


ORIGINAL ARTICLE

Risk of small intestinal bacterial overgrowth in patients receiving proton pump inhibitors versus proton pump inhibitors plus prokinetics

Pruthvi C Revaiah,* Rakesh Kochhar,† Surinder V Rana,† Neha Berry,† Munish Ashat,† Narendra Dhaka,† Y Rami Reddy† and Saroj K Sinha† 

Departments of *Medicine and †Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Key words

orocecal transit time, prokinetics, proton pump inhibitor, small intestinal bacterial overgrowth.

Accepted for publication 31 January 2018.

Correspondence

Dr. Saroj Kant Sinha, MD, DM
Professor, Dept. of Gastroenterology,
Postgraduate Institute of Medical Education and
Research, Sector 12, Chandigarh, 160012, India.
Email: sarojksinha@hotmail.com

Declaration of conflict of interest: None.

Author contribution: Dr Pruthvi CR was responsible for literature search, figures, study design, data collection, data analysis, data interpretation, writing. Dr Rakesh Kochhar was responsible for study design, data analysis and data interpretation. Dr Surinder V Rana was responsible for study design, data collection, data analysis, breath tests, and interpretation. Dr Neha Berry and Dr Munish Ashat were responsible for literature search, figures, data analysis, data interpretation and writing. Dr Narendra Dhaka and Dr Y Rami Reddy were responsible for data collection, data interpretation. Dr Saroj Kant Sinha was responsible for study design, data collection, data analysis, data interpretation and writing.

Financial support: None.

Abstract

Background and Aim: Intestinal dysmotility is considered a risk factor for small intestinal bacterial overgrowth (SIBO). Prokinetics improve intestinal motility and are often prescribed with proton pump inhibitors (PPIs) in patients with gastroesophageal reflux disease (GERD) and/or functional dyspepsia. The present study aimed to evaluate the prevalence of SIBO and the orocecal transit time (OCTT) in patients taking PPI compared with those taking PPI plus prokinetics.

Methods: The study is a single-center, cross-sectional study. Enrolled patients (with age > 12 years) were divided into two groups: patients taking PPIs for more than 3 months (Group A) and those taking PPIs with prokinetics for more than 3 months (Group B) for various indications. Lactulose breath test (LBT) for OCTT and glucose breath test (GBT) for SIBO were conducted for all patients.

Results: Of the 147 enrolled patients, SIBO was documented in 13.2% patients in Group A versus 1.8% in Group B, $P = 0.018$. Median OCTT in Group A was 130 (105–160) min compared with 120 (92.5–147.5) min in Group B ($P = 0.010$). Median OCTT among SIBO-positive patients was 160 (140–172.5) min compared with SIBO-negative patients, where it was 120 (103.75–150) min ($P = 0.002$). The duration and type of PPI used were not associated with the occurrence of SIBO in our study.

Conclusion: The use of prokinetics in patients on PPI may reduce the risk of SIBO by enhancing intestinal motility and may reduce SIBO risk associated with long-term PPI use.

Introduction

Proton pump inhibitors (PPIs) are one of the most commonly used prescriptions in outpatient settings. Usual indications for PPI¹ therapy are the presence of a gastroduodenal ulcer, erosive esophagitis, gastroesophageal reflux disease (GERD), Zollinger–Ellison syndrome (ZES), or as part of the treatment regimen for *Helicobacter pylori*. PPIs act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H⁺/K⁺ ATPase or, more commonly, the gastric proton pump) of the gastric parietal cells, thus significantly decreasing gastric acid secretion. Chronic acid suppression with long-term PPI leads to hypochlorhydria, which alters the intraluminal environment to facilitate the growth of the bacterial flora in the small intestine and contributes to the proximal migration of colonic microflora.^{2,3}

Small intestinal bacterial overgrowth (SIBO)⁴ is a clinical condition where the proximal small intestine becomes colonized with an abnormally large (>10⁵/mL) number of gut microflora and is characterized by symptoms of weight loss, steatorrhea, bloating, malabsorption, and vitamin deficiency. Besides the two main predisposing factors of elevated pH and dysmotility, other risk factors for developing SIBO include diabetes, cirrhosis, pancreatitis, irritable bowel syndrome, intestinal stricture, and surgically created blind loop.^{4,5} The gold standard for the diagnosis of SIBO is the culture of intestinal aspirates, but the glucose breath test (GBT) may serve as a cheap, fairly sensitive, highly specific, noninvasive, and simpler surrogate.^{6,7}

Previous studies^{8,9} have demonstrated abnormal small bowel motility in the pathogenesis of SIBO. Dysmotility

encourages the local proliferation of small bowel microflora and delays their distal progression. Prokinetics are a group of drugs that propel food and bacteria through the stagnant colon and may assist with the clinical improvement of patients with SIBO. Prokinetics are often prescribed in conjunction with PPIs in patients with GERD and/or functional dyspepsia. There are, however, no data in the literature on the effect of the continuation of prokinetics with PPIs on SIBO.

