the COX-2 SI + PPI group received celecoxib (200 mg, twice daily) plus rabeprazole (20 mg, once daily) for 2 weeks. The dosages of celecoxib and rabeprazole, which were also applied to other Japanese clinical trials, were determined based on the dosages approved by the Japanese Ministry of Health and Welfare. Rabeprazole and placebo were prepared in dummy capsules. The study subjects were instructed to take a capsule once per day for 2 weeks. The use of other NSAIDs, aspirin, and antiulcer drugs was strictly prohibited during the study period. After 2 weeks of medication, the subjects completed a questionnaire about GI symptoms, underwent repeated laboratory tests, and underwent second CE.

The study protocol was approved by the institutional review board of the International University of Health and Welfare, Fukuoka Sanno Hospital (FS30), and the study was conducted in accordance with the Helsinki Declaration. This trial was registered as the PPI-NSAID Kyushu University study (PINK study) in the University Hospital Medical Information Network Clinical Trials Registry under registration number UMIN000008883 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000010425&type=summary&language=E). Written informed consent was provided by each subject before entry into the study. All authors had access to the study data and reviewed and approved the final manuscript.

Subjects

Healthy volunteers with normal physical examination and laboratory test results were eligible. The exclusion criteria were as follows: (1) a history of peptic ulcers, (2) a history of recent (within 1 month) NSAID or aspirin use, (3) a history of aspirin-induced asthma, (4) an allergy to sulfonamide, (5) a history of recent treatment with antiulcer drugs, (6) stenosis of the GI tract, (7) a history of ileus, (8) pregnant or nursing women, and (9) the presence of other disorders regarded to be inappropriate for participation in the present study.

Capsule Endoscopy

The baseline and second CEs were performed using an Endo Capsule (Olympus Medical Systems, Tokyo, Japan). After a 12-hour overnight fast, each subject was prepared with sensor arrays and a data recorder, and instructed to swallow the capsule with a small amount of water. When the real-time viewer VE-1 (Olympus Co, Tokyo, Japan) identified the capsule reaching the cecum, we removed the sensor array and data recorder from the subject, and all of the digital video image streams were downloaded to the Olympus WS-1 (Olympus Co).

Two observers (E.W. and Y.M.) who remained blinded to the subjects' group independently assessed the CE images. We defined mucosal injuries as positive CE findings; these injuries were classified as either ulcers or erosions as has been described in our previous study.
A circumscribed mucosal defect with obvious whitish mucous that was estimated to be 3 mm or larger in diameter was defined as an ulcer (Figure 1A). Although it is sometimes difficult to distinguish a small ulcer from an area of erosion, a small mucosal break surrounded by redness was regarded as an erosion (Figure 1B).18 The small intestine was divided equally into the jejunum and the ileum by the small bowel transit time. If the CE findings were discordant between the 2 observers, they discussed the case until a consensus opinion could be obtained.

**Endpoints**

The primary endpoint was the incidence of mucosal injuries at second CE. The secondary endpoints were the incidence of CE findings in the jejunum and in the ileum, the number of ulcers or erosions in subjects with positive CE findings, and the prevalence of GI symptoms and anemia. GI symptoms were assessed at the end of the medication period with use of the Gastrointestinal Symptom Rating Scale.19 Anemia was defined as a decrease in the hemoglobin level of 2.0 g/dL or more from the baseline value.

**Statistical Analysis**

The incidence of small bowel injury caused by administration of celecoxib for 2 weeks has been shown to range from 6% to 16%.13,14 Although the incidence of small bowel injury caused by celecoxib plus rabeprazole is unknown, our previous trial revealed the incidence of small bowel injury caused by 2-week administration of celecoxib and omeprazole was 43%.12 Thus, the sample size of the present study was calculated on the assumption that the incidence of small bowel injury would be 10% in the COX-2 SI group and 43% in the COX-2 SI + PPI group. Thirty subjects per group were required to detect this difference with a .05 significance level and a statistical power of 80%.

The number of mucosal injuries and Gastrointestinal Symptom Rating Scale score were expressed as the median (range); other values were expressed as the mean (standard deviation). The numerical data were compared between the groups using the Mann-Whitney U test, and the categorical data were compared by Fisher exact probability test or the chi-square test. P values of < .05 were considered to be statistically significant in each of the tests.

**Results**

**Subjects**

The study was conducted from October 2012 to September 2013. During the study period, 61 subjects were enrolled. A flow chart of the study subjects is shown in Figure 2. One subject was excluded because he was suspected of having a small bowel tumor at the baseline CE. The remaining 60 subjects were then randomly assigned to the 2 groups. One subject was excluded from the COX-2 SI + PPI group because he took another NSAID without permission during the study period. The second CE enabled total enteroscopy in 59 subjects. However, we were not able to examine CE videos of 2 subjects belonging to the COX-2 SI + PPI group because of technical issues with the Olympus WS-1. Consequently, the COX-2 SI group and COX-2 SI + PPI groups were composed of 30 subjects and 27 subjects, respectively.

