Diarrhea Caused by Proton Pump Inhibitor Administration: Comparisons Among Lansoprazole, Rabeprazole, and Omeprazole

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ABSTRACT

Background: The number of patients who require treatment with proton pump inhibitors (PPIs) is increasing in Japan. One of their adverse effects is diarrhea.

Objectives: We investigated the incidence of diarrhea caused by 3 different PPIs: lansoprazole, rabeprazole, and omeprazole.

Methods: Patients using PPIs for >1 month were enrolled. Enrolled patients recorded daily stool frequency, stool consistency using the Bristol Stool Scale Form, and impaired quality of life caused by diarrhea for 1 month. Their attending physicians described the types and dosages, and duration of PPI administration, as well as other necessary information.

Results: A total of 255 patients participated. Mean age of the patients was 70.7 years old. During the 1-month observation period, 3.5% of the patients complained of diarrhea. There was no significant difference for the incidence of diarrhea among the 3 types of PPIs. Furthermore, no correlations between diarrhea and length and dosage of PPI administration were found.

**Key words:** adverse effect, collagenous colitis, diarrhea, loose bowels, proton pump inhibitor.

**INTRODUCTION**

The number of patients who require regular proton pump inhibitor (PPIs) is increasing in Japan, and those with gastroesophageal reflux disease (GERD) or upper gastrointestinal ulcers often use PPIs to suppress gastric acid secretion. The prevalence of GERD is increasing remarkably in Japan, and is reported to be as high as 17.9% of the population.\(^1\)\(^,\)\(^2\) The prevalence of upper gastrointestinal ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin has also been reported to be increasing.\(^3\)\(^,\)\(^4\)

Although PPIs are generally regarded as safe when used for long periods, several adverse effects, including osteoporosis and vitamin B\(_{12}\) deficiency, have been reported with high doses. In addition, diarrhea is known to be 1 such adverse event observed in long-term PPI users.\(^5\)

There are 3 types of PPIs generally used in Japan: lansoprazole, rabeprazole, and omeprazole. Lansoprazole has been reported to be associated with a high risk of developing collagenous colitis with chronic watery diarrhea,\(^6\)\(^,\)\(^7\) although this remains controversial.\(^8\) Although lansoprazole-related collagenous colitis is a rare clinical condition and generally resolves after cessation of lansoprazole administration, diarrhea impairs the quality of life (QOL) of affected patients regardless of the presence of collagenous colitis.\(^9\)\(^,\)\(^10\) Therefore, we investigated whether lansoprazole causes diarrhea more frequently than other PPIs and whether lansoprazole had a greater risk to cause diarrhea in long-term users.

**METHODS**

Patients receiving PPIs at outpatient clinics of 7 medical centers and 3 primary care physicians in the Sanin area of western Japan were prospectively enrolled in this study. We targeted outpatients who were taking a PPI for \(>1\) month and were \(>20\) years old. Patients diagnosed with irritable bowel syndrome, taking medication for constipation, and taking a PPI on an on-demand basis were excluded. The protocol of this study was evaluated and approved by the ethical committee of Shimane University School of Medicine, and informed consent was obtained from all enrolled patients.

Enrolled patients were instructed to keep a daily record concerning occurrences of diarrhea and loose bowels for 1 month, in which they described the frequency of defecation, stool form according to the Bristol Stool Scale Form, and diarrhea-related QOL impairment. We categorized QOL impairment as 5 grades: grade 1, not embarrassed; grade 2, slightly embarrassed; grade 3, somewhat embarrassed (able to perform usual daily tasks); grade 4, very embarrassed (unable to perform usual daily tasks); grade 5, embarrassed to the point that it was not possible to endure (often in the restroom). Their attending physicians described the type and dosage of the prescribed PPI, duration of administration, underlying disease that required a PPI,
and coadministered drugs. Diarrhea was defined as the state in which the patient had soft stools (grade 6 or 7 according to Bristol Stool Scale Form) at least 3 times a day for ≥8 days during the 1-month observation period, as well as no hard stools (grade 1 or 2) during that period. Loose bowels were defined as the state in which the patient had soft stools (grade 6 or 7) >4 times within the 1-month observation period and no hard stools (grade 1 or 2).

We observed the course of bowel movements in patients diagnosed with diarrhea. When diarrheal symptoms spontaneously improved, we considered that the diarrhea was likely not caused by microscopic colitis or other particular bacterial pathogens. When the symptoms persisted, general antidiarrheal medication was prescribed for a set period of time. If that was not effective, we performed colonoscopy and pathological examinations to investigate the cause of the chronic diarrhea.

