HIGH-RESOLUTION MANOMETRY REVEALS DIFFERENT EFFECT OF POLYETHYLENE GLYCOL, BISACODYL AND PRUCALOPRIDE ON COLONIC MOTILITY IN HEALTHY SUBJECTS: AN ACUTE, OPEN LABEL, RANDOMISED, CROSSOVER, READER BLINDED STUDY WITH POTENTIAL CLINICAL IMPLICATIONS

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Short title: Effect of PEG, bisacodyl and prucalopride on colonic motility

Abbreviations: HRM= high-resolution manometry; HAPCs= high-amplitude propagating contractions; PEG= polyethylene glycol; VAS= visual analogue scale; MI= motility index; SD= standard deviation; LDPS= long distance propagating sequences.

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MC designed the study, performed all the colonic manometry studies, made the quantitative and qualitative analysis of the data and wrote the manuscript.

AT, GP and AH helped to perform the quantitative and qualitative analysis of the data.

ED helped to perform the statistical analysis of the data.

ID performed the colonoscopies to place the manometry catheter

JT designed the study, performed the colonoscopies to place the catheter, contributed to the interpretation of data and provided critical revision of the manuscript.

Competing Interests:

Maura Corsetti is consultant for Allergan, Kyowa Kirin and Sanofi. Jan Tack has given Scientific advice to AlfaWassermann, Allergan, Christian Hansen, Danone, Grünenthal, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Neutec, Novartis, Noventure, Nutricia, Shionogi, Shire, Takeda, Theravance, Tramedico, Tsumura, Zealand and Zeria pharmaceuticals and has served on the Speaker bureau for Abbott, Allergan, AstraZeneca, Janssen, Kyowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda and Zeria

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Abstract

PEG, bisacodyl and prucalopride have been reported to be more effective than placebo in treating patients with constipation but about 50% of the patients still do not respond to these medications. Only bisacodyl and prucalopride are expected to directly stimulate the colonic motility in humans in vivo. As no previous study has done this, the aim of the study was to investigate the effect of PEG, bisacodyl and prucalopride as compared to placebo on colonic motility assessed by means of the high-resolution manometry (HRM) in healthy subjects.

Methods: 10 healthy subjects have been enrolled in an acute, open-label, randomized, reader-blinded, cross-over study and requested to undergo a colonoscopy-assisted HRM measuring their colonic motility before and after oral administration of 13.8 g (two doses) PEG, 10 mg bisacodyl, 2 mg prucalopride and placebo.

Results: in the human prepared colon, oral administration of PEG significantly increases the number of low amplitude long distance propagating contractions (P= 0.007 vs placebo) while bisacodyl significantly increases the number of high amplitude propagating contractions (HAPCs) (all P<0.01 vs PEG, prucalopride and placebo). Prucalopride has no major effect on the number of propagating contractions but increases HAPCs amplitude (P= 0.01).

Conclusions: In humans, PEG, prucalopride and bisacodyl have distinct effects on colonic motility. This information has clinical implication, as it indicates that the combination of prucalopride and bisacodyl, normally not considered in clinical practice, could be effective in treating patients with constipation refractory to single medications.

Key words: prucalopride, bisacodyl, PEG, colon motility, HRM

INTRODUCTION

Chronic constipation is a functional disorder of the gastrointestinal tract, defined by the Rome criteria as a condition with multiple symptoms, including straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction and less than 3 bowel movements (BMs) per week (1). The condition is common, with a prevalence ranging between 4% and 20% in cross-sectional community-based surveys (2). The impact of chronic constipation on quality of life for patients is comparable with that for organic conditions, such as chronic obstructive pulmonary disease, diabetes and depression (2).

