Published in final edited form as:
Neurogastroenterol Motil. 2011 October ; 23(10): 944–e400. doi:10.1111/j.1365-2982.2011.01776.x.

Lubiprostone does not Influence Visceral Pain Thresholds in Patients with Irritable Bowel Syndrome

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Abstract

Background—In clinical trials, lubiprostone reduced the severity of abdominal pain.

Aims—The primary aim was to determine whether lubiprostone raises the threshold for abdominal pain induced by intraluminal balloon distention. A secondary aim was to determine whether changes in pain sensitivity influence clinical pain independently of changes in transit time.

Methods—Sixty-two patients with irritable bowel syndrome with constipation (IBS-C) participated in an 8-week crossover study. All subjects completed a 14-day baseline ending with a barostat test of pain and urge sensory thresholds. Half, randomly selected, then received 48 ug/day of lubiprostone for 14 days ending with a pain sensitivity test and a Sitzmark test of transit time. This was followed by a 14-day washout and then a crossover to 14 days of placebo with tests of pain sensitivity and transit time. The other half of the subjects received placebo before lubiprostone. All kept symptom diaries.

Results—Stools were significantly softer when taking lubiprostone compared to placebo (Bristol Stool scores 4.20 vs. 3.44, $p<0.001$). However, thresholds for pain (17.36 vs. 17.83 mmHg, lubiprostone vs. placebo) and urgency to defecate (14.14 vs. 14.53 mmHg) were not affected by lubiprostone. Transit time was not significantly different between lubiprostone and placebo (51.27 vs. 51.81 hours), and neither pain sensitivity nor transit time was a significant predictor of clinical pain.

Conclusions—Lubiprostone has no effect on visceral sensory thresholds. The reductions in clinical pain that occur while taking lubiprostone appear to be secondary to changes in stool consistency.

Introduction

Lubiprostone is a chloride channel agonist approved for the treatment of chronic constipation and irritable bowel syndrome with constipation (IBS-C). Its primary mechanism of action is secretion of water into the lumen of the small and large intestine[1, 2] leading to acceleration of transit, changes in stool consistency, and relief of subjective symptoms of constipation. However, in clinical trials of patients with IBS-C, it also decreases abdominal pain and discomfort[3, 4] and is effective for the relief of overall symptoms of IBS[4]. It is unknown whether these reductions in clinical pain occur secondary to the effects of the drug on colonic transit or whether they are mediated by a direct effect of lubiprostone on pain thresholds.

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Sweetser and colleagues[5] previously tested the effects of lubiprostone on pain sensitivity in 60 healthy volunteers. A barostat was used to assess the threshold for first sensation and pain following three daily doses of either 24 μg lubiprostone or placebo. The intensity of pain produced by standard distention pressures was also tested. There were no significant differences in either the sensory thresholds or the pain intensity ratings. However, in women there was a trend favoring higher pain thresholds while taking lubiprostone.

The goal of this study was to reassess the effects of lubiprostone on pain thresholds in patients with IBS-C using a larger dose and longer exposure (48 μg per day for 14 days). We also employed a within-subject crossover design to minimize the impact of individual differences in pain sensitivity. Specific hypotheses were: (1) Pain thresholds will be higher (i.e., pain sensitivity will be reduced) at the end of two weeks treatment with lubiprostone 48 μg/day compared to two weeks treatment with placebo. (2) Pain thresholds while taking lubiprostone will remain significantly higher than while taking placebo after adjusting for differences in transit time. (3) Regression analysis will show that pain threshold and transit time make significant independent contributions to clinical pain as reported on the patient's diary.

