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Efficacies of prokinetics and rifaximin on the positivity to glucose breath test in patients with functional dyspepsia: randomized trial

Running head: prokinetics and glucose breath test

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Conflicts of interest

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

YJK, IHJ, CNP: Study concept and design

YJK, CNP: Analysis and interpretation of the data, drafting of the article.

IHJ, JML: Critical revision of the article for important intellectual content

CNP, YJK, IHJ, JML: Final approval of the article.

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List of abbreviations

small intestinal bacterial overgrowth (SIBO), glucose breath test (GBT), functional dyspepsia (FD), positivity (+), hydrogen (H_2), methane (CH_4), negativity (-), postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), irritable bowel syndrome (IBS), irritable bowel syndrome with constipation (IBS-C), irritable bowel syndrome with diarrhea (IBS-D), unspecified IBS (IBS-U), statistically not calculated (NC)

ABSTRACT

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Background and Aim: Prokinetics could eradicate small intestinal bacterial overgrowth. This study aimed to evaluate the efficacy of mosapride, rifaximin, and a combination of mosapride and rifaximin for the treatment of small intestinal bacterial overgrowth.

***Methods*:** We randomly assigned patients with functional dyspepsia diagnosed with small intestinal bacterial overgrowth in a 1:1:1 ratio to receive mosapride, rifaximin, or a combination of both for two weeks. We surveyed the hydrogen–methane glucose breath test and symptom questionnaire before and after the treatment. Primary outcome was eradication rate of small intestinal bacterial overgrowth. Secondary outcomes were changes in the gas concentration, symptoms, and safety.

***Results*:** The eradication rates were 17.2% (5/29) for mosapride, 32.1% (9/28) for rifaximin, and 34.6% (9/26) for the combined groups, with no significant differences among the three groups. Total hydrogen concentration during the glucose breath test significantly decreased in the rifaximin group (P = 0.001). Total methane concentration significantly decreased in the rifaximin and combined groups (P = 0.005). Significant symptomatic improvements were observed in chest and abdominal discomfort with mosapride, in flatulence with rifaximin, and in chest discomfort with the combined groups. Adverse events were similar between the groups.

***Conclusions*:** Although rifaximin has an advantage in reducing gas, mosapride can help to decrease breath hydrogen concentration. Certain intestinal symptoms improved with mosapride alone or combined with rifaximin.

Keywords: Breath test. Mosapride citrate. Prokinetics. Rifaximin. Small intestinal bacterial overgrowth.

INTRODUCTION

Functional gastrointestinal disorders, such as functional dyspepsia (FD) have been linked to

small intestinal bacterial overgrowth (SIBO) (1-3). Major factors, such as impaired intestinal motility and decreased gastric acid or antibacterial secretion can cause SIBO (4). Traditionally, rifaximin has been widely accepted as a primary treatment option (5,6).

Prokinetics or fibers, which are expected to enhance bowel motility, can eradicate SIBO (7-9). Theoretically, drugs with antibacterial and prokinetic effects may maximize their therapeutic effect against SIBO. However, few studies have shown a dual-target therapy for SIBO eradication.

Mosapride citrate, a 5-hydroxytryptamine-4 (5-HT4) agonist, is a representative gastroprokinetic agent that increases gastrointestinal motility and reduces small-bowel transit time (10-12). It is possible that mosapride could be effective as a target or an adjuvant therapy for SIBO.

This study aimed to evaluate the efficacy of mosapride alone, rifaximin, and mosapride combined with rifaximin in patients with FD and SIBO.

METHODS

Study participants

This prospective study was conducted at a teaching referral center. Consecutive patients, aged 20–80 years, who were diagnosed with FD and SIBO and fulfilled the Rome IV criteria and glucose breath test (GBT) were enrolled between September 2017 and December 2019.

