Elobixibat, an ileal bile acid transporter inhibitor, induces giant migrating contractions during natural defecation in conscious dogs

Shinya Taniguchi1 | Tetsuo Yano2 | Masakazu Imaizumi3 | Noriaki Manabe4

Abstract

Background: Chronic constipation affects 14%-17% of the population. Elobixibat, a novel, ileal bile acid transporter (IBAT) inhibitor, has been approved as a new chronic constipation drug in Japan in January 2018. The present study aimed to examine the pharmacological effects of elobixibat on colonic motility in conscious dogs using a telemetry system.

Methods: Six male beagle dogs were surgically implanted with strain gauge force transducers for gastrointestinal (GI) motility recording. The motility index was calculated from GI motility at each recording site in conscious and nonrestraint dogs. The fasted dogs were orally administered elobixibat (3, 10, or 30 mg kg⁻¹) or 30 mg kg⁻¹ of senno-side as positive control or vehicle using a crossover design and washout period of more than 6 days. One hour after drug administration, the dogs were fed chow, and GI motility and defecation were observed for 10 hours; GI motility was quantified to calculate giant migrating contractions (GMCs). Fecal bile acids (BAs) were determined as well.

Key Results: Elobixibat and senno-side significantly increased the number of defecations, fecal wet weight, and water content within 10 hours after administration. Elobixibat dose-dependently decreased the time to first bowel movement, increased the amount of total fecal BAs, and rapidly induced mild GMCs during defecation; however, higher strength of GMCs was observed with senno-side.

Conclusions & Inference: Elobixibat induces bowel movements faster than senno-side through a different mechanism. Elobixibat locally inhibits IBAT in the ileal lumen, leading to elevated fecal BAs in the colon and induced mild GMCs during defecation.

KEYWORDS

bile acid, defecation, elobixibat, giant migrating contraction, motility, secretion

1 INTRODUCTION

Chronic constipation is a common, chronic gastrointestinal (GI) condition reportedly affecting 14%-17% of the population.1,2 There are three categories of GI motility in patients with chronic constipation:

(a) normal transit constipation; (b) slow transit constipation (STC), and (c) outlet obstruction.3 This condition occurs more frequently in female and elderly patients;4 most of whom are considered to have normal intestinal peristalsis. Patients with STC reportedly have fewer high amplitude propagated contractions (HAPCs) than
those of healthy volunteers.\textsuperscript{5} Pharmacotherapeutic agents, such as stimulant laxatives, induce HAPCs and are potentially beneficial to patients with STC.\textsuperscript{6,7}

Elobixibat (PubChem CID: 9939892) is a novel, local-acting, ileal bile acid transporter inhibitor (IBAT, also called apical sodium-dependent bile acid transporter, ASBT), which has been approved in Japan in January 2018. Elobixibat interrupts the enterohepatic circulation of bile acids (BAs), upregulating hepatic BA synthesis.\textsuperscript{8} BAs induce secretion of water and electrolytes into the colonic lumen\textsuperscript{9} and enhance colonic motility, inducing HAPCs.\textsuperscript{10} For patients with chronic constipation, this dual-action agent is more effective than single-action agents, like osmotic agents, secretagogues, or prokinetics. However, no reports have investigated whether elobixibat directly enhances colonic motility, inducing HAPCs.

Elobixibat is a highly potent and selective inhibitor of human, murine, and canine IBAT and ameliorates meat-induced constipation in dogs.\textsuperscript{11} As the colons of adult canines and humans are anatomically similar, canine digestive phenomena, such as colonic fermentation and water and electrolyte absorption, are comparable to processes observed in humans, and canine fecal properties and circadian rhythm are similar to those of humans.\textsuperscript{12,13} Thus, the dog is an appropriate animal model to investigate the pharmacological effects of elobixibat.