The pathogenesis of chronic constipation is unclear but, as alterations of colonic motility have been implicated in the pathophysiology of this functional disorder, the stimulation of intestinal motility has been always considered a relevant target in the treatment of these patients (2). Until recently the main target of colonic stimulation has been the induction of high amplitude propagated contractions (HAPCs). These are contractions normally occurring few times a day in the human colon, especially right after awakening and after meals, which have been associated with defecation (3). However, studies combining the scintigraphy technique and the conventional colonic manometry have demonstrated that the transport of bowel contents also occurs as a consequence of low-amplitude colonic activity (3). Moreover, the recent application of the high-resolution manometry (HRM) to the study of colonic motility has majorly increased the accuracy in detecting colonic motor patterns, in particular the low-amplitude propagating activity (3). Recent papers have demonstrated the presence of two new colonic motor patterns in healthy subjects. The colonic pressurizations consist of low-amplitude pressure increases occurring simultaneously at all colonic sensors with concomitant relaxation at the anal sphincter, which are the most commonly recorded contractions in healthy humans, associated with desire to evacuate gas and/or gas expulsion and are likely to represent the venting system of the human colon (4). The cyclic retrograde propagating activity consist in a sequence of low-amplitude repetitive propagating pressure events which propagated predominantly in a retrograde direction, observed mainly in the recto-sigmoid region, are the most common propagating motor pattern in the healthy colon and they might function as sigmoid brake (5).

Different pharmacological treatments have been demonstrated to be more effective than placebo in treating chronic constipation but about 50% of the patients still do not respond to these medications (2). These include polyethylene glycol (PEG), bisacodyl and prucalopride. They all increase the stool frequency and reduce both straining at stool and hardness of stools, even if their supposed action modality is different. In particular, only stimulant laxatives and prucalopride are supposed to directly act on colonic motility.

PEG is currently the largest selling laxative in multiple regions world-wide. It is an inert polymer that passes virtually unabsorbed through the gut and any eventually absorbed parts are excreted in the

urine. The mechanism of action of PEG, a non-absorbable substance, is to attract water to the lumen and inhibit water absorption due to its increasing effect on the osmotic pressure in the lumen (6). A previous study in patients with constipation has demonstrated that PEG accelerates the transit of contents through the left colon and the rectum but not of the proximal colon, suggesting a possible direct effect of the drug on colonic motility (7). However, when the effect of PEG has been studied by means of the conventional colonic manometry, no effect on colonic motility has been demonstrated in another study in patients with chronic constipation (8).

Bisacodyl is a diphenylmethane derivative demonstrated to have a dual action: an anti-absorptive/secretory effect and a direct prokinetic effect (9, 10). Using intracolonic or rectal instillation, it has been shown that administration of bisacodyl increases motility and induces the occurrence of HAPC within 20 minutes (11, 12, 13, 14). Few studies have investigated the effect of orally administered bisacodyl and have obtained different results, with some studies demonstrating an acceleration of the transit of the right colon (10) and others of the overall colon (15,16). In none of these studies, the effect of oral bisacodyl has been evaluated on motility by mean of colonic manometry but, when its effect has been tested on colonic transit, this has mainly been attributed to its anti-absorptive/secretory action (10).

Prucalopride is highly selective, specific, 5-HT4 receptor agonist with enterokinetic properties (17, 18, 19). In humans, using a scintigraphic technique, Bouras et al. demonstrated that prucalopride accelerates colonic transit in both healthy volunteers and constipated patients (20, 21). Using colonic manometry, De Schryver et al. have demonstrated that prucalopride increases the colonic motility and induces HAPCs in healthy subjects with cleaned colon (22). Moreover, Miner et al have demonstrated that, in the unprepared colon, prucalopride was superior to PEG in inducing HAPCs in patients with chronic constipation (23).

However as almost all the manometry studies have been conducted applying the conventional manometry and none of these have used bisacodyl as comparator, data applying the colonic HRM are needed to achieve a better understanding of the mechanism of action of these drugs in humans. Based on the results of the previous studies, we hypothesized that the effects of PEG on stool frequency and consistency are not due to an increase in colonic motility, whereas that of bisacodyl and prucalopride are. This could implicate either an increase in non-propagating colonic activity or an increase in propagating low and/or high amplitude pressure waves. The aim of this study was to evaluate the effect of three different agents (PEG, bisacodyl and prucalopride) as compared to placebo on colonic motility parameters, as measured by colonic HRM in healthy volunteers.