The present study aimed to evaluate the prevalence of SIBO and the orocecal transit time (OCTT) in patients taking PPI and compare these outcomes with patients taking both PPIs and prokinetics.

Methods

Study and subjects. The study was designed as a single-center, cross-sectional study. Consecutive patients who were taking PPIs or PPIs with prokinetics (itopride or cinitapride or levosulpiride) for more than 3 months for Food and Drug Association (FDA)-approved indications of PPI were recruited from the outpatient clinic of the Department of Gastroenterology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The study was approved by the Ethics Committee of the Institute, and written informed consent was obtained from all patients. Some of the FDA-approved indications where PPIs can be used for more than 3 months included healing of erosive esophagitis, treatment of GERD, risk reduction for gastric ulcer (GU) associated with nonsteroidal anti-inflammatory drugs (NSAIDs), short-term treatment and maintenance therapy of duodenal ulcers, and pathological hypersecretory conditions like ZES.¹⁰ Disorders for which prokinetics are used include gastroparesis (both disease-related and iatrogenic), GERD, postoperative ileus, constipation, and intestinal pseudo-obstruction.¹¹

Enrolled patients (with age > 12 years) were divided into two groups: *Group A*: patients taking PPIs for more than 3 months for various indications and *Group B*: patients taking PPIs with prokinetics for more than 3 months for various indications. *Exclusion criteria* included age < 12 years, pregnant/lactating women, patients with other comorbidities (type 2 diabetes mellitus, hypothyroidism, celiac disease, chronic pancreatitis, cirrhosis, congestive heart failure or renal failure, small intestinal strictures), those with intake of any antibiotics in preceding 6 weeks, or unwillingness to participate in the study. PPIs used in the study included pantoprazole (40 mg/day), rabeprazole (20 mg/day), and omeprazole (20 mg/day). Levosulpiride was the only prokinetic used at the dose of 75 mg/day. Patient details were recorded on a predesigned proforma. Lactulose breath test (LBT) for OCTT and GBT for SIBO were performed for all patients after obtaining consent.

LBT for OCTT. Patients were instructed not to take antibiotics and/or probiotics for 4 weeks before the test and to avoid foods that are likely to generate hydrogen 72 h prior to the test.¹² After a 12-h fast, the patients were asked to brush their teeth before coming for the tests. LBT was started after thorough mouth washing with 40 mL of 1% chlorhexidine solution. Lactulose syrup (10 grams of lactulose) was given to each patient to drink, and breath samples were collected every 15 min for 4 h.

Hydrogen (H₂)/methane (CH₄) breath concentration in parts per million (ppm) was measured by the SC Microlyzer (Quintron, Milwaukee, WI, USA). The time taken for a ≥10 ppm increase in H₂ and/or CH₄ concentrations in two consecutive readings over the fasting value was defined as OCTT. Normal OCTT was measured to be in the range of 75–105 min as per the prior standardization in our laboratory.¹³

GBT for SIBO. For this test, patients were instructed not to consume a high-fiber diet 72 h prior to the test and to avoid antibiotics or probiotics 4 weeks prior to the test.¹² End-expiratory breath was collected in a one-way valve bag after a 12-h fast. Each patient was given 75 g of glucose in 250 mL water, and breath samples were taken every 15 min for 2 h. An increase of ≥10 ppm over the fasting value in H₂ and/or CH₄ concentrations measured by the SC microlyzer in two consecutive readings was considered evidence of SIBO.¹²

The two groups were compared for various demographic parameters like age, gender, body mass index (BMI), various gastrointestinal symptoms, duration of PPI use, duration of prokinetics use, and so on. Point prevalence of SIBO was assessed in both the groups. OCTT was assessed in both the groups and compared between the groups. The relationship between the risk of SIBO and various parameters was assessed.

Statistical analysis. The data were analyzed using SPSS software (IBM, Armonk, NY, USA). Descriptive statistics, counts, and mean ± standard deviation (or median with interquartile range if nonparametric distribution) were used to describe the study sample. The statistical test used for the analysis of categorical data was the Chi-square test if the expected number in all the cells was likely to be >5. If it was less than 5, then Fisher's exact test was used. Numerical data were compared using student t-test across the groups. Numerical data that did not follow a normal distribution were analyzed using the Mann–Whitney *U* test. SIBO in individuals taking PPIs was compared with those individuals taking PPIs with prokinetics. A *P*-value less than 0.05 was considered to be significant.