Methods

Study Design

This was a double-blind, randomized cross-over trial, as outlined in Figure 1. A cross-over design was selected because it requires fewer subjects due to the fact that within-subject variability is less than between-subject variability, and our prior work suggested good reproducibility of pain thresholds over an interval of 3 months[6]. Following enrollment and a two-week symptom monitoring baseline, subjects were randomly assigned to one of two test treatment arms, both of which consisted of the same interventions but in a counter-balanced order. One group received 2 weeks of lubiprostone therapy (48 μg per day) followed by a 2-week washout period, and then took placebo capsules for 2 weeks. The other group started with 2 weeks of placebo capsules followed by 2 weeks of washout, and ended with 2 weeks of lubiprostone therapy (48 ug per day). Two weeks was selected as the duration of the washout period because the reported elimination half-life of lubiprostone and its major metabolite is 1.4 hours or less[7]. After a 24-μg radiolabeled dose of lubiprostone, 60% of the radioactivity is recovered in the urine within 24 hours and another 30% is recovered in the feces within 168 hours. The dose of 48 μg per day was selected for testing instead of the lower 8 μg per day recommended for the treatment of IBS because 48 ug was shown in a Phase II study to be more effective than lower doses for relief of abdominal pain[8]. Clinical symptoms were assessed throughout the study with daily symptom ratings, and symptoms were also measured with the IBS Severity Scale (IBS-SS)[9] at the end of the baseline period and at the end of each of the two intervention periods. Gut transit time and pain sensitivity were assessed at the end of each intervention period. Both subjects and study staff were blinded to the assignment of subjects and the nature of the intervention delivered. Lubiprostone and placebo were provided by the manufacturer in identical capsules and dispensed by the University of North Carolina investigational pharmacy.

Sample size

This study was powered to detect a difference in pain threshold only. An a priori sample size calculation indicated that a minimum of 62 IBS patients would be needed to detect a clinically meaningful treatment difference of 6 mmHg in the pain threshold between two test conditions in a cross-over study at an alpha level of 0.05 and power of 80%. The effect size of 6 mmHg was defined as a clinically meaningful difference because this is half the difference in average pain thresholds observed between 129 IBS patients and 30 healthy

controls in a previous study from our laboratory[10]. Estimates of within subject variability were taken from the placebo arm of a treatment study we previously reported for which the difference in pain threshold over a 3-month period was 1.47 mmHg and the standard deviation of the difference was 8.21 mmHg[6].

Recruitment Method and Inclusion/Exclusion criteria

Advertisements in the form of posted signs in clinics or mass emails to the students and staff of the university invited people with a physician diagnosis of IBS to contact the study staff for screening. The number screened was not recorded. Inclusion criteria were (1) physician diagnosis of IBS, (2) meeting Rome III criteria for IBS-C, and (3) age at least 18 years. Exclusion criteria were: (1) use of laxatives or prokinetic medications within two weeks prior to the study or during the study; (2) use of IBS-specific compounds, opiates, anticholinergics, or any drug likely to cause constipation as a side-effect; (3) use of analgesics for 48 hours prior to the study; (4) hypothyroidism; (5) history of bowel resection except appendectomy or cholecystectomy; (6) psychotic disorder, major depression, substance abuse (other than tobacco), or other psychiatric condition likely to interfere with study participation; (7) renal disease; (8) inflammatory or ischemic disease of the rectum, and (9) evidence that the subject was an unreliable research participant. (10) Because the study involved radiographs, women currently pregnant or planning pregnancy, individuals working with radiation and those who had participated in research involving radiation within the past year were also excluded.

Individuals meeting inclusion criteria were asked to read and sign and informed consent statement describing the study and were randomized to one of two drug-placebo sequences by opening the next in a series of sealed envelopes prepared by the investigational pharmacy. The investigational pharmacy randomized subjects in blocks of size 6 and 4. Seventy-one patients were enrolled in the study over a 26-month period, and 62 completed the trial.

Study Measures

Barostat testing—The barostat test was conducted with a Distender II computer-controlled pump manufactured by G&J Electronics in Willowdale, Ontario, Canada. The device is able to inflate and deflate a thin-walled plastic bag in the rectum via a 0.5 cm diameter polyethylene catheter at pre-specified rates up to 38 ml/sec and to maintain constant bag pressure by adding or subtracting air from the bag.

The testing followed a protocol that we have used in multiple previous studies. Patients were asked to prepare for the test by refraining from eating and by not drinking anything other than water for at least 4 hours prior to testing, and by taking a Fleets enema approximately 2 hours before the test. Subjects were tested in a left lateral position with the barostat bag placed with its lower margin 5 cm above the anal verge.

The individual operating pressure (IOP), i.e., the minimum pressure required to overcome passive resistance to bag inflation (mostly attributable to the weight of overlying adipose tissue) was determined by adding 30 ml of air to the bag, waiting for 3 minutes, and then measuring the pressure in the bag. This IOP value was used as a correction factor for the subsequent pain perception tests; it was subtracted from pressures measured during the pain threshold test to arrive at the “true” trans-mural pressure gradient.