Patients who had taken proton-pump inhibitors, histamine-2 receptor antagonists, antibiotics, probiotics, prokinetics, narcotics, laxatives, bulking, or antidiarrheal agents during the previous three months were excluded. Patients with connective tissue, thyroid, or chronic liver diseases; renal insufficiency; major psychiatric disorder; or a history of gastrointestinal surgery, except laparoscopic appendectomy, were excluded (13,14). Patients with inflammatory bowel disease, restless legs syndrome, pancreatitis, or Parkinson's disease, which can affect bowel motility, were also excluded.

This study was approved by the Institutional Research Ethics Board of St. Vincent's

Hospital, Catholic University of Korea (VC16MISI0218). This study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants. This trial was registered on the International Clinical Trials Registry Platform (no. KCT0004994).

Randomization

Eligible patients were randomly assigned to three groups in a 1:1:1 ratio to receive mosapride (Gasmotin®, DaeWoong; 5 mg three times daily), rifaximin (Normix®, Alfa-Wassermann; 400 mg three times daily), or a combination of mosapride and rifaximin for two weeks. Randomization was performed using a computer-generated list of random numbers. An independent staff member assigned the treatments according to consecutive numbers, which were stored in sealed envelopes. All investigators were blinded to the treatment allocation. The patients were also masked to their allocated groups. We used a placebo to administer similar number of drugs to each arm.

Glucose breath test

Hydrogen (H_2) and methane (CH_4) GBT were performed using a gas chromatograph (Breath Tracker SC; Quintron Instrument Company, Milwaukee, WI, USA) after fasting for at least 12 h. The patients were asked to have a low-residue, carbohydrate-restricted diet a day before the GBT, and were instructed to wash their mouth with 20 mL of 0.05% chlorhexidine for 30 min before the GBT. Physical exercise and cigarette smoking were not allowed 2 h prior to and during the test. The patients ingested 75 g of glucose (DIASOL-S SOLN; Taejoon Pharm Co., Ltd., Seoul, Korea). A baseline end-expiratory breath sample was collected before ingestion, and additional samples were collected every 10 min for 2 h. The positivity of GBT for H_2 (GBT (H_2)+) or CH_4 (GBT (CH_4)+), indicating a diagnosis of SIBO, was defined as 1) an increase in breath H_2 level ≥20 ppm above the baseline within the first 90 min, or 2) CH_4 level ≥10 ppm after ingestion of the glucose solution (15).

Intestinal symptom questionnaire

The validated questionnaire included the ROME IV criteria and additional questions regarding individual bowel symptoms (16,17). Thirteen questions about individual bowel symptoms experienced in the preceding four weeks were asked. The frequency and bothersomeness of each symptom were assessed using a 7-point scale from 0 (never) to 6 (always or extremely). Severity of symptoms was evaluated using the total symptom score, which was defined as the sum of symptom frequencies and bothersomeness scores. Thus, the total score for each symptom ranged from 0 to 12.

Outcome measures

Primary outcome was SIBO eradication rate. Secondary outcomes included the total H_2 and CH_4 concentrations during the GBT and symptom scores. Outcomes were measured two weeks after the end of treatment. Drug safety and tolerability were evaluated by recording adverse events, including symptom severity and duration. Patient compliance was determined by counting the doses and number of medications returned. A patient who took 90% of the prescribed medications was considered compliant.

Sample size calculations

Using data from a previous study (9), we calculated the sample size required to detect a 30% increase in the eradication rate in the combined group compared with that in the rifaximin group. With an α-value of 0.05 and a power of 80%, the number of patients needed per group was found to be 31. Assuming a dropout rate of 10%, the final number of patients was 35 per group.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables. One-way analysis of variance (ANOVA) and Tukey post-hoc tests were used to compare the means among the three groups. To assess changes from baseline, the paired t-test was used to compare symptom scores, and the Wilcoxon's signed-rank test was used to compare gas

concentrations due to the skewed distribution of these data. Significance was considered at $P < 0.05$. All statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics

A total of 105 patients were initially enrolled and randomized. Eighty-three participants completed the study (**Figure 1**). Baseline characteristics of the patients are shown in **Table 1**. Glucose breath test (H_2) positivity was 27.6% (8/29) for mosapride, 17.9% (5/28) for rifaximin, and 30.8% (8/26) for the combined groups. Most of the enrolled patients showed GBT (CH_4) +. No significant differences were observed in the GBT results between groups.