Comparisons among the 3 different PPIs were performed using a $\chi^2$ test. The correlation between the frequency of Bristol Stool Scale Form grade 6 or 7 soft stools and length of PPI administration was examined using regression analysis. The difference in frequency of Bristol Stool Scale Form grade 6 or 7 soft stools between low- and high-dose PPI users was examined using a Mann-Whitney U Test. A $P$ value <0.05 was considered statistically significant.

**RESULTS**

Two hundred seventy-nine patients receiving long-term PPI administration were enrolled in this study, of whom 264 reported their bowel habits by keeping daily records for 1 month. From those, we excluded 9 patients because of insufficient descriptions; thus, a total of 255 patients were analyzed in this study. The mean age of the enrolled patients was 70.7 years old. Patients with diarrhea and loose bowels during the study period comprised 3.5% and 7.1%, respectively, of the total cohort. Of all the patients with diarrhea, 1 patient who took low-dose omeprazole reported significant QOL impairment (grade 5), whereas 3 (1 taking high-dose omeprazole, and 2 taking low-dose omeprazole) reported impairment that varied between grades 4 and 5.

All the patients, except 3 who had diarrhea during the 1-month observation period, were followed and confirmed to recover from the diarrhea spontaneously soon after the observation period without any specific treatment and with continuous administration of the same PPIs. Therefore, in these cases, neither colonoscopy nor stool culture was performed. In 2 of the remaining 3 patients, colonoscopy and histopathological examination did not show any sign of microscopic colitis. In 1 of these 2 patients, bacterial culture of stool specimens was done, but did not show the growth of any specific pathogenetic bacteria. Diarrhea of these cases also spontaneously resolved during the continuous PPI administration. The remaining 1 patient who did not undergo colonoscopy had diarrhea continuously before the start of PPI administration. The frequency and intensity of the diarrhea did not change after the start of PPI administration in this case. Thus, all the diarrhea reported in the observation period was not caused by microscopic colitis or by any specific pathogenetic bacterial infection.
We divided the 255 patients into 3 groups based on the type of PPI administered (lansoprazole, n = 75; rabeprazole, n = 96; omeprazole, n = 84) (Table I). Although there was a small but significant difference for the duration of PPI treatment among the 3 groups, there were no significant differences for the other clinical characteristics. We also compared the numbers of patients with diarrhea and loose bowels during the 1-month observation period among the 3 groups. Patients who had diarrhea comprised 4.0%, 1.0%, and 6.0% of those in the lansoprazole, rabeprazole, and omeprazole groups, respectively (Figure 1), whereas those with loose bowels comprised 8.0%, 4.2%, and 10.1%, respectively (Figure 2). The differences for diarrhea and loose bowels were not significant among the groups, although the rabeprazole-treated group tended to have lower values.

When the percentage of days with grade 6 or 7 soft stools (Bristol Stool Scale Form) during the study period was plotted against the length of PPI administration and dose in each patient, there were no correlations found (Figures 3 and 4).

We also retrospectively investigated how many patients in each PPI-treated group had a change in type of PPI administered before the study period because of diarrhea possibly related to the drug. Only 2 of the 255 patients changed the type of PPI, 1 of whom changed from rabeprazole to lansoprazole and the other from lansoprazole to omeprazole because of diarrhea possibly caused by the PPI. None of the patients discontinued PPI use because of diarrhea during the study period.

Table I. Clinical characteristics of patients taking proton pump inhibitors (PPIs).

<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole</th>
<th>Rabeprazole</th>
<th>Omeprazole</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>75</td>
<td>96</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Dosage of PPI (half-dose: full-dose)</td>
<td>44:31</td>
<td>87:9</td>
<td>33:51</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>40:35</td>
<td>50:46</td>
<td>43:41</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y (min, max)</td>
<td>70.87 (31, 92)</td>
<td>70.58 (36, 87)</td>
<td>70.61 (39, 89)</td>
<td>NS</td>
</tr>
<tr>
<td>Period of PPI administration, mo (min, max)</td>
<td>33.09 (1.180)</td>
<td>29.82 (1.132)</td>
<td>22.89 (1.66)</td>
<td>0.03</td>
</tr>
<tr>
<td>Basal diseases requiring PPI administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflex esophagitis</td>
<td>58</td>
<td>76</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Gastroduodenal disease</td>
<td>13</td>
<td>17</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other co-administered drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Others</td>
<td>57</td>
<td>72</td>
<td>58</td>
<td></td>
</tr>
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</table>

NSAIDs = nonsteroidal anti-inflammatory drugs.
DISCUSSION

We examined and compared the incidence of diarrhea in 255 long-term PPI users in Japan. The rate of occurrence of diarrhea in all patients was 3.5%. Diarrhea is not a rare symptom and frequently reported by a variety of patients, regardless of drug use. One study noted that 2.1% of hospital inpatients reported diarrhea during their hospital stay, and that 1.5% of the causes of admission was diarrhea. Fur-

Figure 1. Percentage of enrolled patients with diarrhea during the 1-month observation period in 3 groups treated with different proton pump inhibitors. There were no statistically significant differences among the lansoprazole, rabeprazole, and omeprazole groups, although the incidence was slightly lower in the rabeprazole group.