METHODS

Subjects

We studied 10 healthy subjects (29±3 years, 4 females) with a normal bowel habit defined by presence of bowel movements between two per day to one every two days. None of the subjects had organic or functional disease affecting the gastrointestinal system. None had previous abdominal surgery other than appendectomy and none was taking laxatives or other medications. Each healthy subject and patient gave his/her written informed consent prior to the study, which was approved by the Ethics Committee of the University Hospitals Leuven. The study is registered in the clinicaltrials.gov as NCT03279341.

Study design

All subjects were studied four times according to an open-label, randomized, crossover, reader-blinded study with 10-21 days washout period. The randomization (1:1) schedule was generated before the start of the study by means of a computerized random generator and was given to a research nurse. The clinical investigators were blinded to the treatment assignments until after the data analysis was complete. Participants were recruited from the local community by public advertisement. On day 1 of each treatment period, after a 12-hour fasting period, all subjects were admitted to the Motility Unit for bowel preparation with tap water enemas, and randomized to receive one of the following treatment sequences: A) oral 13.8g PEG 3350 + electrolytes dissolved in 125mL of water twice a day (in the morning and prior to lunch); B) 10 mg bisacodyl as a single oral tablet with 125mL of water in the morning; C) 2 mg prucalopride as a single oral tablet with 125mL of water in the morning: D) placebo as single oral dose with 125 ml of water in the morning. They then underwent a colonoscopy-assisted positioning of the colonic HRM catheter as previously described (4). The catheter consisted of 40, 2.5 cm spaced, sensors. The colonic pressure recording was started and continued for one hour before drug administration, 3 h before and 3 h after a standardized meal (313.8 kcal, two slices of white bread with cheese and butter, and a vanilla pudding (11.6 g protein (14.7%), 13.8 g fat (39.7%), and 35.8 g carbohydrates (45.6%)). During the recording, the subjects were asked to score every 15 min their feeling of abdominal gas, desire to evacuate gas, desire to defecate, urgency to defecate, abdominal discomfort or pain, or any other sensations on a 100 mm visual analog scale (VAS).

Drug dosing

Dosing for PEG for chronic constipation is usually 1 to 2 doses of 13.8 g sachets based on individual response (2). In this study, PEG was dosed twice (13.8g administered in the morning and then prior to a standardized lunch). A 10 mg once a day dose of bisacodyl was used for this study, as previous studies demonstrated a clinical significant effect of this oral dose on constipation symptoms (24).

The prucalopride dose of 2 mg was used for this study, as it is the recommended dose in adults for the treatment of chronic constipation (2). The drugs were administered by a nurse not involved in the conduction of the colonic manometry or in analysis of the tracings.

Data analysis:

The analysis of colonic manometry tracings was reader-blinded and conducted by MC with the help of AT, GP and AH on de-identified recordings that do not specify which treatment (PEG 3350 + electrolytes, bisacodyl or prucalopride) the subject received. As previously reported (4) propagating sequences were qualified as anterograde (anally propagating) or retrograde (orally propagating) and further sub-classified as HAPCs (if the amplitude of two of the propagating pressure waves was ≥100 mm Hg and that of another one was ≥80 mm Hg) or as low-amplitude propagating sequences in the remaining cases. Then low-amplitude sequences were defined as single, cyclic (repetitive propagating sequences), long distance, or simultaneous/ colonic pressurizations. Colonic pressurizations were defined as isolated or repetitive, low amplitude pressure increases simultaneously occurring in all colonic sensors and associated with anal sphincter relaxation (4). Non-propagating activity (pressure changes not associated morphologically or temporally with pressure patterns recorded in adjacent sensors) were also recognized.

Number of propagating and simultaneous sequences, amplitude (mm Hg), duration (seconds), propagation extent (based on the number of sensors involved in the sequence, cm), as well as the colonic site of origin (right colon, left colon, or rectum) were evaluated. In addition an analysis of the colon motor activity was performed as previously reported (4) and used as overall measure of the colonic motor activity and an approximate index of non-propagating activity. Finally the VAS score of different sensations was averaged per period of 15 min starting from the moment the subjects were awake after the recovery period.