Visceral sensitivity was measured in two ways: by the ascending method of limits (AML) and by sensory decision theory (SDT). For the AML pain and urge threshold assessment, the bag in the rectum was inflated with a series of 30 sec distentions separated by 30 sec rest

periods at zero pressure. Each successive distention was more intense than the last by 2 mmHg, and the patient was asked to rate both pain and urge intensity at the end of each distention on a six-point intensity rating scale (0–5). The lowest pressure assigned a pain rating of 3 ("moderate pain") by the subject defined the AML pain threshold, and the lowest pressure assigned an urge rating of 3 was used to define the AML urge threshold.

Sensory decision testing immediately followed the AML threshold assessment. It incorporates classic SDT methodology adapted for colonic and rectal testing and was developed in our laboratory over a series of studies[11, 12]. The subjects were presented with a series of 16 30-sec distention trials separated by 30-sec rest periods at zero pressure. Half of these trials were at a pressure equivalent to the IOP plus 14 mmHg and the other half at IOP plus 20 mmHg. Subjects were not informed which pressure intensity was used at each distention trial. At the end of each distention, subjects were asked to rate the distention with the same 0–5 rating scale used previously in the AML procedure. From the rating results, perceptual sensitivity was calculated as an index of ability to accurately discriminate between the two different intensities of distention (abbreviated P(A)), and a response criterion was calculated (abbreviated B) as the median intensity rating made by the subject to all 16 of the stimuli pooled together (i.e., independent of stimulus intensity).

Clinical symptom assessment—Clinical symptoms were assessed in two ways: Via daily symptom recordings (diary) and the retrospective IBS Severity Scale (IBS-SS)[9]. In the symptom diary which subjects completed every night, subjects provided global ratings of the intensity of their abdominal pain for the past 24 hours, abdominal distention, dissatisfaction with bowel movements, and interference of bowel symptoms with daily activities. They also rated the consistency of each bowel movement with guidance from the validated 7-point Bristol Stool Scale pictures and associated written descriptors[13]. These ratings were made by logging onto a password-protected internet site or by telephoning and leaving the data on the study nurse's answering machine. To ensure timely completion of the diary, subjects who failed to report symptoms were telephoned the following day to obtain their symptom ratings for the previous day. The IBS-SS was completed at the end of the baseline period and each treatment period. It includes questions about the same symptoms as the first four questions on the diary (because the diary was designed as an adaptation of the IBS-SS for daily symptom monitoring) – i.e., pain intensity, distention intensity, bowel habit dissatisfaction and impact on daily activities, plus an additional question on the number of days in the past 10 that the subject experienced abdominal pain or discomfort. These five ratings are totaled to obtain an overall IBS severity score with a maximum severity score of 500. The IBS-SS has been found to discriminate IBS patients from controls and to separate IBS patients independently categorized by clinicians as mild, moderate, and severe at a high level of significance[9]. The scale has also been shown to be responsive to treatment in multiple treatment studies in IBS[14–16].

Sitzmark test of whole gut transit time—The subjects were given 5 capsules containing 24 circular radio-opaque markers in each and were instructed to take one capsule at breakfast each morning for 5 days (adapted from Abrahamsson and Antov[17]). On the sixth day, subjects reported to the hospital radiology department for an abdominal radiograph. By counting the markers, whole gut transit time could be estimated in hours. We report the total number of Sitzmarks remaining in the abdomen on the sixth day as a measure of whole gut transit time and the number of Sitzmarks in the left hemicolon (i.e., all Sitzmark lying on the right of the midline) as a measure of transit through the ascending colon. All female subjects who were pre-menopausal received a urine pregnancy test before each radiograph to confirm that they were not pregnant.

Procedures: In the course of their participation in the study, subjects completed a total of 7 outpatient visits to the General Clinical Research Center. Study procedures on each visit were as summarized below:

Visit 1: A screening interview was conducted, an informed consent completed, and the subject was given instruction in using the study diary and in taking a Fleets enema.

Visit 2 (2 weeks after Visit 1): The subject's study diary was reviewed to verify that symptoms met eligibility criteria, the IBS-SS questionnaire was administered, barostat test 1 conducted, the study capsules for the first treatment period issued, and instructions given for taking Sitzmarks capsules for the transit time study.

Visit 3 (2 weeks after Visit 2): An abdominal radiograph was taken for the transit time study.

