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EDITORIAL

Analysis of Nausea in Clinical Studies of Lubiprostone for the Treatment of Constipation Disorders

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Nausea is an unpleasant sensation typically experienced in the epigastrium or throat, often accompanied by the impending urge to vomit [1]. While the neural pathways involved with nausea and emesis are generally well defined, the specific pathways involved in the nausea mechanism are not fully elucidated. Within the gastrointestinal tract, mechanical obstruction, organic disorders such as peptic ulcer disease or malignancy, and neuromuscular dysfunction such as chronic intestinal pseudo-obstruction and gastroparesis may all lead to nausea. Medications, chemotherapy, and ingested noxious agents also contribute to the pathogenesis of nausea, mainly through recognition of circulating emetic agents in the blood by central chemoreceptors [2]. Nausea is an oft-cited adverse effect of medications that often prompts therapy discontinuation.

With a prevalence as high as 18% for all subtypes of constipation, understanding the adverse effect profile of medications used to treat constipation is essential [3]. Since 2002, seven new medications have been approved by the US Food and Drug Administration (FDA) indicated for either chronic idiopathic constipation (CIC), irritable bowel syndrome with constipation (IBS-C), or opiate-induced constipation (OIC). Since constipation affects a broad age demographic, a single agent is not always effective in every circumstance or for all etiologies; it also may not be tolerated due to adverse effects.

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Nausea, the most common adverse effect of the prostaglandin analog lubiprostone, can limit patient compliance. Although lubiprostone's principal pharmacologic action is the increase in intestinal ion and fluid transport through the activation of enterocyte ClC type 2 chloride channels, how this mechanism bears on nausea is unknown. Recently, lubiprostone was reported to affect gastrointestinal motility by increasing circular muscle contraction in mouse models [4], possibly explaining the observation that lubiprostone delays gastric emptying and increases gastric volume by inducing pyloric contraction, potentially producing nausea through gastric distension. Another potential pathway leading to nausea is through activation of chemoreceptors from absorbed metabolites. Lubiprostone exerts a local effect at the enterocyte surface where it is almost completely metabolized. Nevertheless, its M3 metabolite appears in low concentrations in the serum, possibly activating central nausea pathways [5].

In this issue of *Digestive Diseases and Sciences*, Cryer et al. [6] highlight the safety and efficacy of lubiprostone through a careful review of randomized controlled trials (RCT) and open-label studies by evaluating the drug in CIC, in IBS-C, and in OIC. Their study provides a comprehensive overview of expected adverse effects in a healthy outpatient population lacking significant medical comorbidities or malignancy. The authors conclude that lubiprostone is generally well tolerated with overall high compliance due to improvement in constipation symptoms with relatively mild and self-limited nausea (typically one episode that does not recur with long-term use). Importantly, there were relatively few cases of severe nausea leading to medication discontinuation.

The available classes of medications used to treat constipation are generally well tolerated; their mild-moderate adverse effects are often tolerated by patients over the

alternative of being constipated. Lubiprostone treatment is associated with the most nausea compared to other medications classes for any indication of constipation (CIC, OIC, IBS-C). RCTs of the guanylate cyclase (GC) activator linaclotide in subjects with IBS-C did not report nausea as an adverse event [7, 8]. In a recent meta-analysis of OIC treatment, the relative risk of μ-opioid receptor antagonists causing nausea in 11 RCTs was 1.07 compared to placebo [9]. Nausea is not dose-dependent and typically does not lead to discontinuation of the medication [10]. Use of the 5-hyroxytryptamine $(HT)_4$ receptor agonist prucalopride for OIC is also not associated with a higher rate of nausea compared to placebo with a relative risk of 1.98 in CIC [11, 12]. In the same meta-analysis, the authors reported a relative risk of nausea of 7.27 in the lubiprostone studies [11].