Table 1 shows the demographic data of the 2 groups. The prevalence of *H pylori* infection tended to be higher in the COX-2 SI + PPI group than in the COX-2 SI group (5 subjects [18.5%] vs 1 subject [3%], respectively;
Two subjects in COX-2 SI group continued to take concurrent medications, 1 for essential hypertension (losartan potassium, 50 mg/day), the other for chronic pancreatitis (camostat mesilate, 300 mg/day). One subject in the COX-2 SI + PPI group took medication for orthostatic hypotension (amezinium metilsulfate, 20 mg/day).

The Capsule Endoscopy Findings

The 2 observers reported concordant results for each of the subjects with regard to the incidence of positive findings on the second CE. Figure 3 shows the incidence of mucosal injuries in the 2 groups. Eleven subjects in the COX-2 SI + PPI group had erosions. Among them, ulcers were also found in 5 subjects. Another subject in the group had ulcers only. In the COX-2 SI group, 4 subjects had erosions, 2 of whom also had ulcers. Another subject in the group had ulcers only. Consequently, the incidence of small bowel injuries was significantly higher in the COX-2 SI + PPI group than in the COX-2 SI group (44.4% vs 16.7%; \( P = .04 \)). These results indicated the subjects in the COX-2 SI + PPI group were at an increased risk of small bowel injury in comparison with the COX-2 SI group (relative risk, 2.67; 95% confidence interval, 1.08–6.58).

We compared the number of mucosal injuries between the 2 groups. The crude data on the mucosal injuries among the subjects with positive CE findings are shown in Supplementary Table 1. The incidence of mucosal injuries was significantly higher in the COX-2 SI + PPI group than in the COX-2 SI group (0 [0–31] vs 0 [0–7]; \( P = .02 \)). In the comparison of the numbers of each type of mucosal injury, we found the number of erosions was significantly higher in the COX-2 SI + PPI group than that in the COX-2 SI group (0 [0–29] vs 0 [0–3]; \( P = .02 \)). The number of ulcers did not differ to a statistically significant extent (0 [0–3] vs 0 [0–7]; \( P = .19 \)).

We then compared the number of mucosal injuries in each segment of the small bowel between the 2 groups (Figure 4). Jejunal mucosal injuries, all of which were erosions, were found only in the COX-2 SI + PPI group (\( P = .003 \)). There was no difference between the 2 groups in the incidence of mucosal injuries in the ileum (37% vs 17%; \( P = .11 \)); nor was there any difference in the incidence of ulcers (22% and 33%) or erosions (10% and 13%).

### Symptoms, Laboratory Data, and Complications

During the 2-week medication period, 2 subjects in each group experienced diarrhea. Among these 4 subjects, 1 subject in the COX-2 SI group also complained of epigastric pain, and another subject in the COX-2 SI + PPI group reported abdominal pain. Consequently, Gastrointestinal Symptom Rating Scale score of the 2 groups after the medication period did not differ (Table 2). There were no cases of anemia at the end of the medication period.

### Table 1. Demographic Data of COX-2 SI and COX-2 SI + PPI Groups

<table>
<thead>
<tr>
<th></th>
<th>COX-2 SI group</th>
<th>COX-2 SI + PPI group</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>30</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>32 (8.5)</td>
<td>34 (8.3)</td>
<td>.67</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>13/17</td>
<td>10/17</td>
<td>.62</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>59 (9.9)</td>
<td>59 (9.8)</td>
<td>.72</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>1</td>
<td>5</td>
<td>.09</td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>2</td>
<td>1</td>
<td>.61</td>
</tr>
</tbody>
</table>

NOTE. Values are expressed as the mean (standard deviation).
Among various NSAIDs, we chose celecoxib, a COX-2 selective inhibitor, to minimize upper GI toxicity caused by NSAIDs and to refrain from administering antiacid secretory medication to the control subjects. As a consequence, we found small bowel mucosal injuries in 16.7% of the subjects in the COX-2 SI group, which was slightly higher than the rate reported by Goldstein et al (7%). These results seem to imply COX-2-dependent pathway is involved in the maintenance of mucosal integrity and in the development of NSAID-induced small bowel injury. However, because celecoxib possesses COX-1 inhibitory properties at higher doses, it remains uncertain whether the results represent the significance of COX-2 inhibition in the pathogenesis of NSAID-induced small bowel injury.

In the present study, the incidence of small bowel injury in the COX-2 SI + PPI group was as high as 44.4%, which was equivalent to the value in patients taking celecoxib and omeprazole in our previous study.12 Intestinal motility,24 mucous content,25 and indigestive solid food content26 have previously been shown to be affected by antiacid secretory drugs. The alteration of bacterial flora in small intestine by the marked suppression of gastric acid secretion has been also indicated.27–29 Wallace et al15 recently demonstrated a significant reduction of Actinobacteria and Bifidobacteria species in the jejunum in parallel with the exacerbation of NSAID-induced small bowel injury under concomitant use of PPIs. Because PPIs alone cause neither small bowel mucosal damage nor inflammation,15 the alteration of luminal environment by PPIs seems to be an exacerbating factor in NSAID-induced small bowel injuries. The obvious difference in the mucosal injuries of the jejunum in the 2 groups further supports the significance of PPIs in NSAID-induced small bowel injury. The luminal microflora of the proximal small bowel seem to be more profoundly altered by gastric acid suppression than the distal small bowel.

