European Journal of Clinical Pharmacy
Print ISSN: 2385-409X, **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Proton pump inhibitors promote lubiprostone-induced nausea in cancer patients: A Retrospective Study

Article History:

Name of Author:
Haruka Kurata[1,2], Rei Tanaka[1,3], Kyoko Mori[1], Yoshiko Kamo[1], Junya Sato[3], Hiroshi Ishikawa[1]

Affiliation: *[1] Department of Pharmacy, Shizuoka Cancer Center, Shizuoka, Japan [2] Department of Pharmacy, Fuji City General Hospital, Shizuoka, Japan [3] Faculty of Pharmaceutical Sciences, Shonan University of medical sciences, Kanagawa, Japan*

Corresponding Author:
Dr. Haruka Kurata
Email: h.kurata01133@gmail.com

Received: 24-02-2026
Revised: 06-03-2026
Accepted: 20-03-2026
Published: 15-04-2026

Abstract: Background: Lubiprostone is a medication that activates chloride channel 2 to relieve chronic idiopathic constipation. The most common side effect associated with lubiprostone is nausea. In this study, we investigated risk factors for lubiprostone-induced nausea in patients with cancer. **Methods:** A total of 79 patients who began inpatient treatment with lubiprostone between November 2017 and August 2022 at Shizuoka Cancer Center were included. Patients were observed for five days following the initiation of lubiprostone. The incidence of nausea and background factors (e.g., age, sex, and concomitant medications) were retrospectively investigated using electronic medical records. Multivariate logistic regression analysis was performed, with the significance level set at 5%. **Results:** The incidence of nausea was 35% (28/79). The incidence tended to be higher with concomitant use of proton pump inhibitors (odds ratio: 2.9, 95% confidence interval: 0.97–8.7, p = 0.057).**Conclusion:** Proton pump inhibitors (PPIs) may be a risk factor for nausea associated with lubiprostone. Prophylactic use of antiemetic agents should be considered, and clinicians should monitor for nausea when lubiprostone is administered with PPIs. Future studies involving larger sample sizes are needed to identify risk factors for lubiprostone-associated nausea.

Keywords: lubiprostone; nausea; prostaglandinergic nausea; proton pump inhibitor; intragastric pH; structural transformation

INTRODUCTION

Chronic idiopathic constipation (CIC) is a frequently encountered problem in cancer patients, occurring in 23–65% of those receiving palliative care [1]. Constipation is caused by various factors; in particular, chemotherapy and opioid use in cancer patients often lead to difficulty in controlling bowel movements.

Lubiprostone is an effective treatment for chronic constipation and acts through a mechanism distinct from that of conventional osmotic or stimulant laxatives. It activates chloride channel 2 in the epithelial membrane of the small intestine, causing chloride ions Cl to flow into the intestinal lumen and sodium ions to be drawn into the intestinal tract to maintain electrical neutrality. This process promotes

defecation by stimulating intestinal water secretion, softening stools, and enhancing transport function in the intestinal tract. Although lubiprostone is effective for managing chronic constipation, the incidence of nausea is higher than that associated with other constipation treatments. In Japan, the incidence of nausea with lubiprostone has been reported to be 14.5 % [2]. Although the precise mechanism underlying lubiprostone-induced nausea remains unclear, it has been suggested that delayed gastric emptying, secondary small intestinal dilation due to increased intestinal fluid secretion [3], and altered gastrointestinal sensation [4] may be involved. Lubiprostone-induced changes in gastrointestinal motility—specifically, increased basal pyloric sphincter tone—have been reported to delay gastric emptying and cause nausea in the form of pyloric spasm [4]. In addition, inhibition of defecation [5] has also been reported to induce nausea, suggesting that nausea tends to occur in patients with defecation disorders. Furthermore, based on previous reports, the occurrence of nausea induced by lubiprostone is dose-dependent [6].

The efficacy of lubiprostone in patients with chronic constipation has been demonstrated by improvements in the weekly frequency of spontaneous bowel movements [2]. Regarding the safety of lubiprostone, the occurrence of nausea following diarrhea is common. The incidence of treatment discontinuation due to nausea after starting lubiprostone has been reported to be 8.7%, 2.1%, and 1.3% in patients with CIC, opioid-induced constipation, and constipation-predominant irritable bowel syndrome, respectively [5].