The aim of this study was to assess GI motility following single-dose administration of elobixibat using a canine intestinal telemetry system. Sennoside was administered as a positive control in this model because it induces giant migrating contractions (GMCs), which are known as canine HAPCs.\textsuperscript{13–15}

2 | MATERIALS AND METHODS

2.1 | Animals

Six 10-month-old male beagle dogs (Beijing Marshall Biotechnology Co., Ltd, Beijing, China) were used in this study. The body weight of the dogs ranged from 11.0 to 14.3 kg. All dogs were housed one per cage in a room with light/dark cycle of 12/12-h (lights on at 7:00 AM) and were fed 300 g/dog/day of laboratory chow (DS-A, Oriental Yeast Co., Ltd, Tokyo, Japan). Water was available to dogs ad libitum. At the commencement of this study, the study protocol was reviewed by the Institutional Animal Care and Use Committee and approved by the general manager of the Nonclinical Research Center (approval No. 2017-0484) according to the guidelines for animal studies in the Nonclinical Research Center.

2.2 | Implantation of strain gauge force transducers and recording of GI motility

GI motility was recorded by means of chronically implanted strain gauge force transducers (SGs), as previously reported.\textsuperscript{13} Each dog received a preoperative intramuscular administration of cefamezin (15 mg kg\textsuperscript{-1}, Astellas Pharma, Tokyo, Japan) and lepetan (0.01 mg kg\textsuperscript{-1}, Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan), followed by intramuscular administration of Ketalar (10 mg kg\textsuperscript{-1}, Daiichi Sankyo Co., Ltd, Tokyo, Japan) and Selectar (2 mg kg\textsuperscript{-1} Bayer Pharmaceutical Co., Ltd, Leverkusen, Germany). Anesthesia was maintained by inhalation of 0.5%-3% isoflurane (Pfizer Co., Ltd., New York, USA). GI tract relaxation was achieved by intramuscular administration of atropine (0.1 mg kg\textsuperscript{-1}, Mitsubishi Tanabe Pharma Co., Ltd, Tokyo, Japan). A median abdominal incision was made, and seven strain gauge force transducers (SGs, No. F-12IS; Star Medical Inc, Tokyo, Japan) were implanted at the serosal surface from the ileum to the colon. To measure circular muscle contraction, SGs were sutured to the seromuscular layer along the transverse axis and at the following seven sites: the ileum, 20 cm proximal to the ileocecal valve (SG1); the ileum, 10 cm proximal to the ileocecal valve (SG2); the ascending colon, 10 cm distal to the cecum (SG3); the transverse colon at the level of common colic trunk artery entry (SG4); the descending colon at the level of caudal mesenteric artery entry (SG5); the sigmoid colon, midway between the entry level of the caudal mesenteric artery and the site of peritoneal reflection (SG6); and the rectum, at the site of the peritoneal reflection (SG7). The wires from each SG were subcutaneously tunneled into the back of the neck, where they connected to a small radio transmitter (DAT-80 T and DAT-85 T, Star Medical Inc, Tokyo, Japan). At more than 1 month after surgery, the animals were used to evaluate the GI motility. For each dog, motility data from each GI site were transmitted to a computer via a telemetry system designed to monitor GI function (Analyze II, Star Medical Inc, Japan), thus allowing the recording and analysis of GI motility and behaviors without use of animal restraints. The recorded mechanical activities were assessed using the software for analysis of GI motility.

2.3 | Observation of GI motility and behavior

Baseline GI motility was initially measured for more than 20 hours. This study was started after confirming that there were no data