Eradication of SIBO

The negative conversion rates of the GBT indicating eradication of SIBO were 17.2% for mosapride, 32.1% for rifaximin, and 34.6% for the combined groups (**Table 2**). In the GBT subtypes, the conversion rates of GBT (H_2) in all the FD patients were 62.5%, 80%, and 62.5%, whereas those of GBT (H_2) in patients with postprandial distress syndrome (PDS) were 83.3%, 75.0%, and 66.7% in the mosapride, rifaximin, and combined groups, respectively (**Table 2**). No significant differences were observed in the conversion rates of GBT (H_2) + and GBT (CH_4) + among the three groups.

GBT profiles

There were no significant differences in the GBT profiles among the groups (**Table 1**). The total H_2 or CH_4 decreased regardless of the treatment modality. Total H_2 was significantly decreased in the rifaxmin group, whereas total CH_4 was significantly decreased in the rifaximin and combined groups (**Table 2**).

Bowel symptoms

There were no significant differences in the mean symptom scores between the groups (data not shown). Mosapride significantly decreased the scores for abdominal and chest discomfort (**Figure 2a**). The flatulence and chest discomfort scores were significantly reduced in the rifaximin (**Figure 2b**) and combined groups (**Figure 2c**).

Adverse events

Serious adverse events were not observed; however, five minor adverse were observed (**Table 3**). There were no significant differences in the incidence of adverse events between the groups.

DISCUSSION

Rifaximin is a common therapeutic drug used for SIBO (18). Rifaximin alone or in combination with mosapride showed an eradication rate of approximately 30%, which was lower than that reported in previous studies. These differences are likely due to the different diagnostic criteria for SIBO. A previous study (15) recommended that a CH_4 level ≥10 ppm is indicative of methanogenic overgrowth, in which the response to rifaximin was relatively low (19).

Prokinectis, such as cisapride, can reduce the prevalence of SIBO (7,20). In our study, the conversion of GBT (H_2) + was >60%. The conversion rate in the mosapride group was not statistically inferior to that in the other groups, and the highest efficacy (83.3 %) was observed in the PDS patients (**Table 2)**. The prokinetic effect on the eradication of SIBO was elucidated. Further studies with larger numbers of patients are required.

Glucose or lactulose can be used as substrates for breath tests, and among these, we conducted a GBT, which can mainly detect proximal SIBO (21,22). In previous studies (23,24), dyspepsia was associated with impaired mucosal integrity in the proximal small

bowel, including the duodenum and jejunum. Accordingly, investigation of SIBO in the proximal small bowel may be more reasonable. Additionally, the prokinetics has the potential to induce rapid intestinal transit, which can cause false positivity in the breath tests. The breath tests using glucose rather than lactulose would lower the false positivity, and have superiority in diagnosing SIBO.

It had been reported that vegetable fiber, which can improve intestinal motility, with rifaximin eradicated SIBO by more than 20% (9). Thus, we hypothesized that dual treatment with prokinetics and antibiotics would maximize the eradication of SIBO. Interestingly, in our study, the addition of mosapride citrate (known to have a direct action on the intestine) to rifaximin did not have a beneficial effect on eradicating SIBO over rifaximin alone. This may be due to differences in drug composition and pharmacodynamics, or only H_2-based GBT. A non-absorbable agent, rifaximin (25), might require a certain amount of time to stay in the bowel to reach the minimum inhibitory concentration for bacteria; this could be hindered by prokinetics inducing rapid intestinal transit. Future studies are needed to determine drug interactions, while investigating intestinal bowel transit or movements.