Results

A total of 147 patients taking PPIs alone (Group A) or PPI with prokinetics (Group B) for more than 3 months were studied (baseline characteristics as described in Table 1). Of these, 91 patients were included in Group A, and 56 patients were included in Group B. The mean age of the patients was 41.71 ± 13.17 years, with a median duration of PPI use with or without prokinetic of 6 months (range 4–18 months). Main indications for which PPI/PPI plus prokinetics were prescribed included GERD (124 patients, 84.4%), chronic gastritis (13 patients, 8.8%), and peptic ulcer disease (2 patients, 1.4%). *H. pylori* status (as assessed by histopathology and serology) was negative in patients with peptic ulcer disease. All patients underwent the LBT and GBT. At the time of enrollment in the study, patients were asked about any adverse effects of the drugs; however, no patient reported any significant adverse effect. However, a formal questionnaire to assess adverse effects was not used. All the results are summarized in Table 2, and the comparison of

Table 1 Baseline characteristics of patients on PPI alone (Group A) and PPI with prokinetics (Group B)

	Overall	PPI only Group A	PPI + prokinetic Group B	<i>P</i> -value
Total of subjects (<i>n</i>)	147	91	56	
Mean age (years) (mean ± SD)	41.71 ± 13.17	42.08 ± 12.95	41.13 ± 13.61	0.672
Age range (years)	13–75	13–75	16–75	
Female:male	73:74	46:45	28:28	0.948
BMI (range) (kg/m ²)	25.39 (21.46–28.25)	25.00 (21.35–27.68)	26.46 (22.06–26.46)	0.987
Median duration of PPI/PPI and prokinetic intake (months)	6	6	6	
Range of PPI/PPI and prokinetic intake (months)	4–18	4–24	5–16.5	
Indication for PPI/PPI and prokinetic intake, <i>n</i> (%)				
1. GERD	84.4	83.5	85.7	
2. Chronic gastritis	8.8	11.0	5.4	
3. GERD/chronic gastritis	4.8	3.3	7.1	
4. Peptic ulcer disease	1.4	1.1	1.8	
5. GERD/peptic ulcer disease	0.7	1.1		
Symptoms, <i>n</i> (%)				
1. Abdominal discomfort	82.3	82.4	82.1	0.966
2. Bloating	80.3	80.2	80.4	0.984
3. Flatulence	59.9	60.4	58.9	0.856
4. Abdominal distension	43.5	44.0		0.896
5. Diarrhea	22.4	24.2	42.9	
6. Others	Weakness (1.4); hoarseness of voice (1.4)	Weakness (2.2); hoarseness of voice (2.2)	19.6	0.522
PPIs used, <i>n</i> (%)				
1. Rabeprazole	62.6	54.9	75.0	0.015
2. Omeprazole	19	22	14.3	0.249
3. Pantoprazole	18.4	23.1	10.7	0.060
Prokinetics used levosulpiride, <i>n</i> (%)	100	—	100	—

BMI, body mass index; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Table 2 Comparison of OCTT and point prevalence of SIBO in both groups

Parameters	PPI only Group A (<i>n</i> = 91)	PPI + prokinetic Group B (<i>n</i> = 56)	<i>P</i> -value
Duration of PPI (months)	6 (5–16.5)	6 (4–24)	0.236
OCTT (range) (min)	130 (105.00–160.00)	120 (92.50–147.50)	0.010
SIBO, <i>n</i> (%)			
Positive	12 (13.18)	1 (1.78)	0.018
Negative	79 (86.82)	55 (98.22)	
OCTT, <i>n</i> (%)			
Normal OCTT	20 (22.0)	17 (30.4)	0.256
Delayed OCTT	68 (74.7)	34 (60.7)	0.173
Fast OCTT	3 (3.3)	5 (8.9)	0.260

OCTT, orocecal transit time; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.

SIBO-positive with SIBO-negative patients is described in Table 3.

Age and symptoms. SIBO-positive patients were found to be statistically younger (median age 36 years) as compared

to the SIBO-negative subgroup (median age 40.5 years) ($P = 0.046$). The most common symptom in the sample after being on either PPI or PPI with prokinetic for at least 3 months was abdominal discomfort (82.3%) followed by bloating (80.3%). Other symptoms were flatulence (59.9%), abdominal distension (43.5%), diarrhea (22.4%), weakness (1.4%), and hoarseness of voice (1.4%). There was no statistically significant difference in symptoms in either groups or SIBO-negative *versus* SIBO-positive patients.