Key Points
- Bile acids (BAs) are known to enhance colonic motility; however, no studies have investigated whether elobixibat directly induces motility in the gastrointestinal tract.
- Elobixibat rapidly induced mild giant migrating contractions (GMCs), promoting natural defecation with elevated fecal BAs in conscious dogs implanted with strain gauge force transducers.
- Rapid GMCs induced by elobixibat suggests that it is potentially beneficial for patients with chronic constipation, including slow transit constipation, who have fewer high amplitude propagated contractions with delayed transit time.
acquisition problems as baseline and that the dogs were generally healthy. At 10:00-11:00 AM, following 18 hours fasting, the dogs were orally administered with either 3, 10, or 30 mg kg⁻¹ of elobixibat (EA Pharma Co., Ltd., Tokyo, Japan) or 30 mg kg⁻¹ of sennoxide (Sennoside AB, dihydro-direinanthrone glucoside, Alps Pharmaceutical Industry Co., Ltd., Hida, Japan). The elobixibat dosage was selected as 3-30 mg kg⁻¹ because fecal weight increase was previously observed at 10 mg kg⁻¹ in a canine constipation model, and the dose was estimated to be approximately 10 times higher than that in human dose (5-15 mg) considering the difference between humans and dogs in terms of in vitro IBAT inhibition potency. The dose of sennoxide was selected according to that previously reported to induce GMC in dogs. Water for injection, adjusted to a pH of 8.5 with NaOH, was used as the vehicle. One hour after administration, the dogs were fed 300 g of laboratory chow. The GI motility effects were assessed for 10 hours after drug administration. Once defecation occurred, the fecal weight and scale form were determined every 2 hours. The fecal scale form was categorized as normal, soft, or mushy form. Following wet weight determination, each stool sample was mixed for homogeneity to measure fecal BA concentration. A portion of the stool samples was collected, quickly cooled with liquid nitrogen, and stored for BA measurement, whereas the remainder was dried with an automatic dry heat sterilizer (HE-21) for dry-weight quantification. The fecal water content was calculated by subtracting the fecal dry weight from the fecal wet weight, and the weight ratio, with the fecal wet weight, was defined as water weight content. Drug administration was performed using a crossover design, with a washout period of more than 6 days, and vehicle or drug was administered as a single dose. The dogs were monitored with a CCD camera connected to a hard disk video recorder.

2.4 Analysis of GI motility and GMCs during defecation

GI motility was quantified using the analysis software, which calculated the area at each recording site. Aggregated values were obtained for each minute before and after drug administration. The analyzed period began 1 hour before administration and ended 10 hours after administration, with each minute within every hour summed and used as a motility index. GMC was defined as a ≥3-fold amplitude increase, relative to baseline, and a confirmed propagated wave. Each maximum amplitude or area of GMC at defecation was individually calculated as the amplitude or area of contraction during GMC, using the analysis software. The GMC index was the summation of the areas of GMC at defecation within 2 and 10 hours after administration. All motility indices, including the amplitude or area of GMC, were analyzed using the same software as described above.

2.5 Total fecal BAs

BA-containing alcohol fractions were collected using a weak alkali treatment, ultrasonic extraction, enzyme treatment, and solid-phase column for the stored canine stools. Using the previously reported LS/ESI-MS/MS method, total fecal BA concentration (µmol g⁻¹ fecal wet weight) was determined by injecting BA-containing alcohol fraction into LCMS 8050 (Shimadzu Corporation; LCMS 8050, Tokyo, Japan) and combining it with a standard product of known concentration. Amount of total fecal BA was calculated by using the data of fecal wet weight and BA concentration.
2.6 | Statistical analysis

We compared the vehicle group and elobixibat groups or sennoside group and elobixibat groups using Bartlett’s test to test the homogeneity of variance. Once homogeneity was confirmed, we performed a Dunnett’s multiple comparison test. If the variance was not homogeneous, we performed the Steel’s multiple comparison test. A comparison between the vehicle group and sennoside group was performed using a test for homoscedasticity (F-test), followed by either a Student’s t test for a case of homoscedasticity, or a Welch’s t test for a case of heteroscedasticity. With regard to the time to initial defecation, we analyzed the dose dependence of action using the Jonckheere-Terpstra test. The significance level of the variance test was set at 5%; the significance levels for intergroup comparisons were set at 1% and 5% (two-sided test). Statistical analysis was performed with EXSUS Version 8.1.0 (CAC Croit Corporation) using SAS 9.4 (SAS Institute Japan Ltd.).

3 | RESULTS

Each elobixibat group significantly increased defecation frequency during the first 2 hours after administration compared with the vehicle group. Within 10 hours of administration, we observed a significant increase in the total defecation count for the 30 mg kg\(^{-1}\) elobixibat group and 30 mg kg\(^{-1}\) sennoside group compared with that for the vehicle group (Figure 1A). Elobixibat decreased the time to first bowel movement in a dose-dependent manner (\(P = 0.0002\) by the Jonckheere-Terpstra test), whereas the effect of sennoside did not reach statistical significance (Figure 1B).