In addition to its adverse effect of nausea, the applicability of the study population to the average patient may be limited. This study does not address whether lubiprostone is effective and well tolerated in medically complex patients as the study design excluded patients with any significant co-morbid medical conditions, specifically in the diabetic population. The effect of lubiprostone in such populations was recently reported in a study by Christie et al. [13] that addressed lubiprostone use in a diabetic population with CIC. The authors reported that lubiprostone improved complete spontaneous bowel movement (CSBM) without increasing nausea compared to placebo as assessed using wireless motility capsule and colon transit time, coupled with quality-of-life questionnaires. The relative lack of increased nausea in the diabetic patients using lubiprostone in Christie et al.'s study relative to placebo sharply contrasts with the data from the Cryer study.

Does this suggest a salutatory effect of lubiprostone in diabetics relative to controls? Perhaps as emerging data show improvement of other conditions associated with dysmotility, Sarosiek et al. recently demonstrated improvement in small intestinal bacterial overgrowth (SIBO) with the use of lubiprostone in CIC patients, potentially because of the increased foregut fluid secretion and subsequent hypothetical cleansing effect of lubiprostone in the small intestine [14, 15]. Cryer et al. did not exclude patients with SIBO from the study cohort; the clinical manifestations of SIBO, namely abdominal bloating and distension, may be confused or overlap with nausea and act as a potential confounding variable.

By extension, considering the selected IBS-C cohort studied by Cryer et al., patients receiving lubiprostone experienced more nausea compared to placebo, suggesting that the drug can exacerbate discomfort in non-diabetic, non-SIBO patients with IBS-C.

In general, control for the factors affecting bowel transit time and even establishing the diagnosis of constipation can be tedious. In the current study, enrollment criteria relied on daily diaries of frequency and characteristic of bowel movements to diagnose constipation. Previous studies have reported the presence of dyssynergic defecation in 27–59% patients with CIC [14], a condition best assessed using anorectal manometry. Although anorectal manometry may be helpful in defining the causes of constipation in future studies, the technique is not only technically cumbersome and expensive for a large cohort study; there also is lack of consensus on its applicability to constipation management [16]. Although the understanding of defecatory disorders is increasing due to the availability of diagnostic tests, including 3D-transit system imaging and manometry, and magnetic resonance imaging (MRI), on a practical basis, defecatory diaries are the most feasible method for large-study enrollment despite evidence of discordance between patient-reported symptom diaries of constipation and objective measures [17]. In the same vein, assessment of nausea may be fraught with confounding variables since nausea itself is a subjective symptom. When assessing for nausea across the included studies, the authors determined a pre-baseline nausea profile through review of the patients' medical histories and the use of concomitant medications which can bias the data. Furthermore, the very high adverse event rates across studies, where up to 50% of patients in the placebo group for CIC experienced an adverse event in one study, increases the complexity of data interpretation.

To date, there are no head-to-head trials comparing lubiprostone with other classes of medications including guanylate cyclase activators such as linaclotide or plecanatide or μ-opioid antagonists (e.g., methylnaltrexone). In practice, each medication is presented as an option when other treatment options fail. Availability may be limited by insurance company formularies and cost. As always, prior to committing patients to more expensive medications, it is essential to confirm patients have attempted an adequate trial of fluid, fiber, and activity. This study, which confirms the predominant symptom of nausea when using lubiprostone, should be considered and weighed against the efficacy and adverse effect profile of other medications when prescribing the drug for all indications. Recently, plecanatide at 3 and 6 mg doses was reported to increase complete spontaneous bowel movements to 2.5 and 2.2/week, respectively, compared to 1.2/week in placebo [18]. Nonetheless, there were greater amounts of patients discontinuing the medication [47/931 (5.0%)] due to adverse events, most commonly diarrhea. Moreover, the expected cost of approximately $12/day may be prohibitive [19]. Similar data from a recent systematic review and meta-analysis of linaclotide in IBS-C found that linaclotide reduces the number of failures to achieve symptom relief by 165/1000 patients compared to placebo; nevertheless

31/1000 patients discontinued therapy due to severe diarrhea [20]. In a recent review of IBS-C and CIC studies, diarrhea experienced while taking linaclotide led to study withdrawal in 4.5–5.7% of patients compared to 0.2–0.3% in placebo groups. When faced with a patient with predominantly nausea or vomiting, a provider may try the less costly medication despite its overall inferior safety profile compared to a more costly medication. In general, PEG-based therapies should be considered as a first line in most patients due to their overall safety and effectiveness.