Visit 4 – end of Treatment Period 1 (1–3 days after Visit 3): Unused intervention capsules were collected from the subject and counted, the IBS-SS questionnaire and treatment assignment perception question was administered and barostat test 2 was performed.

Visit 5 (2 weeks after visit 4): The IBS-SS questionnaire was administered, the intervention capsules for Treatment Period 2 were issued, and instructions were given for taking Sitzmarks for the transit study.

Visit 6: An abdominal radiograph was taken for the transit time study.

Visit 7 – end of Treatment Period 2 (1–3 days after Visit 6): Unused medication capsules were collected and counted, the IBS-SS questionnaire and perceived treatment arm questionnaire were administered, and a barostat test 3 was completed.

Subjects were paid $500 for completing the study. The study was reviewed and approved by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill before enrollment was initiated. The trial was registered with ClinicalTrials.gov as NCT 01166789.

Data analysis

By design, a random half of the subjects received lubiprostone followed by placebo, and the other half of subject received the placebo before lubiprostone. General linear models for repeated measures (SPSS version 19.0) was used to analyze the data. Treatment intervals 1 and 2 constituted the repeated measure and order was a between-subjects factor. For dependent measures recorded during baseline (pain thresholds recorded by barostat, urge thresholds recorded by barostat, and diary measures of stool consistency, abdominal pain, bloating, dissatisfaction with bowel habits, and interference with life) the baseline value was entered as a covariate. Transit measures were not assessed during baseline to minimize radiation exposure, so no covariate was available for this measure. All dependent variables were assumed to be normally distributed on continuous, equal interval scales. In these GLM models, support for the hypothesis of a drug effect would be reflected in a significant treatment period by order effect. Linear regression analysis was used to test the third hypothesis, namely that pain threshold and transit time both make independent significant contributions to clinical pain, and this was tested separately for each treatment period. Alpha was set to 0.05 for all analyses to minimize Type II statistical errors. The data are reported as means and 95% confidence intervals (CI).

Results

Patient characteristics

Average age of patients was 41.95+13.56 (mean+S.D.) years, and 85.5% were women. Race composition was 66.1% white, 19.0% black, and 3.2% Asian. Average IBS-SS severity score at the end of baseline (computed from the questionnaire) was 295.65 [CI 274.08, 317.21] with 8.1% of subjects scoring in the mild range (score <175), 46.7% of patients scoring in the moderate range (i.e., 175–300)[9] and the remaining 45.2% in the severe range (i.e., >300).

Adherence with taking study drug

Patients were instructed to take two capsules daily. There was no difference in the average number of capsules taken during Lubiprostone versus the average number taken during placebo administration (1.96 per day [CI 1.81, 2.03] vs. 1.98 per day [CI 1.89, 2.06]; t(54)=0.351, p=0.727), and adherence with medication taking was excellent overall.

Test for carry-over effects

To test for carry-over effects after medication use, the IBS-SS questionnaire was administered at the end of the washout period. There was no significant carry-over effect, although there was a tendency for patients receiving active drug during Treatment Period 1 to have a lower IBS-SS at the end of washout than subjects receiving placebo in Treatment Period 1 (245.67 [CI, 212.90, 278.44] vs. 261.67 [228.90, 294.44], p=.492),

Stool consistency and whole gut transit time

Table 1 shows that average Bristol Stool Scale scores computed from the daily diary were significantly greater (softer stools) when patients were taking active drug compared to placebo after adjusting for order of administration. Table 1 also shows that the proportion of days with hard/lumpy stools or no stools was significantly lower on active drug compared to placebo after adjusting for order of administration. However, neither whole gut transit time nor transit through the right hemicolon was significantly different on drug compared to placebo. The correlation between transit time as measured by the Sitzmark test and average stool consistency measured by the Bristol Stool Scale was rho = −0.346 (p=0.007) for the placebo condition and rho = −0.113 (p=0.366) for the lubiprostone condition.

Abdominal pain and other IBS symptoms

There were no differences between lubiprostone and placebo for diary ratings of abdominal pain, distention, dissatisfaction with bowel habits, or interference with life activities (Table 1). Similarly, there were no differences between drug and placebo on the IBS-SS questionnaires completed at the end of each treatment period.