PPI used in the study. PPIs used in the study were rabeprazole (62.6%), omeprazole (19%), and pantoprazole (18.4%). There was no statistically significant association between a particular PPI and SIBO prevalence. However, pantoprazole use demonstrated a trend toward significant association with SIBO ($P = 0.064$). Similarly, the median duration of PPI in the SIBO-positive group *versus* the SIBO-negative group was 8 (6–24) months *versus* 6 (4–18) months ($P = 0.07$), respectively.

GBT for SIBO. Evidence of SIBO was present in 13 (8.8%) patients, while it was normal in 134 (91.2%) patients. The prevalence of SIBO was greater in Group A (13.18%) than Group B (1.78%) ($P = 0.018$). With regard to GBT, 23.1% ($n = 3$)

Table 3 Comparison of SIBO-positive versus SIBO-negative group

Parameters	SIBO positive (n = 13)	SIBO negative (n = 134)	P-value
Total, n (%)	13 (8.8)	134 (91.2)	0.018
Age, n (range) (years)	36 (25–43.5)	40.5 (33–50.25)	0.046
Diarrhea, n (%)	4 (30.8)	29 (21.6)	0.489
Abdominal discomfort, n (%)	12 (92.3)	109 (81.3)	0.466
Flatulence, n (%)	11 (84.6)	77 (57.5)	0.057
Abdominal bloating, n (%)	12 (92.3)	106 (79.1)	0.465
Abdominal distension, n (%)	8 (61.5)	56 (41.8)	0.170
Gender, n (%)			
Male	8 (61.5)	66 (49.3)	0.398
Female	5 (38.5)	68 (50.7)	
BMI (kg/m ²)	25.33 ± 5.49	25.35 ± 4.65	0.987
Type of PPI, n (%)			
Rabeprazole	8 (61.5)	84 (62.7)	1.000
Omeprazole	0 (0.0)	28 (20.9)	0.130
Pantoprazole	5 (38.5)	22 (16.4)	0.064
Duration of PPI (range) (months)	8 (6–24)	6 (4–18)	0.071
OCTT, n (range) (min)	160 (140–172.50)	120 (103.75–150.00)	0.002
OCTT, n (%)			
Normal OCTT	0 (0.0)	37 (27.6)	0.039
Delayed OCTT	13 (100)	89 (70.6)	0.023
Fast OCTT	0 (0.0)	8 (6)	1.000

BMI, body mass index; OCTT, orocecal transit time; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.

patients had a methane peak, and 76.9% (n = 10) patients had a hydrogen peak.

LBT for OCTT. OCTT was delayed in 102 (69.4%) and was normal in 45 (30.6%) patients. It was delayed in 68 (74.7%) patients in the PPI only group versus 34 (60.7%) patients in the PPI + prokinetic group. Median OCTT was more prolonged in Group A (130 min) compared with Group B (120 min) (P = 0.010). OCTT was more prolonged in SIBO-positive patients compared to SIBO-negative patients (160 min vs 120 min, P = 0.002). None of the SIBO-positive patients had normal OCTT (P = 0.039). OCTT was significantly prolonged among the 12 SIBO-positive patients in PPI group compared to SIBO-negative patients in the PPI group (160 vs 120 [105–150] min, P = 0.006).

Discussion

In our single-center, cross-sectional study on 147 patients, SIBO was documented more frequently (12/91, 13.2%) in Group A (PPI only) than in Group B (1/56, 1.8%, PPI + prokinetics) (P = 0.018). Median OCTT in Group A was 130 (105–160) min compared to Group B, in which it was 120 (92.5–147.5) min (P = 0.010). OCTT was prolonged in 68 of 91 patients (74.7%) in Group A and 34 of 56 (60.7%) patients in Group B. Median OCTT

among SIBO-positive patients was 160 (140–172.5) min compared to SIBO-negative patients where it was 120 (103.75–150) min (P = 0.002).

The symbiotic relation between a human and his or her gut microbiome has flourished over millions of years.¹⁴ Human genetics, geography, diet, exposure to antibiotics, and chronic gastrointestinal inflammatory states are some of the major modifiers of gut flora.^{15–18} The two processes that most commonly predispose people to bacterial overgrowth are diminished gastric acid secretion and small intestine dysmotility.^{5,19,20} SIBO is defined as a bacterial population in the small intestine exceeding 10⁵–10⁶ organisms/mL. The use of PPIs has demonstrated a predisposition to SIBO by altering the intraluminal environment and bacterial flora.^{5,21} Many of the studies regarding the prevalence and incidence of SIBO in patients taking PPI have been performed in the Western population, while the data on the southeast populations are limited. Apart from geographical differences, the Indian population has different dietary preferences and is exposed to different environment. Therefore, this population's gut microbiome is different compared to Western populations.²² Hence, the prevalence and severity of SIBO in Indian population may vary. Of 91 patients taking PPI who underwent GBT in our study, 12 patients (13.18%) had SIBO. The percentage of patients positive for SIBO in patients taking PPI was lower compared to previous studies. In earlier studies, Compare *et al.* reported this value to be 11 of 42 (26.19%), Lombardo *et al.* reported it to be 100 of 200 (50%), and Ratuapli *et al.* reported it to be 126 of 566 (22%) (Table 4).^{9,23–30}