The gas type and concentration during GBT are associated with intestinal symptoms (26). Hydrogen is associated with diarrhea, whereas CH_4 is related to constipation in patients with irritable bowel syndrome (IBS) (27,28).(순서) In our study, rifaximin significantly reduced both total breath H_2 and CH_4. Although mosapride alone numerically decreased the total gas concentration, it did not significantly reduce both gas types. The combined regimens significantly reduced only the CH_4. Pharmacodynamic interactions between drugs should be considered in the study. Rifaximin may have insufficient time to kill intestinal bacteria because of the rapid intestinal transit from mosapride in the background with elevated breath H_2, which is expected to predominantly cause diarrhea. However, combined regimens have some effect on CH_4 predominant status with delayed transit because mosapride might have a limitation in producing rapid transit to reduce the effect of rifaximin to eradicate SIBO. Considering the gas subtypes, H_2 was significantly decreased in the rifaximin group, and CH_4 was significantly decreased in the rifaximin and combined groups.

Mosapride alone significantly improved the chest and abdominal discomfort, whereas the combined regimens significantly improved the chest discomfort. Few studies have been conducted on medications other than antibiotics to improve symptoms in patients with SIBO. Mosapride could be used for specific symptoms, which might be associated with a decrease in the total gas concentration during GBT by enhancing the contractility of the gastrointestinal tract and promoting the movement of luminal contents, including bacteria, in an anterograde direction, regardless of complete eradication of SIBO. However, FD and IBS can have visceral hypersensitivity, which could also play a role in symptom perception. Whether visceral hypersensitivity affects gastrointestinal symptoms should be explored.

Limitation of this study is as follows: a high dropout rate of approximately 20% was observed in the study, and there were no same-shaped placebo drugs for rifaximin. However, we tried to reduce the bias caused by the drugs by creating similar placebo drugs for each group and administering the same number of drugs. The GBT was analyzed separately by the gas type, but the number of participants with H_2-positivity was limited. Therefore, a large number of patients are required. Additionally, the measurement of intestinal transit time or gastric emptying time for objective gastrointestinal transit evaluation is necessary in future studies.

In conclusion, although rifaximin has the advantage of reducing gas, prokinetics could help decrease the H_2 concentration. Additionally, certain symptoms significantly improved with mosapride alone or in combination with rifaximin. If there is a clinical concern regarding the re-challenge of antibiotics for recurrent SIBO, prokinetics could be another therapeutic option.