The fecal wet weight and fecal water content of each subject, within each administration group, are presented in Figure 2. Within 2 hours of administration, we observed a significant increase in the fecal wet weight in the elobixibat groups compared with that in the vehicle group. In contrast, within 10 hours of administration, we observed a significant increase in fecal water content in elobixibat groups receiving 10 and 30 mg kg\(^{-1}\) as well as the sennoside group compared with that in the vehicle group.

Table 1 shows the fecal form examination results at defecation. The fecal form was normal within 2 hours after administration of either vehicle or elobixibat at 3 and 10 mg kg\(^{-1}\). However, for 30 mg kg\(^{-1}\) elobixibat as well as sennoside, we observed soft or muddy stools in addition to normal stools within 2 or 10 hours. No other GI or general side effects were noted.

Typical traces before and after defecation are shown in Figure 3. GMC, starting from the ascending colon, was observed at the time of all bowel movements in the ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The mean amplitude in elobixibat groups was similar to that in the vehicle and the mean area mostly within approximate two times

![FIGURE 2](image-url)  
**FIGURE 2** Effect of elobixibat on (A and B) total fecal wet weight (g) and (C) water content (%) within 2 or 10 hours after administration. *\(P < 0.05\), **\(P < 0.01\): significant difference between the vehicle group and elobixibat group (Dunnett’s multiple comparison test). ##\(P < 0.01\): significant difference between the vehicle group and sennoside group (Student’s t test). Results presented as mean ± standard deviation on (A and B) or mean + standard deviation on (C). Dots represent each animal

| TABLE 1 | Summary of fecal scale form count within 2 or 10 hours after administration |
|----------|------------------|------------------|------------------|
|          | Vehicle | Elobixibat | Sennoside |
| **0–2 h** | \(0\)  | 3     | 10   | 30  | 30   |
| Dose (mg kg\(^{-1}\)) | \(1\)  | 5     | 5    | 5   | 3    |
| Total No. of feces | \(1\)  | 5     | 5    | 2   | 2    |
| Normal | \(0\)  | 0     | 0    | 0   | 0    |
| Soft  | 0     | 0     | 0    | 3   | 1    |
| **0–10 h** | \(8\)  | 9     | 12   | 16  | 15   |
| Dose (mg kg\(^{-1}\)) | \(0\)  | 3     | 10   | 30  | 30   |
| Total No. of feces | \(7\)  | 6     | 5    | 2   | 4    |
| Normal | 1     | 2     | 3    | 5   | 3    |
| Soft  | 0     | 1     | 4    | 9   | 8    |
| Mushy | 0     | 1     | 4    | 9   | 8    |
compared to the vehicle group at each recording site 0-10 hours after administration. Also, no significant differences were found between the elobixibat groups and the vehicle group in GMC index. On the contrary, no significance but a much higher amplitude or area of GMC was observed in the sennoside group. In the transverse colon, a significantly higher GMC index was observed in the sennoside group compared with vehicle group (Table 2). On the basis of these observations, elobixibat induced mild GMC, similar to the vehicle but not higher than sennoside. There is no differentiation for the extent of propagation among all groups.

In addition, within 10 hours after administration, only transient changes or changes unrelated to the dose were observed in the motility indices of all administration groups, with no clear treatment effects (Figure 4).

We analyzed the number of defeation, time to first bowel movement, fecal wet weight, fecal water content, the amplitude or

![Image of typical tracing of intestinal contractile activity during defeation after administration.](image-url)
|            | 0-2 h          | 0-10 h         |
|------------|----------------|----------------|
|            | No. of GMC (mean ± SD) | GMC index (g·min) | Area of GMC (g·min) | Amplitude of GMC (g) | Ascending colon | Transverse colon | Descending colon | Sigmoid colon | Rectum | Ascending colon | Transverse colon | Descending colon | Sigmoid colon | Rectum |
|            |                | Ascending colon | Transverse colon | Descending colon | Sigmoid colon | Rectum |
| 0-2 h      | 0.2 ± 0.4      | 0.5 ± 1.1      | 0.5 ± 1.3        | 0.7 ± 1.8       | 1.0 ± 2.6     | 1.4 ± 3.3 |
| Vehicle    | 0.8 ± 0.4*     | 3.4 ± 2.9      | 2.5 ± 2.2        | 2.2 ± 2.4       | 2.2 ± 3.8     | 3.5 ± 6.4 |
| 3 mg kg⁻¹  | 0.8 ± 0.4*     | 5.4 ± 7.2      | 4.4 ± 6.5        | 4.0 ± 3.4       | 5.7 ± 8.0     | 3.2 ± 2.5 |
| 10 mg kg⁻¹ | 0.8 ± 0.4*    | 2.0 ± 2.6      | 5.1 ± 7.5        | 1.1 ± 1.6       | 2.3 ± 3.2     | 2.5 ± 4.2 |
| 30 mg kg⁻¹ | 0.5 ± 0.5      | 8.5 ± 12.7     | 9.2 ± 13         | 5.1 ± 8.0       | 0.7 ± 1.6     | 3.0 ± 5.1 |
| Sennoside  | 0.5 ± 0.5      | 8.5 ± 12.7     | 9.2 ± 13         | 5.1 ± 8.0       | 0.7 ± 1.6     | 3.0 ± 5.1 |