We have used GBT for the diagnosis of SIBO instead of LBT as various studies^{12,31} have demonstrated GBT to have greater diagnostic accuracy than LBT. In another study from our center,¹² LBT and GBT were compared to diagnose SIBO among 175 diarrhea-predominant IBS patients and 150 healthy controls. The study concluded that positive GBT for SIBO was significantly higher in patients than controls; however, when using LBT, a positive test was not significantly different in patients and controls. The advantage of GBT is that glucose is readily absorbed in the small bowel and cannot reach the colon, thereby avoiding false positive results. We have used a cut-off increase of ≥10 ppm in H₂ and/or CH₄ concentrations from baseline to indicate a positive breath test. The most frequently used cut-off value for test positivity is 10–12 ppm.³² In the previous studies^{12,13} from our center as well in recent reviews,^{33,34} a cut-off value of 10 ppm from baseline has been used to indicate a positive breath test.

The prevalence of SIBO was low in our study. The prevalence of parasitic infection and gut colonization is higher in Indian and southeast Asian populations as compared to the West.³⁵ This leads to broader diversity and superior stability of gut microbiota, which may explain the decreased prevalence of SIBO in this subgroup.³⁶ Secondly, the southeast Asian patient group is more prone to developing acute diarrhea, which further decreases the concentration of gut microbiota.³⁷ There is also a higher prevalence of SIBO with increasing age as adults have a higher likelihood of gastrointestinal surgery and/or medication use, which may alter the intraluminal environment.³⁸ In addition, factors that increase the risk of SIBO (e.g. altered gut motility, diverticulosis, and atrophic gastritis) are more prevalent in adults. The average age of our patients was 36 years in Group A and

Table 4 Existing literature demonstrating the association of PPI and SIBO

Study and year	Test type	Geography	PPI association with SIBO	Cut-off value (ppm)	Sample size of PPI group	SIBO positives in PPI group (%)	Mean age of whole sample (years)	PPI used	Duration of PPI
Fried <i>et al.</i> (1994) ²⁴	Aspirates	Switzerland	Yes	NA	25	56	53.4	Omeprazole	5.7 weeks of mean duration
Thorens <i>et al.</i> (1996) ²⁸	Aspirates	Switzerland	Yes	NA	19	53	42	Omeprazole	4 weeks
Hutchinson <i>et al.</i> (1997) ²⁹	GHBT	United Kingdom	No	H ₂ > 20	22	45	78.5	Omeprazole	Median duration of 9.5 months.
Pereira <i>et al.</i> (1998) ²⁶	Aspirates	United Kingdom	Yes	NA	8	62.5	76	Omeprazole	8 weeks
Lombardo <i>et al.</i> (2010) ²⁵	GHBT	Italy	Yes	H ₂ > 10	200	50	37	Esomeprazole Lansoprazole Omeprazole Rabeprazole Pantoprazole	Median duration of 36 months
Compare <i>et al.</i> (2011) ²³	GHBT	Italy	Yes	H ₂ > 12	42	26.19	37	Esomeprazole	6 months
Choung <i>et al.</i> (2011) ³⁰	Aspirates	United States	No	NA	249	10	53	NA	NA
Ratuapli <i>et al.</i> (2012) ²⁷	GHBT	United States	No	H ₂ > 20 or CH ₄ > 15	566	22	60.9	NA	NA
Jacobs <i>et al.</i> (2013) ⁹	Aspirates	United States	Yes	NA	65	58.4 (10 ³ CFU/mL) 32.2 (10 ⁵ CFU/mL)	44	NA	NA

CFU, colony-forming unit; GHBT, glucose hydrogen breath test; H₂, hydrogen; CH₄, methane; NA, not available; ppm, parts per million; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.

40.5 years in Group B. Hence, younger age may influence the low number of SIBO-positive results.