Figure 2. Percentage of enrolled patients who had loose bowels during the 1-month observation period in 3 groups treated with different proton pump inhibitors. There were no statistically significant differences among the lansoprazole, rabeprazole, and omeprazole groups, although the incidence was slightly lower in the rabeprazole group.
thermore, the prevalence of diarrhea-predominant irritable bowel syndrome in a clinic population was reported to be as high as 31%, whereas antibiotics were reported to cause diarrhea in up to 25% of patients in another study. In comparison with those reports, the occurrence of diarrhea in our PPI-administered patients was low, indicating the safety of the drugs. The occurrence rate of diarrhea observed in this study was similar to that reported by Reilly for PPI users, and confirmed the generally weak correlation between PPI administration and diarrhea.

It was reasonable that patients taking higher doses of a drug for longer periods should have a greater chance to experience an adverse effect. Because the diarrhea observed in the study patients was neither dosage nor time dependent, the diarrhea observed in the patients receiving PPIs might not be a toxic adverse reaction to the drug.

We compared the incidence of diarrhea and loose bowels among patients receiving 3 different kinds of PPIs, and found no significant differences. None of the present cohort had collagenous colitis. Therefore, our results did not support our speculation that lansoprazole caused diarrhea more frequently than other PPIs partly because of induction of collagenous colitis. A number of investigators reported that lansoprazole caused microscopic colitis, including collagenous colitis, although contrasting evidence was also presented. Because nearly all reports of PPI-related microscopic colitis were case series or case–control studies, a prospective randomized study is necessary to determine whether lansoprazole is associated with a higher risk of microscopic colitis.
In addition to collagenous colitis, PPI administration might cause diarrhea via several different mechanisms, including easier colonization of enteropathogenic bacteria, inadequate protein digestion in the stomach, and a possible influence on H, K-ATPase in the colonic mucosa. In the absence of gastric acid, several kinds of bacteria, including *Clostridium difficile*, Salmonella, and Campylobacter species, were reported to easily colonize in the gut, causing enterocolitis accompanied by diarrhea or loose bowels.\(^{19,20}\) Therefore, inhibition of gastric acid secretion by PPI administration may cause diarrhea. Takahashi et al\(^{21}\) reported the presence of nongastric H, K-ATPase in the human colon and suggested a role for this pump in regulation of colonic fluid secretion. Thus, in addition to collagenous colitis, any type of PPI may cause diarrhea as an adverse effect, although the risk might not be high and not clinically relevant.

Freston et al\(^{22,23}\) reported a similar incidence of diarrhea between lansoprazole, omeprazole, and placebo treated groups in clinical studies, and also reported that most of the diarrhea observed resolved spontaneously while patients continued PPIs. In addition, a recently reported cohort study, comparing PPI and antireflux surgery as a long-term treatment of GERD, showed a similar incidence of diarrhea between the 2 treatment strategies.\(^{24}\) Therefore, PPI-related diarrhea might not be a critical adverse effect that significantly decreases the therapeutic value of PPI.

This prospective observational study had some possible limitations, including its open-label design and the small size of the cohort. Chande et al\(^{25}\) reported only 14 cases of lansoprazole-induced microscopic colitis in a PubMed literature review from 1980 to August 2006. From the expected incidence of microscopic colitis in patients.
treated with PPIs, the size of our study was too small to make any conclusions regarding relative incidence of microscopic colitis with the different PPIs. Future larger studies are necessary to clarify the risk of diarrhea associated with administration of different PPIs.

**CONCLUSIONS**

Our findings indicated that the incidence of diarrhea related to PPI use in Japan was <5%. Furthermore, there was no difference in diarrhea occurrence among the 3 different PPIs examined.

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**CONFLICTS OF INTEREST**

Dr. Kinoshita served as a consultant for Eisai Co, Ltd, AstraZeneca Pharmaceuticals, and Takeda Pharmaceutical Company Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

**REFERENCES**


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