Nausea is a factor that can make the continuation of treatment difficult in some cases. However, limited data are available regarding the efficacy and safety of lubiprostone in cancer patients. A study by Sada et al. demonstrated that the effectiveness of lubiprostone in cancer patients was comparable to that in non-cancer patients.[7] However, the incidence of diarrhea and nausea was higher among cancer patients, and the treatment discontinuation rate due to adverse events was significantly elevated [7]

Previous studies have identified certain risk factors for lubiprostone-induced nausea, such as female sex [5, 8, 9] and younger age (<65 years) [5].However, risk factors for nausea in cancer patients remain unclear. Therefore, this study aimed to investigate the incidence of lubiprostone-induced nausea in cancer patients and explore potential risk factors.

Methods

Study participants

This study included patients from Shizuoka Cancer Center who began inpatient treatment with lubiprostone between November 2017 and August 2022. Patients with severe constipation, subileus, or organic constipation were excluded. In addition, patients who were discharged during the observation period (33 patients) or whose treatment was discontinued (26 patients) were excluded. A total of 79 patients were analyzed.

Investigation items

The observation period was set to five days from the initiation of lubiprostone treatment. This period was selected based on the frequent occurrence of nausea and vomiting, as well as treatment interruption, during the first five days of therapy [5]. The primary endpoint was defined as the incidence of nausea. Nausea was assessed using the Common Terminology Criteria for Adverse Events version 5.0, with Grade 1 or higher nausea as the evaluation threshold. Background factors, including age, sex, and cancer type, were examined. Treatment-related factors—such as dosage, concomitant medications (opioids, antiemetics, PPIs or histamine H_2-receptor antagonists, magnesium oxide, naldemedine, stimulant laxatives, anti-cancer drugs with emetogenic risk, and radiation therapy)—were also analyzed. The emetogenic risk of chemotherapy and the risk of radiation-induced nausea were classified according to cancer treatment guidelines [10-12].

Statistical analyses

Univariate logistic regression analysis was performed on background factors (age, sex) and treatment-related factors (dosage, concomitant medications, anti-cancer drugs, and radiation therapy). Multivariate logistic regression analysis was performed by selecting variables such as PPIs, naldemedine, and anti-cancer drugs, based on clinical relevance and statistical criteria ($p < 0.1$). Statistical analyses were performed using Microsoft Excel software, and the significance level was set at 5%.

Ethical considerations

This study was conducted in accordance with the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects and was approved by the Ethics Committee of Shizuoka Cancer Center (approval number: J2022-142-2022-1-3).

Results

Nausea Incidence and Patient Background

Of the 138 patients considered for inclusion, 33 were discharged during the observation period and 26 discontinued treatment. A total of 79 patients were included in the final analysis. The incidence of nausea was 35% (28/79). Table 1 presents the background characteristics of the patients.

Table 1. Patient Characteristics (N=79)

Characteristic	n	%
Age Median (min–max)	68 (21–88)	
Age <65 years	33	42
Female	30	38
Oral intake	74	94
Chronic constipation	49	62
Opioid-induced constipation	30	38
Constipation-predominant IBS	0	-
Hematological malignancy	22	28
Lung cancer	20	25
Gastrointestinal cancer	11	14
Brain cancer	8	10
Head and neck cancer	7	8.9
Hepato-biliary-pancreatic cancer	6	7.6
Others	5	6.3
Lubiprostone ≥48 μg/day	67	85
Lubiprostone 24 μg once daily	12	15
Opioid	30	38
Antiemetics	15	19
PPI	50	63
H_2 RA	7	8.9
Magnesium oxide	62	79
Naldemedine	14	18
Stimulant laxative	40	51
Anticancer drugs	43	54
High emetogenic risk	16	20
Moderate emetogenic risk	16	20
Low emetogenic risk	7	8.9
Minimal emetogenic risk	4	5.1
Radiation therapy	18	23
Whole body (High risk)	0	-
Abdomen/Whole brain (Moderate)	4	5.0
Brain/Head/Chest/Pelvis (Low)	13	17
Limbs (Minimal)	1	1.3

Severe constipation, sub-ileus, or organic constipation are excluded. Antiemetics are included Prochlorperazine maleate, metoclopramide, domperidone. PPI=Proton pump inhibitors; H_2RA=histamine H_2 receptor antagonist

Logistic regression analysis of nausea occurrence and non-occurrence groups

Univariate logistic regression analysis showed a positive association between nausea and the use of antiemetics, PPIs, naldemedine, and anti-cancer drugs (Table 2). In multivariate logistic regression analysis, concomitant use of PPIs was associated with a higher incidence of nausea (odds ratio: 2.9, 95% confidence interval: 0.97–8.7, p = 0.057) (Table 3).