Results presented as mean ± standard deviation.

*P < 0.05: significant difference between the vehicle group and elobixibat group (Dunnett's multiple comparison test)
**P < 0.01: significant difference between the vehicle group and sennoside group (Student's t-test)
***P < 0.05: significant difference between the vehicle group and sennoside group (Welch's t-test)
area of GMC, and GMC index for direct comparisons between the sennoside and elobixibat groups using Dunnett’s or Steel’s multiple comparison test. Consequently, the number of defecation in the elobixibat group receiving 3 mg kg⁻¹ or the fecal water content in the elobixibat group receiving 3 and 10 mg kg⁻¹ showed a significant decrease compared with the sennoside group \( P < 0.01 \), but there was no significant difference in the elobixibat group receiving 30 mg kg⁻¹ for all endpoints.

The total fecal BAs of elobixibat groups are shown in Figure 5. The use of 30 mg kg⁻¹ elobixibat significantly increased the amount of total BAs and their concentration within 10 hours after administration, compared with the vehicle group.

The direct correlation between the fecal BA concentration and fecal wet weight or fecal water content is shown in Figure 5. Both graphs show direct linear relationship using Pearson correlation \( R^2 \); \( P \)-value = 0.179:0.04 and 0.423:0.0008, respectively, particularly
the fecal BA concentration showed clear correlation with the fecal water content.

4 | DISCUSSION

Clinical trials in the United States and Japan confirm the clinical utility of elobixibat. However, no previous studies have investigated its pharmacological actions on the GI tract, other than those examining GI transit effects in patients with functional constipation in the United States. This study is the first report on the pharmacological actions of a single administration of elobixibat on defecation, GI motility, and fecal BAs in dogs.

In the present study, initial defecation was observed within 2 hours after administration of elobixibat (3 mg kg⁻¹ or more), and the time to initial defecation was remarkably, and dose-dependently, shortened in comparison with the vehicle. Moreover, our results suggest that bowel movements occurred more quickly following elobixibat than sennoside administration. Elobixibat is a local-acting inhibitor of IBAT, which is located on the apical membrane in the terminal ileum, thereby delivering BAs into the colon, which is responsible for its efficacy. Within 2 hours after administration, elobixibat may attribute to increased BA levels in the colon, which enhanced colonic motility and promoted water secretion into the colon. Sennoside reaches the colon and is metabolized by colonic microbiota before it can exert a prostaglandin E2 (PGE2)-induced laxative effect. Therefore, the difference in first-onset time between elobixibat and sennoside may be due to differing mechanisms of action.

Additionally, elobixibat increased the fecal water content and led to the production of soft or muddy stools. The mechanism elobixibat is different from that of sennoside, which is known to induce fluid secretion and GMCs in the colon by increasing PGE2 synthesis. The increase in fecal water content by sennoside was reproduced in the present study. As previously mentioned, BA promoted water secretion in the colon. On the basis of these findings, it is suggested that increased fecal water content is a result of promoted water secretion by increased BAs into the colon.