The most common symptom in SIBO-positive patients in our study was abdominal discomfort and bloating. This was similar to other previous studies where Sachdev *et al.*¹⁹ and Lombardo *et al.*²⁵ also showed bloating to be the most common symptom. In our study, the point prevalence of SIBO did not differ significantly among the used PPI, namely, pantoprazole, rabeprazole, and omeprazole. However, pantoprazole demonstrated a trend for significant association with SIBO ($P = 0.06$). In previous studies, omeprazole was associated with increased incidence of SIBO in contrast to our study.^{24,26,28,39} Whether a particular PPI increases the risk of SIBO or not needs to be explored.

Small intestinal transit time is delayed in SIBO. Roland *et al.*⁴⁰ demonstrated that patients with underlying SIBO have significant delays in small intestinal transit time compared with those without (6.6 h vs 4 h). Ghoshal *et al.*⁷ demonstrated that OCTT was longer in patients with SIBO than in those patients without SIBO (170 [60–250] min vs 120 [50–290 min], $P = 0.02$). Cumulative evidence suggests that OCTT is delayed in patients with SIBO and comorbid inflammatory bowel disease, gall stone diseases, diabetes and cirrhosis with minimal hepatic encephalopathy compared to the SIBO-negative subgroup in these studies.^{41–44} In our study, median OCTT was more prolonged in the PPI group compared to PPI + prokinetics group (130 [105–160] min vs 120 [92.5–147.5] min, $P = 0.010$). Median OCTT was also significantly prolonged in

SIBO-positive patients compared to SIBO-negative patients (160 [140–172.5] min vs 120 [103.7–150] min, $P = 0.002$). This finding also supports the hypothesis that SIBO is related to slower gastrointestinal transit.

Prokinetic medications¹¹ enhance the contractility of the GI tract, correct gastric dysrhythmias, and promote the movement of luminal contents in the anterograde direction. Prokinetic agents have been shown to improve intestinal motility, and use of this therapeutic approach has been proven to be useful in the reduction of bacterial overgrowth. Prokinetics such as cisapride, erythromycin, metoclopramide, domperidone, levosulpiride, itopride, and cintapride accelerate gastric emptying and improve gastrointestinal symptoms in patients with functional dyspepsia. In our study, all the patients in Group B ($n = 56$) were using levosulpiride as a prokinetic. Mulyadi *et al.*⁴⁵ from Indonesia showed that SIBO occurred in 61.8% patients on placebo compared to 2.9% on domperidone. Similarly, in the present study, SIBO occurred in fewer patients (1.8%) taking levosulpiride with PPI compared to patients taking PPIs alone (13.2%), $P = 0.018$. We did not come across any other study documenting the incidence of SIBO in patients on prokinetics with PPI compared to PPI alone and whether the addition of prokinetic to a PPI reduces the incidence of SIBO.

Long-term PPI intake is associated with SIBO. The median duration of drug intake in our study was 6 (4–24) months in Group A and 6 (5–16.5) months in Group B. Median duration of PPI in the SIBO-positive group versus the SIBO-negative

group was 8 months *versus* 6 months ($P = 0.07$), respectively. Although not statistically significant, these outcomes demonstrate that patients with a longer duration of PPI are more prone to develop SIBO. Compare *et al.*²³ demonstrated that the incidence of SIBO increases when the duration of PPI intake is longer than 6 months, which is in concordance with our study. Lombardo *et al.*²⁵ demonstrated that the incidence of SIBO increases when the median duration of PPI treatment is longer than 12 months (2 months–7 years). It is possible that the risk of SIBO increases with increasing duration of PPI use secondary to profound hypochlorhydria, but this needs to be studied further. In our study, the duration of intake of PPI did not differ significantly between the two groups. Thus, the observed difference in the point prevalence of SIBO cannot be attributed to this factor.

Functional dyspepsia and IBS are known to have an underlying dysmotility as a contributing factor, and prokinetics may be useful for its treatment. Even though chronic gastritis and peptic ulcer are not standard indications for prokinetics, in our practice, like most countries in Asia and Far East, a trial of prokinetics is given to patients not responding to PPI alone in view of underlying intestinal dysmotility. In addition, ours being a tertiary referral center, most patients referred have already been on PPI for variable duration without significant relief in symptoms. Hence, these patients were given a trial of prokinetics. Our study has demonstrated that use of PPI with prokinetics may reduce the risk of SIBO occurrence. This occurs by possibly enhancing intestinal motility, as shown in the study, by shortening of OCTT in the prokinetic group. Addition of prokinetics may also reduce SIBO risk observed with long-term PPI use. However, the long-term use of commonly used prokinetics like levosulpiride, cisapride, domperidone, and metoclopramide is associated with adverse effects like extrapyramidal symptoms, hyperprolactinemia, and arrhythmias. Hence, the risk–benefit ratio should always be assessed when adding prokinetics for prolonged periods for these indications.