Table 2. Univariate Logistic Regression Analysis of Factors Associated with Nausea (N=79)

Factor	Nausea Present (n=28)	Nausea Absent (n=51)	OR	95% CI	*P*-value
Age <65	15 (53.6%)	18 (35.3%)	2.12	0.83–5.41	0.118
Female	12 (42.9%)	18 (35.3%)	1.38	0.54–3.53	0.508
Oral intake	23 (82.1%)	51 (100%)	-	-	-
Dose ≥48 μg/day	24 (85.7%)	43 (84.3%)	1.12	0.30–4.10	0.868
Opioid use	8 (28.6%)	22 (43.1%)	0.53	0.20–1.42	0.205
Antiemetics	10 (35.7%)	5 (9.8%)	5.10	1.53–17.0	0.008*
PPI	22 (78.6%)	28 (54.9%)	3.01	1.05–8.67	0.041*
H_2RA	2 (7.1%)	5 (9.8%)	0.71	0.13–3.91	0.692
Magnesium oxide	23 (82.1%)	39 (76.5%)	1.42	0.44–4.53	0.558
Naldemedine	2 (7.1%)	12 (23.5%)	0.25	0.05–1.21	0.085
Stimulant laxatives	17 (60.7%)	23 (45.1%)	1.88	0.74–4.81	0.187

Anticancer drugs	20 (71.4%)	23 (45.1%)	3.04	1.13–8.18	0.027*
High emetogenic chemo	8 (28.6%)	8 (15.7%)	2.15	0.71–6.55	0.178
Moderate emetogenic chemo	6 (21.4%)	10 (19.6%)	1.12	0.36–3.49	0.847
Low emetogenic chemo	3 (10.7%)	4 (7.8%)	1.41	0.30–6.80	0.669
Minimal emetogenic chemo	3 (10.7%)	1 (1.96%)	6.00	0.59–60.7	0.129
Radiation therapy	8 (28.6%)	8 (15.7%)	2.15	0.71–6.55	0.178

Statistically significant at $p < 0.05$. OR = odds ratio; 95% CI=95% Confidence interval; PPI = proton pump inhibitor; H_2RA = histamine H_2-receptor antagonist.

Table 3. Multivariate Logistic Regression Analysis of Factors Associated with Nausea

Factor	OR	95% CI	*P*-value
PPI	2.9	0.97–8.7	0.057
Naldemedine	0.41	0.08–2.2	0.290
Anticancer drugs	2.6	0.91–7.5	0.074

PPI=proton pump inhibitor; OR=Odds ratio; 95% CI=95% Confidence interval

DISCUSSION

In this study, the incidence of nausea in patients receiving lubiprostone along with PPIs was as high as 79%, compared to 24% in those not receiving PPIs. This trend was also confirmed by logistic regression analysis. The high incidence of nausea associated with concomitant PPI use should be acknowledged in clinical practice. Although this finding suggests a clinically significant emetogenic effect of lubiprostone in patients receiving PPIs, it has not been widely recognized.

While previous reports have suggested that female sex [5, 8, 9], and younger age (under 65 years) [5] are risk factors for lubiprostone-induced nausea, this study is the first to identify an association between PPI use and nausea. We hypothesize that the following mechanisms may underlie the PPI-related effect: structural changes in lubiprostone, a prostaglandin E1 analog, and its agonistic activity at prostaglandin receptors (EP1, EP2, EP3, and FP). Although the prostaglandin activity of lubiprostone has been reported to be limited in smooth muscle tissues expressing these receptors [13], Walter W. Chan et al. reported that lubiprostone increased contraction of the mouse pyloric sphincter in a dose-dependent manner. Furthermore, they noted that EP1 receptors may be present in pyloric tissues and that lubiprostone may induce pyloric sphincter contraction via the EP1-mediated pathway.

It has also been reported that lubiprostone exists as monocyclic (prostaglandin-like structure) and bicyclic (prostaglandin-dissimilar structure) ring–chain tautomers [14]. Prostaglandinergic activity is thought to be exerted by the monocyclic form; however, the extent to which the equilibrium shifts toward the monocyclic form with changes in intragastric pH remains unclear. Nevertheless, because similar ring–chain tautomeric compounds have shown pH-dependent equilibrium shifts [15], it is possible that prostaglandinergic activity is enhanced by PPI-induced alterations in intragastric pH. Further basic research is needed to verify these hypotheses by examining structural and pharmacological correlations.