Sensory thresholds

Pain thresholds could not be calculated for 20 of 62 patients by the ascending method of limits because they reached intolerable levels of urgency to defecate before reporting moderate levels of pain in one or more periods, and urge thresholds could not be calculated for 14 patients because they reached intolerable levels of pain before reporting a moderate urge sensation in one or more periods. Missing data were similar for drug and placebo (11 vs. 14 missing pain values and 6 vs. 5 missing urge thresholds respectively) which indicates that missing data was unrelated to drug administration; consequently, these subjects were excluded from analysis of pain and urge sensitivity. Pain and urge thresholds for the evaluable patients are shown in figures 2 and 3. A significant drug effect after adjustment for order of testing would be indicated by a significant interaction between drug treatment

and period, but both interaction terms were non-significant ($F<1.0$, $p>.90$ in both cases). Figures 2 and 3 show that sensory thresholds increase with successive barostat tests, but the magnitude of increases in pain and urge thresholds from the first to the third barostat test were less than the 6 mmHg which we defined a priori as a clinically insignificant change. Moreover, when the data were pooled across treatment periods, There were no significant differences between lubiprostone and placebo either for pain thresholds or urge thresholds ($t<1.0$ in both cases).

The sensory decision theory indices for visceral sensitivity are shown in Table 2. Neither the neurosensory sensitivity index, P(A), nor the response criterion, B, showed a significant difference between active drug and placebo.

By limiting the analysis to the first intervention period, we could test for the effects of lubiprostone versus placebo on pain and urge thresholds while adjusting for transit time. There was no significant difference between lubiprostone and placebo following this adjustment ($F(1,46)=0.329$, $p=0.569$). Regression analyses applied to each intervention period separately confirmed that none of three variables – drug, whole gut transit time, or abdominal pain threshold – was a significant predictor of abdominal pain (data not shown).

Discussion

The principal finding of this study is that lubiprostone at a dose of 48 μg per day does not have a significant impact on the sensory thresholds for pain or urgency to defecate. Sensory decision theory, which separates psychological and neurosensory influences on pain reporting, likewise failed to show a difference between lubiprostone and placebo. These data confirm the report by Sweetser and colleagues[5] who found no significant effect of lubiprostone on pain sensitivity in 60 healthy controls. Because the Sweetser study was conducted in healthy subjects and tested pain sensitivity after only 3 days of taking 24 μug of lubiprostone per day, it was possible that an effect might have been missed. However, in our study no difference in sensory thresholds was seen although 92% of subjects had moderate to severe IBS symptoms, they were treated for 14 days before testing, and a higher daily dose of 48 μg per day was administered. Thus, it is unlikely that lubiprostone has an effect on visceral sensory thresholds.

A second aim of this study was to determine whether the effects of lubiprostone on clinical pain in IBS patients is mediated by changes in transit time or by changes in pain sensitivity. However, no significant reductions in the average intensity of abdominal pain were found when comparing lubiprostone to placebo. This was not a consequence of poor adherence or the absence of a clinical response to drug: lubiprostone had the expected effect of significantly changing stool consistency towards softer or looser stools and compliance with medication use was very good.

We did not observe a significant difference in transit time as measured by the Sitzmark study between lubiprostone and placebo intervals despite the significant difference in stool consistency ratings. This was unexpected since a previous study showed a significant acceleration of colonic transit time by lubiprostone[18]. This earlier study used a different method for measuring colonic transit, namely measurement of the distribution of a radioisotope 24 and again 48 hours after ingestion, suggesting the possibility that the Sitzmark transit test used in our study (modified from Abrahamsson and Antov[17]) may have been insensitive. However, we believe this explanation is unlikely because, during the placebo treatment period, we were able to replicate the significant negative correlation between transit time and stool consistency that was previously reported by Lewis and colleagues using a Sitzmark technique[13]. It was only during the lubiprostone treatment

period that transit time showed a non-significant relationship to stool consistency. We speculate that this occurred because the secretion of water into the bowel that is induced by lubiprostone has a direct effect on stool consistency and only an indirect effect on transit time.

A possible limitation of this study is that it may have been underpowered to detect a significant effect of lubiprostone on pain thresholds. Prior to the study we calculated that 62 subjects would be needed to have 80% power to detect a clinically meaningful difference of 6 mmHg in pain thresholds between lubiprostone and placebo, and we enrolled 62 patients. However, missing data, which occurred because some patients requested early discontinuation of the sequence of distentions because of an intolerable urge to defecate, left us with an analysis sample of 42 patients for pain thresholds. Missing data appeared to be random with respect to drug vs. placebo, however, so we believe this is unlikely to have obscured a true effect of lubiprostone on pain thresholds. Moreover, we did not observe an effect of lubiprostone on the urge threshold.