Statistical analysis

The outcome parameters were compared by means of student t test for paired and unpaired samples. Differences were considered to be significant at the 5% level and Bonferroni correction was applied to multiple comparisons. Colonic motility index (MI; averaged every 15 min in the right and left colon and in the rectum, and expressed as ratio of the baseline value) of four periods (pre-prandial, first, second and third hour after the meal) was compared between treatments by means of a mixed models analysis with post-hoc t-tests and Bonferroni correction. Sensation VAS scores were also evaluated by means of mixed models. All data are presented as mean ± SD.

Sample size:

As no information were available on the possible effect of PEG, prucalopride and Bisacodyl on colonic motor patterns recently defined by HRM and no previous studies have evaluated the

response to oral bisacodyl, the study was powered on the assumption that bisacodyl would have induced at least one HAPCs in 9 out 10 healthy subjects, as previously reported, when intra-colonic administered (11). Previous studies conducted in prepared colon with placebo, prucalopride and PEG orally assumed have demonstrated that placebo induced HAPCs only in one healthy subject out of 10 and that prucalopride at a higher dose (4 mg) that that planned in the current study (2 mg) and PEG did not induce more HAPCs than placebo (4, 8, 22). It was calculated that to detect a true difference of 80% in the number of subjects developing at least one HAPC in response to Bisacodyl as compared to placebo, prucalopride, and PEG with 80% power and associated type I error probability of 0.017 we had to enroll 10 healthy subjects. We use a type I probability error of 0.017 to account for three active-treatment group comparisons with placebo.

RESULTS

The catheter was clipped to the right colon mucosa in 23/40 studies, and at least to the splenic flexure in the remaining cases, with no difference according to treatment arm. In one subject the administration of prucalopride resulted in the expulsion of the catheter after the occurrence of a HAPC, two hours after the drug administration. In none of the other cases the catheter was displaced at the fluoroscopic control at the end of the study.

Effect of PEG, bisacodyl and prucalopride on the colonic motility index

Baseline MI did not differ between treatments in the right colon (2.6±0.36 for PEG, 3.6±0.72 for prucalopride, 3.6±0.87 for bisacodyl, 3.9±0.26 for placebo, NS), left colon (2.7±0.49, 3.6±0.49, 3.2±0.74, 3.6±0.41, NS) and rectum (2.7±0.53, 4.1±0.79, 3.2±0.81, 3.8±0.50, NS). Using mixed models analysis, a significant treatment effect was found in each region of the colon (all $P \leq 0.001$) (Figure 1 A, B, C). In the right colon, the ratio of the baseline value was significantly higher after PEG ($P=0.01$) and borderline significant after prucalopride ($P=0.05$) as compared to placebo for all the time points after the meal. In the left colon, the ratio was significantly higher after PEG than placebo for all the time points after meal ($P=0.01$). In the rectum, the ratio was significantly higher after PEG than placebo during the first hour after meal ($P=0.01$).

Effect of PEG, bisacodyl and prucalopride on the different colonic motor patterns

Low-amplitude propagating sequences:

Table 1 reports the number of low-amplitude anterograde and retrograde contractions during the treatment with placebo, PEG, bisacodyl and prucalopride.

In the placebo arm the number of retrograde contractions increased after the meal while the anterograde contraction numbers did not change. In contrast, the number of low-amplitude anterograde contractions increased after the administration of PEG, bisacodyl and prucalopride

while the number of retrograde contractions did not change. However, using mixed models, no statistically significant effect of drugs was observed in the number of both anterograde and retrograde contractions. Also, no statistically significant differences were found in low-amplitude characteristics (amplitude, duration and velocity) between different treatments (data not shown).