The involvement of sex hormones may partially explain why female sex and younger age have been identified as risk factors for lubiprostone-induced nausea in previous studies. Premenopausal women are affected by hormonal changes related to menstruation. Prostaglandins, which increase in the early phase of menstruation, may irritate smooth muscle and cause gastrointestinal disturbances [16], potentially contributing to nausea. The monocyclic form of lubiprostone may amplify prostaglandinergic activity in gastrointestinal tissues and thereby induce nausea. Although there was a tendency for higher nausea incidence in younger and female patients, no significant difference was observed in this study. The reason for this discrepancy is unknown but may be attributed to differences in patient backgrounds, as the previous study was conducted in non-cancer patients with chronic constipation.

Histamine H_2-receptor antagonists (H_2RAs), which are gastric acid secretion inhibitors like PPIs, did not significantly increase the incidence of nausea. This may be due to differences in acid-suppressing potency between PPIs and H_2RAs. A previous study reported that PPIs significantly increased intragastric pH compared to H_2RAs, and the duration of intragastric pH ≥ 3 was significantly longer with PPIs than with H_2RAs [17]. The elevation in intragastric pH caused

by PPIs may promote the conversion of lubiprostone to its monocyclic form, which may contribute to nausea. Furthermore, in this study, no chemotherapy regimens included H_2RAs as part of the premedication.

This study has several limitations. It employed a retrospective design and relied on the accuracy and completeness of medical records. It was also conducted at a single institution with a relatively small patient sample. In addition, although the emetogenic risk of anticancer agents was classified, individual risk factors for chemotherapy-induced nausea and vomiting were not assessed. It should also be noted that PPI users often have conditions such as gastric ulcers, duodenal ulcers, or reflux esophagitis, or are at high risk for these diseases. As the incidence of nausea in patients with peptic ulcer disease has been reported to be 13.6% [18], nausea in this population may reflect underlying disease in addition to the effects of lubiprostone .

CONCLUSION

Despite some limitations, our findings suggest that PPI use may be a risk factor for lubiprostone-induced nausea—an observation that represents a novel contribution to the field.
Lubiprostone has been reported to cause pyloric constriction and delayed gastric emptying. It may induce nausea by increasing gastric volume and promoting gastric distention. To prevent treatment discontinuation due to lubiprostone-induced nausea, several management strategies may be considered, including the concomitant use of prokinetic agents such as domperidone or metoclopramide, dose reduction of lubiprostone, or switching to alternative constipation treatments such as linaclotide (an epithelial modifier) or elobixibat (a bile acid transporter inhibitor). Changing from a PPI to another therapy may also be appropriate. For patients who can discontinue PPI therapy, substituting a gastric mucosal protective agent such as rebamipide may be a clinically suitable alternative. Future studies involving larger populations and rigorous methodological design are needed to further validate these findings.

Data Availability
The dataset supporting the conclusions of this article is included within the article.

