Increased Incidence of Small Intestinal Bacterial Overgrowth During Proton Pump Inhibitor Therapy

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BACKGROUND & AIMS: Proton pump inhibitors (PPIs) can cause diarrhea, enteric infections, and alter the gastrointestinal bacterial population by suppressing the gastric acid barrier. Among patients that received long term PPI treatment, we evaluated the incidence of small intestinal bacterial overgrowth (SIBO; assessed by glucose hydrogen breath test [GHBT]), the risk factors for development of PPI-related SIBO and its clinical manifestations, and the eradication rate of SIBO after treatment with rifaximin. **METHODS:** GHBTs were given to 450 consecutive patients (200 with gastroesophageal reflux disease who received PPIs for a median of 36 months; 200 with irritable bowel syndrome [IBS], in absence of PPI treatment for at least 3 years; and 50 healthy control subjects that had not received PPI for at least 10 years). Each subject was given a symptoms questionnaire. **RESULTS:** SIBO was detected in 50% of patients using PPIs, 24.5% of patients with IBS, and 6% of healthy control subjects; there was a statistically significant difference between patients using PPIs and those with IBS or healthy control subjects ($P < .001$). The prevalence of SIBO increased after 1 year of treatment with PPI. The eradication rate of SIBO was 87% in the PPI group and 91% in the IBS group. **CONCLUSIONS: SIBO, assessed by GHBT, occurs significantly more frequently among long term PPI users than patients with IBS or control subjects. High dose therapy with rifaximin eradicated 87%–91% of cases of SIBO in patients who continued PPI therapy.**

Keywords: PPI; Small Intestinal Bacterial Overgrowth; Glucose Hydrogen Breath Test; Rifaximin.

Proton pump inhibitors (PPIs) are potent drugs producing profound suppression of gastric acid secretion. They are known to have an excellent safety profile. However, suppression of gastric acid barrier raises a number of problems including the overgrowth of bacteria in the stomach and duodenal fluids. PPIs are known to alter the gastrointestinal bacterial population in about 50% of patients on long term treatment with any type of effective antisecretory drug.[1] Based on a large study including 5387 subjects and on a systematic recent review evaluating 2948 patients, gastric acid suppression has been shown to be associated with an increased risk of diarrhea, with an odds ratio of 4.9, and an increased risk of infection with an odds ratio of 2.55.[2,3] So far, however, available data are controversial regarding the relevance of related clinical sequelae. Small intestinal bacterial overgrowth (SIBO) is a clinical condition characterized by different degrees of malabsorption that occurs when the proximal small intestine becomes colonized by a large number ($>10^5$/mL colony-forming units) of endogenous symbiotic bacterial flora normally restricted to the colon. Normally SIBO is prevented by the action of the intestinal immune system, gastric acid and pancreatic enzyme secretion, normal intestinal motility, and ileocecal valve function. Interestingly enough, recently it has been reported that as much as 84% of subjects with irritable bowel syndrome (IBS) have a positive lactulose breath test, suggesting the presence of SIBO.[4,5]

The gold standard for SIBO diagnosis is considered aspiration and culture of duodenal-jejunal content: it measures bacterial load and identifies bacterial species, but it is cumbersome, invasive, and has low reproducibility (as low as 38%) and low sensitivity because of its limited accessibility to the proximal tract of the gut.[6]

Hydrogen breath tests are indirect, surrogate tests for SIBO, yet present several advantages: they are noninvasive, easily repeatable, sensitive enough, and highly specific for SIBO diagnosis.[6–8]

Although current treatment for SIBO is based on empirical courses of broad spectrum antibiotics, high doses of rifaximin have recently been proven to lead to a significant gain in therapeutic efficacy without increasing the incidence of side effects.[9]

Aims of this study were to evaluate in patients on chronic treatment with PPIs: (1) SIBO prevalence, as assessed by glucose hydrogen breath test (GHBT); (2) risk factors for SIBO development; and (3) eradication rate of SIBO after treatment with rifaximin.