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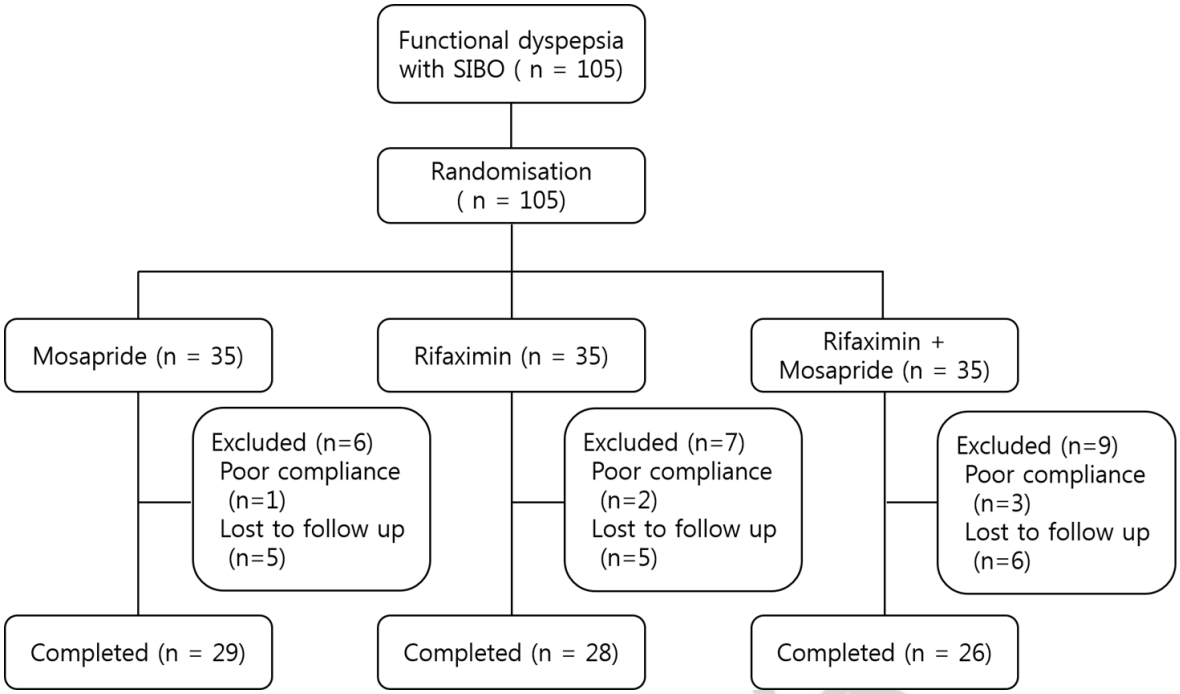

Figure 1. Flow diagram.