The total number of long-distance propagating sequences (LDPS) increased numerically during PEG, bisacodyl and prucalopride as compared to placebo, but reached statistical significance only for PEG (P= 0.007) (Figure 2 A). Considering the different observations periods, using mixed models, no statistically significant effect of treatments was found (Figure 2 C). However, in the PEG treatment subgroup, the main increase of LDPS occurred during the prandial period in the PEG condition. Figure 3 reports an example of LDPS observed in a subject after PEG administration.

Pan-colonic pressurizations:

Figure 2 shows the number of colonic pressurizations during the treatment with placebo, PEG, bisacodyl and prucalopride. The total number of colonic pressurizations did not differ between treatments (Figure 2 B). Considering the different observation periods, using mixed models, no statistically significant effect of treatments was found (Figure 2 D). However, when considering the trend in number of colonic pressurization during the different treatments, a significant increase (P= 0.01) followed by a significant decrease (P= 0.005) was observed respectively during the prandial and post-prandial period in the placebo group. Similar trends, even if not statistically significant, were observed in the bisacodyl and prucalopride group, but the increase was already observed in the pre-prandial period after prucalopride administration. In all subjects, periods with repetitive colonic pressurizations were observed as reported in Figure 4. In contrast the number of colonic pressurizations was stable in the PEG group and this was even significantly lower as compared to placebo during prandial period (P=0.001).

High-amplitude propagating contractions:

Bisacodyl induced HAPCs in a significantly higher number of subjects as compared to prucalopride (10 vs. 3, Fisher's exact test P= 0.003), PEG (10 vs. 1, P=0.0001) and placebo (10 vs 1, P= 0.0001). The mean number of HAPCs induced by bisacodyl was 6±3 while only one HAPC appeared in the three subjects after prucalopride. The mean time for the occurrence of first HAPC after administration of bisacodyl was 298±46 min. The amplitude of HAPCs was significantly higher after prucalopride than after bisacodyl (292±14 vs 200±12 mm Hg, P= 0.01), while duration, length and velocity did not differ between treatments (details not shown). Figure 5 shows an example of HAPCs observed after bisacodyl.

Sensations reported during recording

Using mixed models, no significant effect of treatments was found for any sensations between placebo, PEG, bisacodyl and prucalopride, even though the sensations of pain increased at the end of the recording period after bisacodyl coincident with the occurrence of HAPCs (data not shown).

Side effects

The study was generally well tolerated by all healthy subjects. Two healthy subjects (males) reported the occurrence of headache after administration of PEG (45 min before meal in one case and 100 min after meal in the other). One healthy subject (female) reported the occurrence of headache after administration of bisacodyl (100 min after meal) and vomited at the end of the study. One healthy subject (male) reported the occurrence of headache after administration of prucalopride (100 min after meal). He was also reported headache after PEG. In none of this cases was there a need to stop the recording because of side effects. In contrast, two healthy subjects (females) had to stop the study after administration of prucalopride because of nausea and vomiting. One also reported headache after bisacodyl. In both cases, before the start of the episodes of nausea, the colonic manometry recordings showed the presence of repetitive colonic pressurizations starting about 3 hours after the administration of prucalopride and lasting for about 2 hours before the occurrence of symptoms like in Figure 6.

DISCUSSION

To our knowledge, this is the first study comparing the effect of PEG, prucalopride and bisacodyl with placebo in healthy humans. The results show that PEG, prucalopride and bisacodyl have distinct effects on colonic phasic activity. While PEG mainly increases low amplitude phasic activity, bisacodyl mainly induces high amplitude phasic activity, while prucalopride has no major effect on colonic phasic activity but increases HAPCs amplitude and the number of colonic pressurizations. These results were unexpected but in line with past and more recent data of the literature.

PEG is conceptualized to be an osmotic laxative but in the present study the drug, orally administered twice daily, significantly increased the motility index and the number of low-amplitude long-distance propagating sequences. In animal studies these long-distance sequences have been reported to occur in presence of minimal luminal distension by liquids. This suggests that the effect we observed with PEG could be related to the colon distension secondary to increased gut water content. However it should be noted that an old in vitro study conducted on isolated segments of distal rabbit colon has demonstrated that PEG could activate the peristaltic reflex releasing tachykinins and acetylcholine at the level of intrinsic sensory neurons (25). In humans, recent studies using MRI have demonstrated that the administration of PEG, even if at a higher dose in respect to the one used in the present study, increases small bowel water content and induces a distension of the colon

associated with occurrence of strong contractions of the colon (26). As colon distension is one of the known stimuli to activate colonic motility, the present study suggest that a combination of direct effect and indirect action caused by colon distension could be the basis of the effect of PEG in humans.