HAPC, referred to as GMC in dogs, contributes to defecation and is induced by meals. As diet influences secretion of BAs by the duodenum, preprandial administration of elobixibat effectively inhibits IBAT. In the present study, elobixibat was administered before meals, similar to its clinical use. Furthermore, it is well known that direct administration of BAs into the colon induces HAPCs in humans. The results of the present study suggest that GMCs

FIGURE 5  Amount of total fecal bile acids (A) and their concentration (B) within 10 hours after administration. The direct correction between the fecal BA concentration and the fecal wet weight (C) or fecal water content (D). *P < 0.05: significant difference between the vehicle group and elobixibat group (Steel’s test). Results presented as mean ± standard deviation. Dots represent each animal.
are induced by increasing the BA levels in the colon, following administration of elobixibat. The results revealed that, although elobixibat induced GMCs, the amplitude, area, and also GMC index within 10 hours after administration did not differ significantly compared with that of the vehicle. A previous study reported a twofold increase in the frequency of the proximal colonic propagating sequence (PS) in humans, after rectal instillation of 1 mmol chenodeoxycholic acid.10 The PS was relatively low amplitude, compared with bisacodyl, a stimulant laxative.25 These findings suggest that elobixibat may be a mild GMC inducer during natural defecation compared with stimulant laxatives. BA is a biological component, thought to induce HAPC that resemble biological reactions. Interestingly, although sennoside also induced GMCs in the colon, the efficacy, such as number of defecations and fecal weight, was comparable with that of 30 mg kg−1 elobixibat. Therefore, it is suggested that elobixibat mildly induces GMCs without reducing the efficacy in comparison to sennoside. In current phase 3 trials, most patients who experienced abdominal pain were typically mild and recovered without changing dosage or titrating dose down.16 “Mild GMC” by elobixibat means natural GMC induced by bile acids and may mostly be felt as mild pain and be adapted if it occurs as a side effect.

Previous studies have reported that the colonic transit time in patients with chronic constipation is delayed26 and that the number and duration of mass movements are significantly reduced in constipated patients than in healthy volunteers.27 Elobixibat has potential benefits for patients with chronic constipation, including STC, who have fewer HAPCs with delayed transit time.5 This study has some limitations. First, elobixibat was administered as a single dose. Another limitation was that we used healthy dogs. Future studies must be conducted to confirm the efficacy of elobixibat with multiple doses on GI motility, particularly GMCs, in constipated animal models.

In conclusion, elobixibat rapidly induces mild GMCs, promoting natural defecation in healthy dogs. Elobixibat has potential benefits for patients with chronic constipation, including STC, who have fewer high amplitude contractions with delayed transit time.

ACKNOWLEDGMENTS

The authors thank Hajime Takei, Junshin Clinic Bile Acid Institute in Japan, for determination of the fecal bile acids.

DISCLOSURE

NM has served as an advisor to EA Pharma Co., Ltd. No competing interests declared.

AUTHOR CONTRIBUTIONS

ST was involved in designing, oversight, data interpretation, and drafting the manuscript, editing all subsequent drafts, and finalizing the manuscript. TY was involved in designing, oversight, data analysis, interpretation, and editing the subsequent drafts of the manuscript. MI was involved in designing, performing, and data and statistical analysis of the study. NM was involved in designing, providing details of methods for motility, including GMC, is the senior author, edited the manuscript, and is the corresponding author. All authors reviewed and approved the final draft of the manuscript for submission.