Methods

Patients

Between January 2006 and September 2008, 450 consecutive subjects were enrolled in 3 different groups. In group 1 were 200 patients affected by gastroesophageal reflux disease and using PPIs for at least 2 months. Group 2 had 200 patients with IBS (Rome III diagnostic criteria) in absence of PPI treatment for at least 3 years. The rationale for using IBS as "pathologic" control (PC) stands on the large prevalence of SIBO in IBS patients and the overlapping of symptoms between the 2 clinical conditions. In group 3 were 50 healthy subjects, as "normal" controls (NC), in absence of PPI therapy for at least 10 years.

Abbreviations used in this paper: CI, confidence interval; GHBT, glucose hydrogen breath test; IBS, irritable bowel syndrome; NC, normal control; OR, odds ratio; PC, pathologic control; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.

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Constipation and diarrhea were defined according to Rome III criteria.

Patients who used antibiotics in the last 6 months, currently using eukinetics or laxatives, or who had submitted to colonoscopy or barium enema in the last month before test were excluded. Neoplasia, malabsorption diseases, previous gastrointestinal surgery, and metabolic/hormonal disturbances were also exclusion criteria. In diarrhea-predominant IBS, in particular, malabsorption was excluded on the ground of personal and family history, clinical examination, current biochemical tests (vitamins A, D, E, K, B_{12}, abtTG), endoscopy, and imaging procedures.

SIBO Evaluation

Each subject was submitted to GHBT (EC 60 Gastrolyzer 2; Bedfont Scientific Ltd, Rochester, UK) after low carbohydrate diet, an overnight fasting, and chlorhexidine mouthwash. Breath samples were collected before oral administration of 50 g of glucose in 250 mL of water, and after, every 15 minutes for 120 minutes. The accuracy of the Gastrolyzer was ±2% of reading; the sensor sensitivity was 1 ppm.

The test was considered positive and indicative of the presence of SIBO when an increase over the baseline level was >10 ppm, on the basis of validation data from the literature.[10–12]

Gastrointestinal Symptoms

At the entry of the study eligible patients completed a gastrointestinal symptom questionnaire using a 4-point scale consisting of 0: absence; 1: mild; 2: moderate; and 3: severe grade for each of the 5 considered symptoms: pain severity, pain duration, pain frequency, bloating, and constipation/diarrhea.

An arbitrary symptom index was rated by the clinician as mild (0–5), moderate (6–10), or severe (11–15) on the basis of the reported symptoms, by simply adding all parameter scores.

SIBO Eradication

Patients affected by SIBO belonging to PPI and PC groups were treated with rifaximin 400 mg 3 times per day for 2 wks, while continuing PPI therapy. GHBT was reassessed 2 months after the completion of treatment and symptoms were simultaneously recorded. Symptom improvement was defined as a reduction of at least 75% in intensity and frequency.

Physical Examination and Safety Parameters

Each patient was submitted to a thorough physical examination. Peripheral blood cell counts within the last 3 months and any variation in body weight in the last 6 months were recorded at the entry of the study. Any new symptom during rifaximin treatment was also recorded.

The protocol was approved by the Ethical Investigation Committee of our institution, and informed consent was obtained from all patients.

Statistics

Statistical analysis of data was carried out by SPSS software, version 12 for Windows (SPSS Inc, Chicago, IL). For quantitative variables the Mann–Whitney test was used. The χ^2 test with Yates correction was performed to evaluate SIBO prevalence in all studied groups.

Results

Demographics

Overall 450 subjects were evaluated in this study:

- 200 patients with gastroesophageal reflux disease using PPIs (esoprazole 35%, lansoprazole 30%, omeprazole 15%, rabeprazole 10%, pantoprazole 10%): mean age 39 ± 19 years; 120 male, with a median duration of PPI treatment of 36 months (range, 2 months to 7 years), at standard dosage for at least 3 fourths of the considered time. At the observation time 68% of them were *H. pylori* negative.
- 200 patients with IBS (40% diarrhea, 40% constipation, 20% mixed subtypes) as PC, in absence of PPI treatment for at least 3 years, mean age 37 ± 19, 102 male.
- 50 subjects, as NC, mean age 35 ± 16 years, 29 male.