Our study inherently has some limitations. We have used GBT to diagnose SIBO. However, despite its limitations, the current gold standard for diagnosis is a culture of aspirates. Secondly, we studied only the point prevalence of SIBO and OCTT after prolonged use of PPI or PPI with prokinetics. Whether any of these patients had pre-existing SIBO prior to starting the drugs remains uncertain as baseline GBT was not conducted and cannot be answered with the present study design. Furthermore, it is possible that the risk of SIBO increases with increasing duration of PPI use. To document this, future studies would need to enroll the patients prospectively before starting the drug and follow them regularly, with an assessment of OCTT and SIBO at a certain intervals, say every 3 months or so. Such a study can also assess the clinically relevant consequences of SIBO in this group of patients. The present study has created the base for the design of such a study.

Conclusion

Our study is the first study from India to show shorter OCTT and lower prevalence of SIBO in patients on both PPI and prokinetics compared to patients on PPI alone. This finding supports the hypothesis that SIBO is related to slower gastrointestinal transit. The duration and type of PPI used were not associated with the

occurrence of SIBO in our study. Hence, the addition of prokinetics to the treatment of patients on PPI may reduce the risk of SIBO associated with the prolonged use of PPI; however, it would be prudent to look for the side effects of prokinetics in patients who receive these for a prolonged period.

References

- 1 Fock KM, Ang TL, Bee LC, Lee EJ. Proton pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? *Clin. Pharmacokinet.* 2008; **47**: 1–6.
- 2 Theisen J, Nehra D, Citron D *et al.* Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. *J. Gastrointest. Surg.* 2000; **4**: 50–4.
- 3 Williams C. Occurrence and significance of gastric colonization during acid-inhibitory therapy. *Best Pract. Res. Clin. Gastroenterol.* 2001; **15**: 511–21.
- 4 Krajicek EJ, Hansel SL. Small intestinal bacterial overgrowth: a primary care review. *Mayo Clin. Proc.* 2016; **91**: 1828–33.
- 5 Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol. Hepatol. (N.Y.)* 2007; **3**: 112–22.
- 6 Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology.* 1988; **95**: 982–8.
- 7 Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. *Indian J. Gastroenterol.* 2006; **25**: 6–10.
- 8 Vantrappen G, Janssens J, Hellemans J, Ghooys Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. *J. Clin. Invest.* 1977; **59**: 1158–66.
- 9 Jacobs C, Coss Adame E, Attaluri A, Valestin J, Rao SS. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. *Aliment. Pharmacol. Ther.* 2013; **37**: 1103–11.
- 10 Yadlapati R, Kahrilas PJ. When is proton pump inhibitor use appropriate? *BMC Med.* 2017; **15**: 36.
- 11 Quigley EM. Prokinetics in the management of functional gastrointestinal disorders. *J. Neurogastroenterol. Motil.* 2015; **21**: 330–6.
- 12 Rana SV, Sharma S, Kaur J, Sinha SK, Singh K. Comparison of lactulose and glucose breath test for diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Digestion.* 2012; **85**: 243–7.
- 13 Rana SV, Sharma S, Sinha SK, Prasad KK, Bhasin DK, Singh K. Orocecal transit time in patients with celiac disease from North India: a case control study. *Trop. Gastroenterol.* 2008; **29**: 98–100.
- 14 Daliri EB, Wei S, Oh DH, Lee BH. The human microbiome and metabolomics: current concepts and applications. *Crit. Rev. Food Sci. Nutr.* 2017; **57**(16): 3565–76.
- 15 Rowland IR. Factors affecting metabolic activity of the intestinal microflora. *Drug Metab. Rev.* 1988; **19**: 243–61.
- 16 Simon GL, Gorbach SL. The human intestinal microflora. *Dig. Dis. Sci.* 1986; **31**(Suppl. 9): 147S–62S.
- 17 Eckburg PB, Bik EM, Bernstein CN *et al.* Diversity of the human intestinal microbial flora. *Science.* 2005; **308**: 1635–8.
- 18 Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012; **486**: 207–14.
- 19 Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. *Ther. Adv. Chronic Dis.* 2013; **4**: 223–31.
- 20 Bures J, Cyrany J, Kohoutova D *et al.* Small intestinal bacterial overgrowth syndrome. *World J. Gastroenterol.* 2010; **16**: 2978–90.