ORCID

Norlaki Manabe http://orcid.org/0000-0002-5010-3708

REFERENCES

1. 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(9):1582-1591.
2. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC Gastroenterol. 2008;8:5.
3. Camilleri M, Ford AC, Maue GM, et al. Chronic constipation. Nat Rev Dis Primers. 2017;3:17095.
4. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004;99(4):750-759.
5. Rao SS, Sadeghi P, Beaty J, Kavlock R. Ambulatory 24-hour colonic manometry in slow-transit constipation. Am J Gastroenterol. 2004;99(12):2405-2416.
6. Portalatin M, Winstead N. Medical management of constipation. Clin Colon Rectal Surg. 2012;25(1):12-19.
7. Bassotti G, Chiarioni G, Germani U, Battaglia E, Vantini I, Morelli A. Endoluminal instillation of bisacodyl in patients with severe (slow transit type) constipation is useful to test residual colonic propulsive activity. Digestion. 1999;60(1):69-73.
8. Acosta A, Camilleri M. Elobixibat and its potential role in chronic idiopathic constipation. Therap Adv Gastroenterol. 2014;7(4):167-175.
9. Mejkian HS, Phillips SF, Hofmann AF. Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. J Clin Invest. 1971;50(8):1569-1577.
10. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. Am J Physiol Gastrointest Liver Physiol. 2002;282(3):G443-G449.
11. Gillberg PG, Dahlström M, Starke I, Östlund-Lindqvist AM. S1301 The IBAT Inhibition by A3309—A potential mechanism for the treatment of constipation. Gastroenterology. 2010;138(5):S-224.
12. Flexinous T, Delvaux M. Colonic motility. In: Kumar D, Wingate D, eds. An Illustrated Guide to Gastrointestinal Motility, 2nd edn. Edinburgh: Churchill Livingstone; 1993:427-448.
13. Hirabayashi T, Morikawa Y, Matsufuji H, Hoshino K, Hagane K, Ozaki K. Stimulatory action of mitemcinal (GM-611), an acid-resistant non-peptide motilin receptor agonist, on colonic motor activity and defeacation: spontaneous and mitemcinal-induced giant migrating contractions during defeacation in dogs. Neurogastroenterol Motil. 2009;21(10):1085-e91.
14. Fioramonti J, Staumont G, Garcia-Villar R, Bueno L. Effect of sennosides on colon motility in dogs. Pharmacol. 1988;36(1):23-30.
15. Staumont G, Fioramonti J, Frexinos J, Bueno L. Changes in colonic motility induced by sennosides in dogs: evidence of a prostaglandin mediation. Gut. 1988;29(9):1180-1187.
16. Nakajima A, Seki M, Taniguchi S, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomised,
double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol. 2018;3:537-547.

17. Karaus M, Sarna SK. Giant migrating contractions during defecation in the dog colon. Gastroenterology. 1987;92(4):925-933.

18. Kakiyama G, Muto A, Takei H, et al. A simple and accurate HPLC method for fecal bile acid profile in healthy and cirrhotic subjects: validation by GC-MS and LC-MS. J Lipid Res. 2014;55(5):978-990.

19. Muto A, Takei H, Unno A, et al. Detection of Δ4-3-oxo-steroid 5β-reductase deficiency by LC-ESI-MS/MS measurement of urinary bile acids. J Chromatogr B Analyt Technol Biomed Life Sci. 2012;900:24-31.

20. Chey WD, Camilleri M, Chang L, Rikner L, Graffner H. A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. Am J Gastroenterol. 2011;106(10):1803-1812.

21. Nakajima A, Seki M, Taniguchi S. Determining an optimal clinical dose of elobixibat, a novel inhibitor of the ileal bile acid transporter, in Japanese patients with chronic constipation: a phase II, multi-center, double-blind, placebo-controlled randomized clinical trial. J Gastroenterol. 2018;53(4):525-534.

22. Wong BS, Camilleri M, McKinzie S, Burton D, Graffner H, Zinsmeister AR. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. Am J Gastroenterol. 2011;106(12):2154-2164.

23. Beubler E, Kollar G. Stimulation of PGE2 synthesis and water and electrolyte secretion by senna anthraquinones is inhibited by indomethacin. J Pharm Pharmacol. 1985;37(4):248-251.

24. Bharucha AE. High amplitude propagated contractions. Neurogastroenterol Motil. 2012;24(11):977-982.

25. Kamm M, Van Der Sijp JM, Lennard-Jones J. Colorectal and anal motility during defaecation. Lancet. 1992;339(8796):820.

26. Manabe N, Wong BS, Camilleri M, Burton D, McKinzie S, Zinsmeister AR. Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287 patient cohort. Neurogastroenterol Motil. 2010;22(3):293–e82.

27. Bassotti G, Gaburri M, Imbimbo BP, et al. Colonic mass movements in idiopathic chronic constipation. Gut. 1988;29(9):1173-1179.

How to cite this article: Taniguchi S, Yano T, Imaizumi M, Manabe N. Elobixibat, an ileal bile acid transporter inhibitor, induces giant migrating contractions during natural defecation in conscious dogs. Neurogastroenterol Motil. 2018;30:e13448. https://doi.org/10.1111/nmo.13448