When considering the influence of gastric acid suppression on NSAID-induced small bowel injuries, the types of antiacid secretory drugs need to be taken into account. Satoh et al30 recently demonstrated protective effect of lansoprazole against small bowel injuries in indomethacin-treated rats; such an effect was not found with any other antiacid secretory drugs. However, more recent experiments have demonstrated exacerbating effects of PPIs, including lansoprazole.15,31 Such controversy in the findings regarding the effects of PPIs may be a consequence of differences in the experimental methods, especially with regard to the dosage of antiacid secretory drugs and in the control of microflora. Further investigations should examine the correlation between intraluminal pH and small bowel injuries.

Various guidelines32 recommend concomitant administration of COX-2 selective inhibitors plus PPIs for the prevention of upper GI complications in patients with high GI and low cardiovascular risks. In contrast, results of our present and previous studies12 seem to suggest

### Table 2. Abdominal Symptoms and Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>COX-2 SI group (n = 30)</th>
<th>COX-2 SI + PPI group (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSRS pre</td>
<td>1.2 (1.1–1.4)</td>
<td>1.3 (1.1–1.7)</td>
<td>.43</td>
</tr>
<tr>
<td>GSRS post</td>
<td>1.2 (1.0–1.6)</td>
<td>1.1 (1.0–1.5)</td>
<td>.92</td>
</tr>
<tr>
<td>Hemoglobin level pre, g/dL</td>
<td>14.4 (1.3)</td>
<td>15.0 (1.5)</td>
<td>.19</td>
</tr>
<tr>
<td>Hemoglobin level post, g/dL</td>
<td>14.3 (1.4)</td>
<td>14.7 (1.6)</td>
<td>.60</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
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</table>

NOTE. The GSRS values are expressed as the median (standard deviation). The hemoglobin levels are expressed as the mean (standard deviation). Anemia was defined as positive with a decrease of at least 2.0 g/dL in the hemoglobin level.

GSRS, Gastrointestinal Symptom Rating Scale; pre, before taking celecoxib plus rabeprazole or a placebo; post, after taking celecoxib plus rabeprazole or a placebo.
that the risk of small bowel injury increases with concomitant use of PPIs and COX-2 selective inhibitors. However, our results should be interpreted cautiously, because none of the subjects in the present study showed anemia, whereas there was significant difference in the incidence of mucosal injuries in the 2 groups. Further investigations with clinically significant endpoints seem to be necessary to reach a conclusion regarding the effects of the combined administration of NSAIDs and PPIs on mucosal injuries.

The present study had some limitations. First, it was conducted in a relatively young and healthy population under short-term administration of NSAIDs. Therefore, our results may not be applied to patients who are at increased risk for NSAID-induced GI toxicity. Second, we were unable to take \( H\ pylori \) status, which is known to be associated with GI blood loss in patients taking NSAIDs or COX-2 SI,\(^{33} \) into consideration because there were only 6 \( H\ pylori \)-positive subjects. Third, the small sample size might have contributed to a higher incidence of small bowel injury in our COX-2 SI group. However, because the incidence of small bowel injury in the COX-2 SI + PPI group was equivalent to that in our previous study,\(^{12} \) and because the protocol of the present study was similar to that of Goldstein et al, the incidence of the injury in the COX-2 SI group may be representative of the Asian population. Furthermore, even though the incidence in the COX-2 SI group was high, it was significantly lower than that in the COX-2 SI + PPI group.

In conclusion, our prospective study demonstrated that the incidence of small bowel injury was higher in subjects treated with celecoxib plus rabeprazole than those treated with celecoxib alone. It thus can be suggested PPIs increase the risk of small bowel injury by NSAIDs including COX-2 selective inhibitor, whereas its clinical significance remains to be clarified.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org) and at [http://dx.doi.org/10.1016/j.cgh.2015.10.022](http://dx.doi.org/10.1016/j.cgh.2015.10.022).

**References**

33. Lanas A, Goldstein JL, Chan FK, et al. Risk factors associated with a decrease ≥ 2 g/dL in hemoglobin and/or ≥ 10% hematocrit in osteoarthritis patients taking celecoxib or a nonselective NSAID plus a PPI in a larger randomized controlled trial (CONDOR). Aliment Pharmacol Ther 2012;36:485–492.
## Supplementary Table 1. Crude Numbers of Small Bowel Injuries Among the Subjects With Positive CE Findings

<table>
<thead>
<tr>
<th>Erosion</th>
<th>Ulcer</th>
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<tr>
<td></td>
<td>Jejunum</td>
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<tr>
<td>COX-2 SI group</td>
<td></td>
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<tr>
<td>1</td>
<td>0</td>
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<td>2</td>
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<td>5</td>
<td>0</td>
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<td>COX-2 SI + PPI group</td>
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