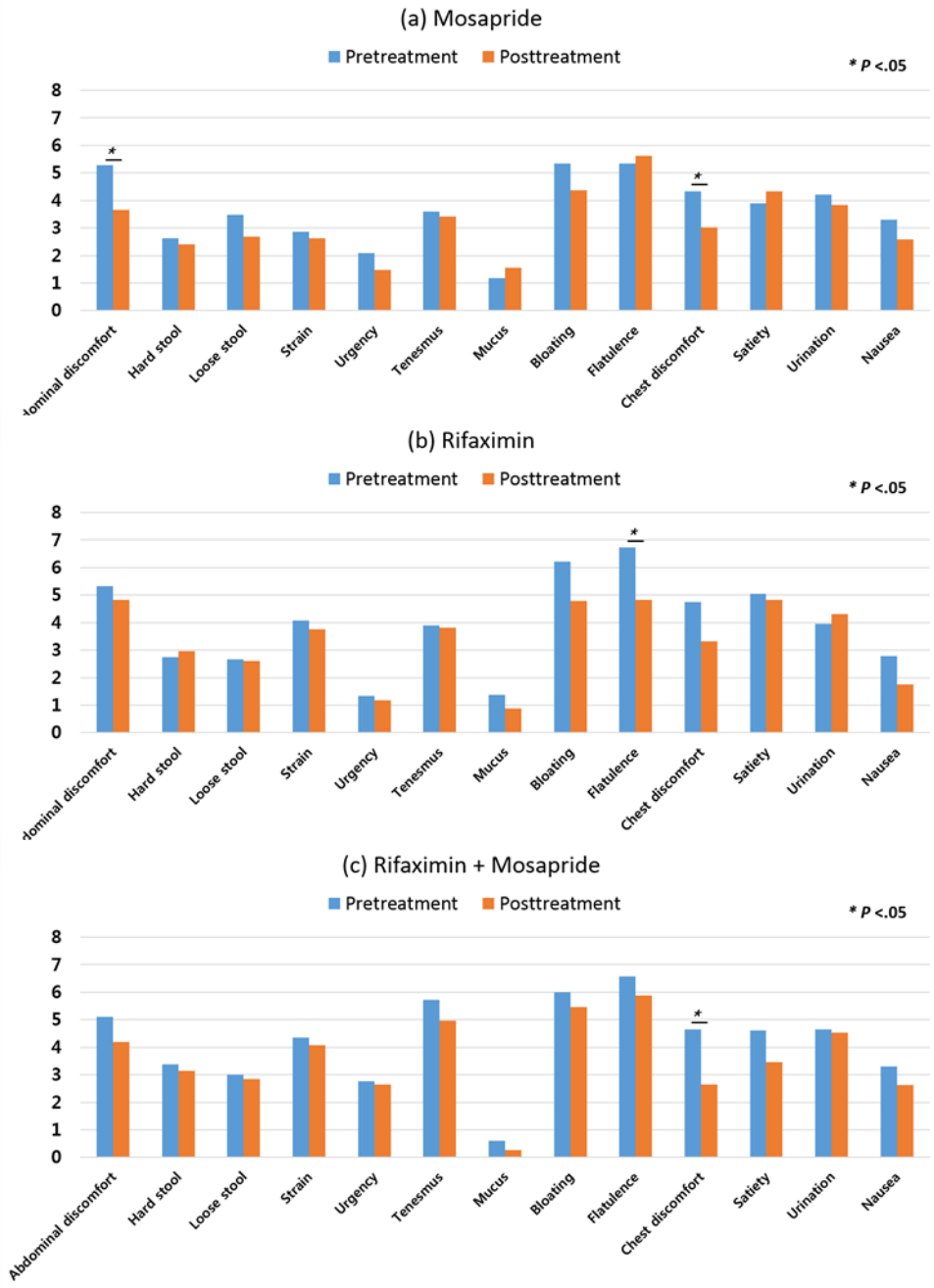

Figure 2. Intestinal symptom scores after (a) mosapride (b) rifaximin (c) rifaxmin plus mosapride treatment

Tables

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Table 1. Baseline demographic

	Mosapride (n = 29)	Rifaximin (n = 28)	Combined (n = 26)	*P* val
Age, year	50.2 ± 13.3	51.3 ± 15.9	51.1 ± 15.4	0.959
Male	10 (34.5)	10 (35.7)	6 (23.1)	0.547
BMI, kg/m^2	22.6 ± 3.0	23.7 ± 3.5	23.8 ± 3.4	0.330
Smoking	3 (10.3)	4 (14.3)	1 (3.8)	0.425
Alcohol	4 (13.8)	6 (21.4)	5 (19.2)	0.743
Diabetes	4 (13.8)	3 (10.7)	2 (7.7)	0.768
Hypertension	6 (20.7)	4 (14.3)	3 (11.5)	0.628
FD				
PDS	19 (65.5)	24 (85.7)	15 (57.7)	0.066
EPS	10 (34.5)	4 (14.3)	11 (42.3)	
IBS overlapped	7 (24.1)	6 (21.4)	10 (38.5)	0.327
IBS-C	0	0	3 (11.5)	
IBS-D	2 (6.9)	3 (10.7)	1 (3.9)	
IBS-U	5 (17.2)	3 (10.7)	6 (23.1)	
GBT profiles				
H_2 positivity,	8 (27.6)	5 (17.9)	8 (30.8)	0.519
CH_4 positivity	29 (100)	26 (92.9)	26 (100)	0.134
Total H_2, ppm	314.3 ± 201.7	279.6 ± 191.8	270.9 ± 204.3	0.690
Total CH_4, ppm	205.8 ± 58.1	216.1 ± 146.6	239.7 ± 178.4	0.642