A potential problem with a cross-over design such as the one used here is that treatment effects may carry over from one treatment period to another. To minimize this we introduced a washout period between treatment periods that is known to be much greater than the elimination half-life of lubiprostone in the body[7]. We also tested for carry over effects by administering the IBS-SS questionnaire at the end of washout as well as at the end of each treatment period. This failed to show a significant difference in symptom severity at the end of washout between patients treated with lubiprostone vs. those treated with placebo in the preceding treatment period. In the only study[19] in the literature to systematically evaluate the relapse rate for constipation following 4 weeks of lubiprostone 24 μg twice daily, 44% of patients with chronic constipation who were responders to lubiprostone relapsed by the third week after being switched to placebo. However, the average severity of constipation had not returned to baseline by this time.

Another limitation of the study is that we failed to observe a significant effect of lubiprostone on diary ratings of abdominal pain and other IBS symptoms as others have shown. This may be a consequence of not powering the study to detect these differences.

In conclusion, our data and those of Sweetser et al[5] suggest that the reductions in clinical pain reported in trials of lubiprostone[3, 4] are unlikely to be due to changes in pain sensitivity. Based on our data, we speculate that reductions in clinical pain may be due to changes in stool consistency. This shift towards softer stools may reduce the frequency with which the lumen of the bowel is distended sufficiently to induce pain.

Acknowledgments

Acknowledgment of Financial Support: Supported by grant 07-004L from Takeda Pharmaceuticals North America, Inc., and by National Institutes of Health grants R24 DK067674 and UL1 RR025747

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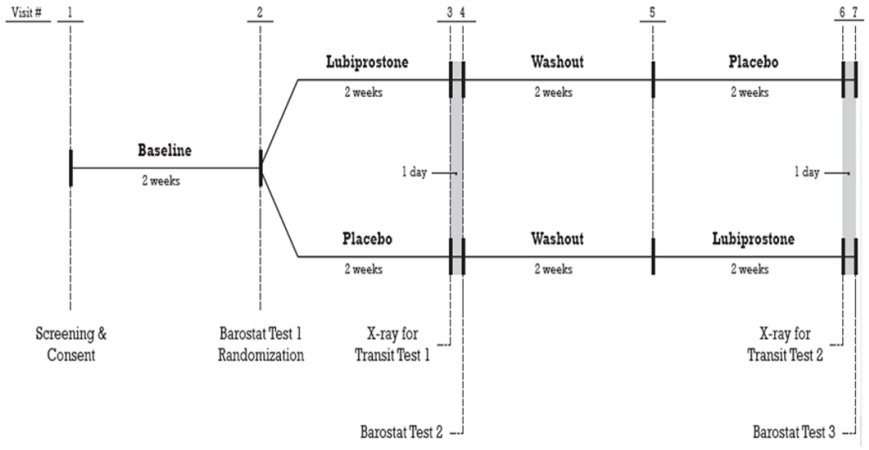

Figure 1.
Study design.

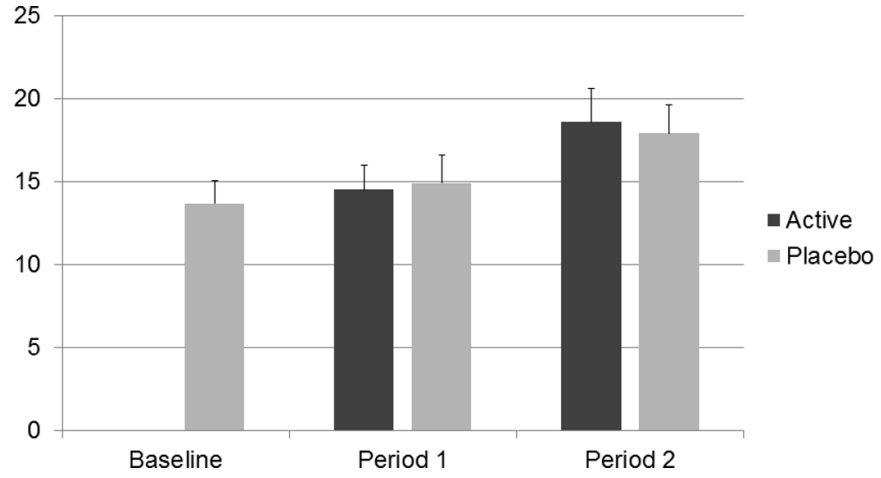

Figure 2.
Thresholds for moderate pain (rating of 3 on a 0–5 scale), determined by the ascending method of limits. Light gray, baseline or placebo; black, lubiprostone 48 ug/day.