Bisacodyl has always been recognized to play an important role in the treatment of chronic constipation as previous studies have demonstrated that the intra-colonic administration of the drug was able to induce HAPCs in all the healthy subjects, and bisacodyl is commonly used as rescue therapy in placebo-controlled trials in chronic constipation (2). The bisacodyl administration test is also used in clinical practice to exclude the presence of colonic inertia in patients with refractory constipation subjected to colonic manometry (2). However, the present study is the first confirming that oral administration of bisacodyl is able to induce at least one HAPC in all healthy subjects within a timeframe of a maximum 5-6 hours after the administration. However, the present study does not allow to clarify what the mechanisms behind the stimulation of these contractions are. Recent in vitro studies have demonstrated that the active metabolite of bisacodyl stimulate the secretion in both the small bowel and colon humans samples and increases the tone mainly of longitudinal smooth muscle of the colon (27). However, whether this actually happens in vivo and whether gut distension induced by the accumulation of secretion is involved in the generation of this colonic activity is still unclear.

Prucalopride has been shown to stimulate colonic motility in animals and in humans. However previous studies in humans have concentrated on HAPCs (22,23). The present study is the first to suggest that prucalopride may also have an interesting effect on colonic pressurizations which we recently demonstrated to be the most frequent colonic motor pattern in healthy humans. The present study confirmed recent data about the effect of prucalopride in increasing the amplitude of HAPCs (23). The fact we didn't observe a significant increase of HAPCs after prucalopride could be due to the fact that in contrast to previous studies our study was conducted within a relative short time frame in a prepared colon. Moreover, even if the result did not reach a statistically significant level (probably related to the reduced sample size due to premature interruption of three studies, two for side effects and the other for expulsion of the catheter), we observed the occurrence of repetitive colonic pressurizations in most of our healthy subjects after prucalopride administration. These colonic motor patters have been demonstrated to be induced by neostigmine and to be associated with sensation of desire of expel gas and with actual flatus in healthy subjects (4). Considering prucalopride is a 5-HT4 agonist, the present data seems to confirm the role of acetylcholine in the serotonergic control of these colonic motor events. Recent data acquired in animal studies have suggested that these simultaneous colonic motor patterns could represent the colon motor response to maintained distension of long segment of the large bowel (28). These results could have an interesting clinical implication. Anecdotally, in the experience of the authors, patients using prucalopride refers to a perception of an improvement in their ability to expel gas. This has been also reported in patients with pseudo-obstruction treated with prucalopride (29). As preliminary results also reported an effect

of prucalopride in reducing rectal compliance (30), all together these data could suggest that prucalopride actually increase the physiological colonic motility predisposing the colon to react when also distended by intraluminal content. However these are just speculation at the moment which ongoing studies will have to confirm.

The findings concerning the period preceding the occurrence of nausea and vomiting about three hours after administration of prucalopride are interesting. As demonstrated in Figure 6, the occurrence of nausea and vomiting was preceded by a long period characterized by repetitive colonic pressurizations associated with the subject's feeling of continuous desire to defecate and nausea, which calmed down for about one hour and then restarted culminating in a stronger feeling of nausea and vomiting with the need to stop the test. Whether this suggest that the side effects in two female healthy subjects represent an exaggerated colonic motor response to the medication is unknown, but it would be interesting to understand whether a low dose of prucalopride would have induced a different motor response. Similar considerations apply to the dosage of Bisacodyl.