Bowel symptoms, mean ± SD				
Abdominal discomfort	5.3 ± 3.9	5.3 ± 3.5	5.1 ± 3.4	0.975
Hard stool	2.6 ± 3.4	2.7 ± 2.8	3.4 ± 3.2	0.635
Loose stool	3.5 ± 3.3	2.7 ± 3.0	3.0 ± 2.9	0.618
Strain	2.9 ± 3.4	4.1 ± 3.8	4.4 ± 3.5	0.262
Urgency	2.1 ± 2.5	1.3 ± 2.4	2.8 ± 2.8	0.131
Tenesmus	3.6 ± 3.6	3.9 ± 3.8	5.7 ± 3.6	0.077
Mucus	1.2 ± 2.0	1.4 ± 2.2	0.6 ± 1.4	0.319
Bloating	5.3 ± 3.8	6.2 ± 3.9	6.0 ± 3.8	0.667
Flatulence	5.3 ± 3.6	6.7 ± 3.2	6.6 ± 3.3	0.240
Chest discomfort	4.3 ± 3.2	4.7 ± 3.9	4.7 ± 3.8	0.912
Satiety	3.9 ± 3.4	5.0 ± 3.3	4.6 ± 3.8	0.470
Urination	4.2 ± 3.6	4.0 ± 3.7	4.7 ± 3.8	0.786
Nausea	3.3 ± 3.5	2.8 ± 2.7	3.3 ± 3.6	0.794

BMI, body mass index; FD, functional dyspepsia; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; IBS, irritable bowel syndrome; GBT, glucose breath test; H_2, hydrogen; CH_4, methane

Table 2. Conversion rate of GBT positivity and change of total gas concentration during GBT after treatment

	Mosapride	Rifaximin	Combined*	*P* val
GBT, complete*				
FD	5/29 (17.2)	9/28 (32.1)	9/26 (34.6)	0.289
PDS	4/19 (21.1)	6/24 (25.0)	5/15 (33.3)	0.713
EPS	1/10 (10.0)	3/4 (75.5)	4/11 (36.4)	0.057
IBS	2/7 (28.6)	3/6 (50.0)	3/10 (30.0)	0.660
GBT (H_2)				
FD	5/8 (62.5)	4/5 (80.0)	5/8 (62.5)	0.769
PDS	5/6 (83.3)	3/4 (75.0)	4/6 (66.7)	0.801
EPS	0/2 (0.0)	1/1 (100.0)	1/2 (50.0)	0.233
IBS	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)	NC
GBT (CH_4)				
FD	5/29 (17.2)	8/26 (30.8)	9/26 (34.6)	0.310
PDS	4/19 (21.1)	6/23 (26.1)	5/15 (33.3)	0.721
EPS	1/10 (10.0)	2/3 (66.7)	4/11 (36.4)	0.229
IBS	2/7 (28.6)	3/6 (50.0)	3/10 (30.0)	0.660
Total con†, ppm,				
GBT (H_2)				
Pre-treat	314.3 ± 201.7	279.6 ± 191.8	270.9 ± 204.3	
Post-treat	258.2 ± 250.0	169.7 ± 103.0$^{\$}$	209.8 ± 210.5	
GBT (CH_4)				
Pre-treat	205.8 ± 58.1	216.1 ± 146.6	239.7 ± 178.4	
Post-treat	173.4 ± 99.5	169.6 ± 127.4††	177.5 ± 151.3$^{\$}$	

*conversion of both GBT (H_2) and GBT (CH_4) positivity,

†total concentration of H_2 and CH_4 during GBT before and after treatment ($^{††}P < 0.01$, $^{\$}P < 0.05$)

GBT, glucose breath test; FD, functional dyspepsia; IBS, irritable bowel syndrome; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; H_2, hydrogen; CH_4, methane ; NC, statistically not calculated

Table 3. Adverse events

Adverse events	Mosapride (n = 29)	Rifaximin (n = 28)	Combined* (n = 26)	*P* val
Total, n (%)	1 (3.4)	3 (10.7)	1 (3.8)	0.439

Serious	0 (0)	0 (0)	0 (0)	1.000
Minor	1 (3.4)	3 (10.7)	1 (3.8)	0.439
Bloating	1 (3.4)	0 (0)	0 (0)	
Reflux	0 (0)	1 (3.6)	0 (0)	
Abdominal discomfort	0 (0)	2 (7.1)	1 (3.8)	

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