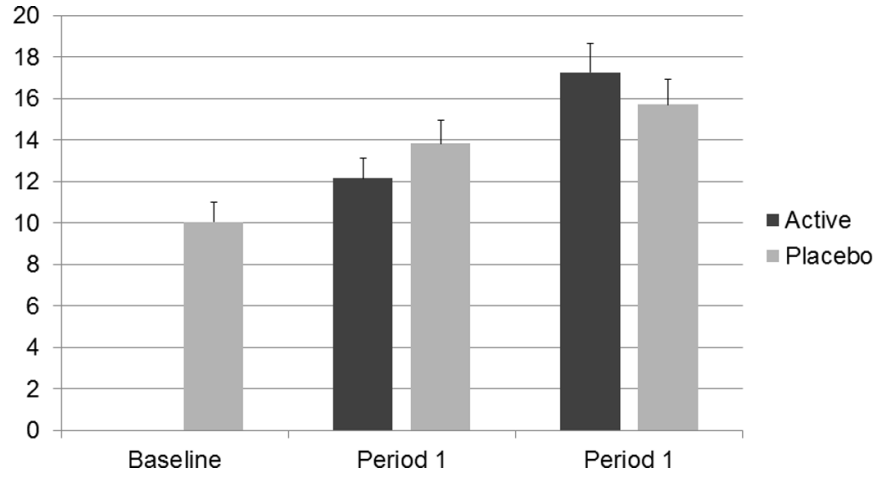

Figure 3.
Threshold for sustained urge to defecate, determinded by the ascending method of limits. Light gray, baseline or placebo condition; black, lubiprostone 48 ug/day.

Table 1

	Number of subjects	Baseline	Treatment Period 1		Treatment Period 2		Drug X Period Interaction (p)
			Active	Placebo	Active	Placebo	
Sitzmark Transit Study:							
Total Sitzmarks on Day 6	62	--	49.25+5.13	60.77+5.30	54.54+5.01	42.84+4.86	.981
Right hemicolon on Day 6	62	--	20.91+2.39	23.63+2.46	22.57+2.75	17.59+2.66	.614
Stool Consistency:							
Average Bristol Score (0–10)	60	3.20+0.15	4.27+0.17	3.41+0.18	4.21+0.17	3.46+0.16	.000
Days with hard/lumpy stools or no stools (%)	60	59.4+3.9	32.4+3.8[D]	50.9+3.9	42.7+3.5	43.5+3.4	.011
Daily Symptom Ratings:							
Pain (0–10 scale)	60	4.08+0.31	4.21+0.33[P]	3.52+0.35	3.28+0.29	3.23+0.28	.136
Bloating (0–10 Scale)	60	4.89+0.30	4.71+0.35	4.29+0.36	3.93+0.36	3.89+0.35	.424
Bowel habit dissatisfaction	60	6.12+0.30	5.47+0.36	5.06+0.35	4.46+0.35	4.43+0.33	.504
Life interference (0–10 scale)	60	3.59+0.31	3.59+0.34[P]	3.02+0.35	3.03+0.26	2.80+0.25	.036
IBS-SS Questionnaire:							
IBS-SS score (0–500)	62	295.65+10.79	266.26+14.66	262.99+15.14	240.90+15.86	233.22+15.36	.643

Table 2

	Baseline	Placebo	Lubiprostone
P(A) for pain	0.58 [CI, 0.55, 0.61]	0.60 [CI, 0.57, 0.63]	0.59 [CI, 0.56, 0.63]
P(A) for urge	0.67 [CI, 0.63, 0.71]	0.68 [CI, 0.65, 0.71]	0.68 [CI, 0.65, 0.72]
B for pain	3.41 [CI, 3.14, 3.67]	3.55 [CI, 3.25, 3.86]	3.47 [CI, 3.17, 3.77]
B for urge	2.44 [CI, 2.18, 2.69]	2.68 [CI, 2.40, 2.95]	2.66 [CI, 2.41, 2.90]