- 21 Lo WK, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. *Clin. Gastroenterol. Hepatol.* 2013; **11**: 483–90.
- 22 Dehingia M, Devi KT, Talukdar NC *et al.* Gut bacterial diversity of the tribes of India and comparison with the worldwide data. *Sci. Rep.* 2015; **5**: 18563.
- 23 Compare D, Pica L, Rocco A *et al.* Effects of long-term PPI treatment on producing bowel symptoms and SIBO. *Eur. J. Clin. Invest.* 2011; **41**: 380–6.
- 24 Fried M, Siegrist H, Frei R *et al.* Duodenal bacterial overgrowth during treatment in outpatients with omeprazole. *Gut.* 1994; **35**: 23–6.
- 25 Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin. Gastroenterol. Hepatol.* 2010; **8**: 504–8.
- 26 Pereira SP, Gainsborough N, Dowling RH. Drug-induced hypochlorhydria causes high duodenal bacterial counts in the elderly. *Aliment. Pharmacol. Ther.* 1998; **12**: 99–104.
- 27 Ratuapli SK, Ellington TG, O'Neill MT *et al.* Proton pump inhibitor therapy use does not predispose to small intestinal bacterial overgrowth. *Am. J. Gastroenterol.* 2012; **107**: 730–5.
- 28 Thorens J, Froehlich F, Schwizer W *et al.* Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut.* 1996; **39**: 54–9.
- 29 Hutchinson S, Logan R. The effect of long-term omeprazole on the glucose-hydrogen breath test in elderly patients. *Age and aging* 1997; **26**: 87–89.
- 30 Choung R, Ruff K, Malhotra A *et al.* Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. *Aliment. Pharmacol. Ther.* 2011; **33**: 1059–1067.
- 31 Yu D, Chesseman E, Vanner S. Combined oro-caecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects oro-caecal transit, not small intestinal bacterial overgrowth in patients with IBS. *Gut.* 2011; **60**: 334–40.
- 32 Gasbarrini A, Corazza GR, Gasbarrini G *et al.* Methodology and indications of H₂ breath testing in gastrointestinal diseases: the RomeConsensus Conference. *Aliment. Pharmacol. Ther.* 2009; **30**(29 Suppl 1): 1–49.
- 33 Rana SV, Malik A. Breath tests and irritable bowel syndrome. *World J. Gastroenterol.* 2014; **20**: 7587–601.
- 34 Rana SV, Malik A. hydrogen breath tests in gastrointestinal diseases. *Indian J. Clin. Biochem.* 2014; **29**: 398–405.
- 35 Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasit. Vectors.* 2014; **7**: 37.
- 36 Lee SC, Tang MS, Lim YA *et al.* Helminth colonization is associated with increased diversity of the gut microbiota. *PLoS Negl. Trop. Dis.* 2014; **8**: e2880.
- 37 Monira S, Shabnam SA, Alam NH, Endtz HP, Cravioto A, Alam M. 16S rRNA gene-targeted TTGE in determining diversity of gut microbiota during acute diarrhoea and convalescence. *J. Health Popul. Nutr.* 2012; **30**: 250–6.
- 38 Cares K, Al-Ansari N, Macha S *et al.* Risk of small intestinal bacterial overgrowth with chronic use of proton pump inhibitors in children. *Eur. J. Gastroenterol. Hepatol.* 2017; **29**: 396–9.
- 39 Lewis SJ, Franco S, Young G, O'Keefe SJ. Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole. *Aliment. Pharmacol. Ther.* 1996; **10**: 557–61.
- 40 Roland BC, Ciarleglio MM, Clarke JO *et al.* Small Intestinal Transit Time Is Delayed in Small Intestinal Bacterial Overgrowth. *J. Clin. Gastroenterol.* 2015; **49**: 571–6.
- 41 Gupta A, Dhiman RK, Kumari S *et al.* Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. *J. Hepatol.* 2010; **53**: 849–55.
- 42 Kaur J, Rana SV, Gupta R, Gupta V, Sharma SK, Dhawan DK. Prolonged orocecal transit time enhances serum bile acids through bacterial overgrowth, contributing factor to gallstone disease. *J. Clin. Gastroenterol.* 2014; **48**: 365–9.
- 43 Rana S, Bhansali A, Bhadada S, Sharma S, Kaur J, Singh K. Orocecal transit time and small intestinal bacterial overgrowth in type 2 diabetes patients from North India. *Diabetes Technol. Ther.* 2011; **13**: 1115–20.
- 44 Rana SV, Sharma S, Malik A *et al.* Small intestinal bacterial overgrowth and orocecal transit time in patients of inflammatory bowel disease. *Dig. Dis. Sci.* 2013; **58**: 2594–8.
- 45 Mulyadi YGR, Abdullah M, Shatri H. The effect of domperidone on intestinal motility and bacterial overgrowth in patients with liver cirrhosis. *Indonesian J. Gastroenterol. Hepatol. Dig. Endosc.* 2012; **13**: 130–5.