Ongoing clinical trials include evaluation of probiotics, Fecal Microbial Transplant (FMT), and vibrating capsule for the treatment of various constipation subtypes in addition to new medications. With new and emerging medication options to treat constipation, clinicians are increasingly incorporating rational treatment strategies with targeted therapies for their patients. Given these results, where does lubiprostone fit in the management of constipation? While risk-stratifying patients prior to drug administration is an important cornerstone of safe medical practice, lubiprostone is already regarded as well tolerated and carries an extremely small risk of any serious, irreversible adverse event. This point is already borne out in clinical practice as seen by the empiric use constipation medications prior to further diagnostic study. Yet, knowing the most common adverse effects across all indications for lubiprostone and other constipation medications is important prior to initiating any new medications in order to help set realistic expectations for patients. Importantly though, the results of this study cannot be extrapolated to patients with diabetes or chronic medical conditions that may predispose to constipation.

References

1. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterology*. 2016;150:1380–1392.
2. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. *Therap Adv Gastroenterol*. 2016;9:98–112.
3. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:1582.
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;19:312–318. doi:10.5056/jnm.2013.19.3.312.
5. Chamberlain SM, Rao SS. Safety evaluation of lubiprostone in the treatment of constipation and irritable bowel syndrome. *Expert Opin Drug Saf*. 2012;11:841–850.
6. Cryer B, Drossman D, Chey W, Webster L, Habibi S, Wang M. Analysis of nausea in clinical studies of lubiprostone for the treatment of constipation disorders. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-017-4680-1.
7. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol*. 2012;107:1714–1724 **(quiz p. 1725)**.
8. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107:1702.
9. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. *Am J Gastroenterol*. 2013;108:1566.
10. Garnock-Jones KP. Naloxegol: a review of its use in patients with opioid-induced constipation. *Drugs*. 2015;75:419–425.
11. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60:209–218. doi:10.1136/gut.2010.227132.
12. Sloots CE, Rykx A, Cools M, Kerstens R, De Pauw M. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. *Dig Dis Sci*. 2010;55:2912–2921. doi:10.1007/s10620-010-1229-y.
13. Christie J, Shroff S, Shahnavaz N, et al. A randomized, double-blind, placebo-controlled trial to examine the effectiveness of lubiprostone on constipation symptoms and colon transit time in diabetic patients. *Am J Gastroenterol*. 2017;112:356–364.
14. Rao SS, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. *J Neurogastroenterol Motil*. 2016;22:423–435. doi:10.5056/jnm16060.
15. Sarosiek I, Bashashati M, Alvarez A, et al. Lubiprostone accelerates intestinal transit and alleviates small intestinal bacterial overgrowth in patients with chronic constipation. *Am J Med Sci*. 2016;352:231–238.
16. Grossi U, Carrington EV, Bharucha AE, Horrocks EJ, Scott SM, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defecation. *Gut*. 2016;65:447–455. doi:10.1136/gutjnl-2014-308835.
17. Knudsen K, Krogh K, Ostergaard K, Borghammer P. Constipation in Parkinson's disease: subjective symptoms, objective markers, and new perspectives. *Mov Disord*. 2017;32:94–105. doi:10.1002/mds.26866.
18. Miner PB Jr, Koltun WD, Wiener GJ, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. *Am J Gastroenterol*. 2017;112:613–621. doi:10.1038/ajg.2016.611.
19. Clinical Resource. Treatment of constipation in adults. Pharmacist's Letter/Prescriber's Letter, April 2017. https://prescriber.therapeuticresearch.com/Content/Segments/PRL/2015/Jun/Treatment-of-Constipation-in-Adults-8517. Accessed August 30, 2017.
20. Atluri D, Chandar A, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2014;26:499–509.