BIBLIOGRAPHY

1. Larkin PJ, Sykes N, Centeno C, Ellershaw J, Elsner F, Eugene B, et al. The management of constipation in palliative care: Clinical practice recommendations. Palliat Med. 2008;22:796–807. https://doi.org/10.1177/0269216308096908
2. Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R. Lubiprostone increase spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol. 2015;13:294–301.e5. https://doi.org/10.1016/j.cgh.2014.08.026
3. Camilleri M, Bharucha AE, Ueno R, Burton D, Thomforde G, Baxter K, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. Am J Physiol Gastrointest Liver Physiol. 2006;290:G942-7. doi:10.1152/ajpgi.00264.2005.
4. Chan WW, Mashimo H. Lubiprostone increases small intestinal smooth muscle contractions through a prostaglandin E Receptor 1 (EP1)-mediated pathway. J Neurogastroenterol Motil. 2013;19:312–8. https://doi.org/10.5056/jnm.2013.19.3.312
5. Cryer B, Drossman DA, Chey WD, Webster L, Habibi S, Wang M. Analysis of nausea in clinical studies of lubiprostone for the treatment of constipation disorders. Dig Dis Sci. 2017;62:3568–78. https://doi.org/10.1007/s10620-017-4680-1
6. Rivkin A, Chagan L. Lubiprostone: Chloride channel activator for chronic constipation. Clin Ther. 2006;28:2008–21. https://doi.org/10.1016/j.clinthera.2006.12.013
7. Sada H, Kajizono M, Ushio S, Esumi S, Kitamura Y, Sendo T. The efficacy and safety of lubiprostone for constipation in cancer patients compared with non－cancer patients : A retrospective cohort study. Biol Pharm Bull. 2020;43:1699–706. https://doi.org/10.1248/bpb.b20-00398
8. Eguchi T, Yoshizaki T, Takagi M, Ikeoka S, Hashimura H, Okamoto N, et al. Risk factors for adverse events in patients with chronic constipation following lubiprostone administration. Dig Dis. 2021;39:10–5. https://doi.org/10.1159/000508864
9. Yamamoto T, Osumi S, Yanagisawa D, Yamato H, Aoyagi H, Isono A, et al. Possible effect of concomitant prokinetics and herbal medicines against nausea in patients taking lubiprostone. BioMed Res Int. 2017;Article ID3762179:. https://doi.org/10.1155/2017/3762179
10. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, et al. Antiemetics: ASCO guideline update. J Clin Oncol. 2020;38:2782–97. https://doi.org/10.1200/JCO.20.01296
11. Herrstedt J, Clark-Snow R, Ruhlmann CH, Molassiotis A, Olver I, Rapoport BL, et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting Published online January 11, 2024. ESMO Open. 2024;9.

https://doi.org/10.1016/j.esmoop.2023.102195
12. Japanese Society of Clinical Oncology. JSCO guideline for antiemetic therapy. 3rd ed. Tokyo: JSCO; 2023. Available from: http://www.jsco-cpg.jp/antiemetic-therapy/. Accessed 20 Sep 2025.
13. Viatoris Pharmaceuticals, Inc. Amitiza® capsules interview form. 14th ed. Revised. 2024.
14. Google Patents. Process for the preparation of lubiprostone. Available from: https://patents.google.com/patent/US8846958B2/. Accessed 20 Sep 2025.
15. Guasch L, Sitzmann M, Nicklaus MC. Enumeration of ring-chain tautomers based on SMIRKS rules. J Chem Inf Model. 2014;54:2423–32. https://doi.org/10.1021/ci500363p
16. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: A critical review. Hum Reprod Update. 2015;21:762–78. https://doi.org/10.1093/humupd/dmv039
17. Takeyama Y, Matsui T, Yao T, Motomura A, Arita M, Okada M, et al. Comparison of the therapeutic effects and acid suppression of H2-receptor antagonist and proton pump inhibitor in patients with gastric body ulcer—a prospective controlled trials—. Nihon shokakibyo Gakkai zasshi. 1999;96:502–10.
18. Aro P, Storskrubb T, Ronkainen J, Bolling-Sternevald E, Engstrand L, Vieth M, et al. Peptic ulcer disease in a general adult population: the Kalixanda study: a random population-based study. Am J Epidemiol. 2006;163:1025–34. doi:10.1093/aje/kwj129

Acknowledgements
We would like to thank Editage (www.editage.com) for the English language editing.

Funding
This study received no funding

Author information
Authors and Affiliations
Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka
Kyoko Mori, Yoshiko Kamo, Ishikawa Hiroshi
Department of Pharmacy, Fuji City General Hospital, 50 Takashimacho, Fuji City, Shizuoka

Haruka Kurata
Faculty of Pharmaceutical Sciences, Shonan University of medical sciences, 16-48 Kamishinano, Totsuka-ku, Yokohama, Kanagawa, Japan
Rei Tanaka, Junya Sato

Contributions
RT conceptualized and designed the study. KM and YK helped with a procedure to carry out acquisition of the patient data. HK collected the data and wrote the manuscript. JS and RT revised and wrote the manuscript. RT contributed to the discussion on basic pharmacology. JS and RT contributed to the discussion on clinical pharmacology. All authors read and approved the final manuscript.

Corresponding author
Correspondence to Haruka Kurata

Declarations
Ethics approval and consent to participate
This study was conducted in accordance with the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects and was approved by the Ethics Committee of Shizuoka Cancer Center (approval number: J2022-142-2022-1-3). Information about study inclusion was posted on the hospital's bulletin, and consent was obtained via the opt-out method.
Consent for publication
Not applicable.
Competing interests
The authors declare that they have no competing interests.