The present study was conducted in a small group of healthy subjects with a prepared colon after acute administration of pharmacological treatments used in clinical practice to treat patients with functional constipation. These conditions are far from physiological, but this study discloses aspects with potential clinical impact. These medications have been all demonstrated to be more effective than placebo (2). However, in clinical practice, about 50% of patients with chronic constipation do not respond to these medications (2, 31). It is common practice to suggest the combination of stimulant laxatives or prokinetics with osmotic laxatives in patients not responding to a single pharmacological agent. This indication is based on the assumption that the former agents mainly stimulate colonic motility and the latter primarily improve stool consistency. This study shows that actually PEG could exert a synergic effect with bisacodyl stimulating low-amplitude contractions while bisacodyl triggers the HAPCs. However, the most interesting implication is that also the combination of prucalopride with bisacodyl should be considered. This study demonstrates that they act on different colonic motor patterns and the first could actually lower the threshold for colon motor reaction to bisacodyl. In this regard, it is interesting to note that in the prucalopride pivotal studies it was observed that 92% of patients refractory to constipation who needed to use escape treatment with bisacodyl while they were on the active drug had a bowel movement within 24 hours (unpublished observations). The motility effects observed in the present study provide a plausible mechanistic explanation for such effects. Future studies will need to confirm this but the authors are combining bisacodyl and prucalopride in their patients refractory to these single medications with positive results.

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Table 1. Table 1 reports the number of low-amplitude anterograde and retrograde contractions during the treatment with placebo, PEG, bisacodyl and prucalopride. Data are mean±SD.

Treatment Arm	Type of low-amplitude contractions	Recovery Period	Pre-prandial Period	Prandial Period	Post-prandial Period
Placebo	Anterograde	1±1	8±1	4±1	7±2
	Retrograde	0.6±1	2±2	11±2	13±2
PEG	Anterograde	2±0.1	10±1.3	4±0.4	17±1.8
	Retrograde	1±1.0	3.8±0.3	1±1	5.5±0.5
Bisacodyl	Anterograde	1.6±0.05	14±1.6	4±0.2	8.8±0.3
	Retrograde	1.5±0.09	6.3±0.6	3.5±0.2	4.3±0.3
Prucalopride	Anterograde	3.5±0.2	6.3±0.7	2±1	6.8±0.5
	Retrograde	1±1	8±0.8	1.6±0.1	5±0.6

FIGURE LEGENDS

Figure 1. Motility index (MI) of the right, left colon and rectum during the pre-prandial and postprandial period after the administration of PEG, bisacodyl, prucalopride and placebo. Data are mean±SD. *P= 0.01 vs placebo.

Figure 2. Total number of low-amplitude long distance propagating sequences (LDPS) (panel A) and colonic pressurizations (Panel B) and number of LDPS (panel C) and colonic pressurizations (panel D) during the pre-prandial and postprandial period after the administration of PEG, bisacodyl, prucalopride and placebo. Data are mean±SD. *P< 0.01 vs placebo.

Figure 3. Color plot example of repetitive low-amplitude long distance propagating sequences (LDPS) after the administration of PEG in one subject.

Figure 4. Color plot example of repetitive colonic pressurizations after the administration of prucalopride in one subject.

Figure 5. Color plot example of repetitive HAPCs after the administration of bisacodyl in one subject. In this case the first HAPC appeared 5.30 hours after Bisacodyl consumption.

Figure 6. Panel A. Color plot tracing of the period preceding the occurrence of actual vomiting (total of three hours) after the consumption of prucalopride in one subject. Note that occurrence of repetitive colonic pressurizations starting about 3 hours after the assumption of prucalopride and lasting for about 2 hours. During this period the subjects reported the feeling of continuous desire to evacuate gas and nausea, this period was followed by another where pressurizations stopped, to restart about 1 hours later, triggering again the feeling of nausea and actual vomiting. Panel B. Color plot tracing of two 2-minute periods of the tracing reported in Panel A. Note the presence of three colonic pressurizations (blue arrows) associated with anal sphincter relaxation and of artefacts associated with anal sphincter contraction (red arrows). The colonic pressurizations present superimposed low-amplitude long distance propagating sequences starting in the left colon.