Prevalence of SIBO

Overall, 50% of patients using PPI treatment, 24.5% of patients with IBS, and 6% of NC resulted in SIBO-positive, as assessed by GHBT, the difference being statistically significant (PPI vs IBS: $P < .001$; odds ratio [OR], 3.14; 95% confidence interval [CI], 2.06–4.80; PPI vs NC: $P < .001$; OR, 16.0; 95% CI, 4.8–53.0; IBS vs NC: $P < .005$; OR, 6.12; 95% CI, 3.8–7.5) (Figure 1). The mean time of peak was 58±24 minutes in PPI users, 60±36 minutes in IBS patients, and 62±37 minutes in NC. Plotting the data using the cutoff level of 12[6,8,9] the percent values and statistical significance remained practically unchanged.

Prevalence of SIBO in the age groups was similar except in the 41–60 years range, where SIBO was more frequent in PPI users than in the IBS group ($P < .01$) (Figure 2).

The prevalence of SIBO according to the duration of PPI treatment is shown in Figure 3. Using a logarithmic model for a parametric analysis, the sample dimension was too small to realize a good continuous analysis of the variable "month of PPI treatment" vs SIBO prevalence, and $R^2 = 0.92$ was found.

The difference between group 2–12 months versus group >13 months considered as a whole was statistically significant ($P < .001$; OR, 11; 95% CI, 5.5–21.8).

Severity of SIBO symptoms, as assessed by symptom index, was 100% mild during the first 6 months of PPI treatment.

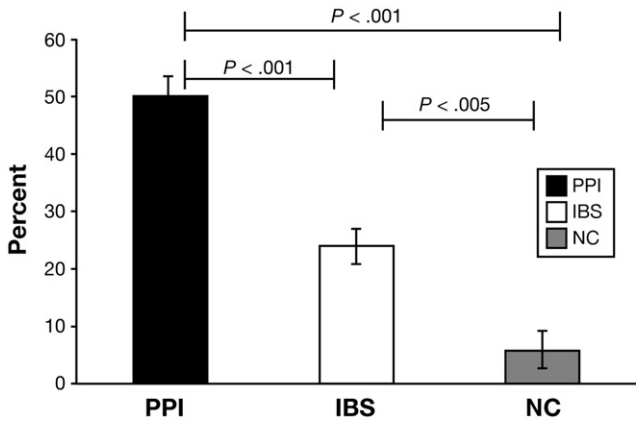

Figure 1. Prevalence of small intestinal bacterial overgrowth (mean value ± standard deviation), as assessed by glucose hydrogen breath test.

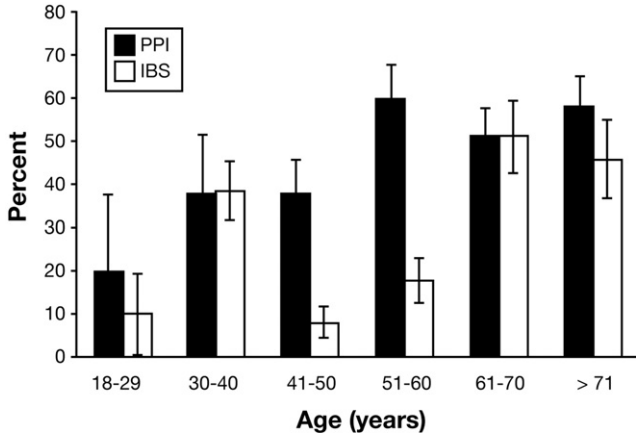

Figure 2. Age distribution (mean value ± standard deviation) in PPI and IBS GHBT-positive patients.

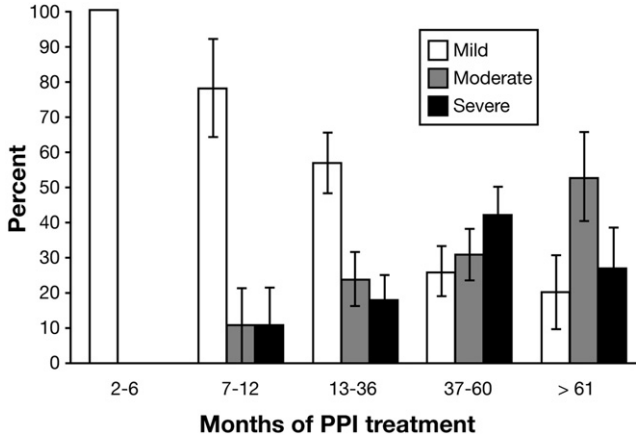

Figure 4. Severity of symptoms (mean value ± standard deviation) assessed by symptom index score in different classes of duration of PPI therapy (months).

Within the first year of treatment severity of symptoms scored moderate in 11% and severe in 11%. In the second and third year symptom index scored mild in half of the cases and moderate to severe in the other half of the cases. After the third year of PPI treatment the severity of SIBO-associated symptoms was moderate in 30% and severe in about 40% of the cases (Figure 4). The symptoms involved were primarily bloating (in about 50% of the cases) and diarrhea (30%): what varied over the observational period of time was their severity. Constipation and abdominal pain accounted for about 10%, respectively, and did not substantially vary over time.

The prevalence of different types of SIBO-related symptoms is shown in Figure 5. Bloating and weight loss were more frequent in the PPI group than in the IBS group in a statistically significant way ($P < .001$). Macrocytic/megaloblastic anemia was more frequent in the PPI group without reaching statistical significance.

SIBO Eradication

Eradication of SIBO, following high-dose rifaximin open-label treatment, as assessed by GHBT, was 87% in the PPI group and 91% in the IBS group (not significant). Eradication of SIBO according to PPI treatment duration was 93% in the group with PPI treatment less than 12 months and 86% in the remaining group (13–60 months), with no statistically significant difference. After SIBO eradication, bloating was improved or absent in 90%, diarrhea in 94%, and abdominal pain in 92% of the cases. In noneradicated patients, bloating was improved or absent in 30%, diarrhea in 35%, and abdominal pain in 20% of the cases. Tolerability of rifaximin was excellent with only 2% of minor side effects (headache, nausea of mild grade) with prompt remission after cessation of treatment.

Discussion

The gold standard for the diagnosis of SIBO is yet to be defined, as direct tests of culture have substantial limitations for accessibility and performance difficulties.[5] Hydrogen breath tests are indirect diagnostic methods based on the fact that detection of hydrogen in expired breath is considered a measure

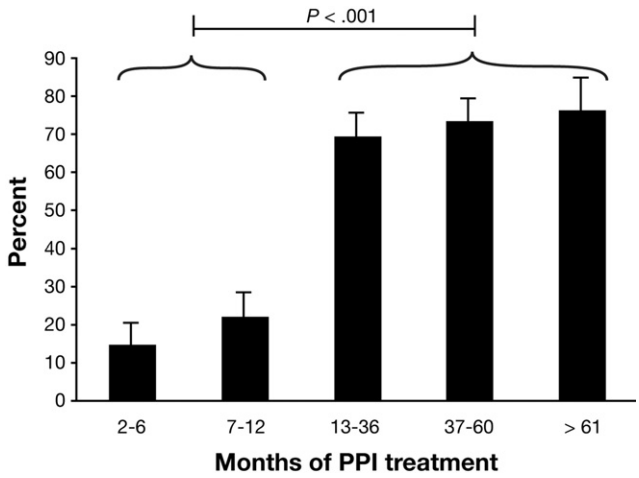

Figure 3. Prevalence of small intestinal bacterial overgrowth (mean value ± standard deviation) in PPI-treated patients according to the duration of therapy.

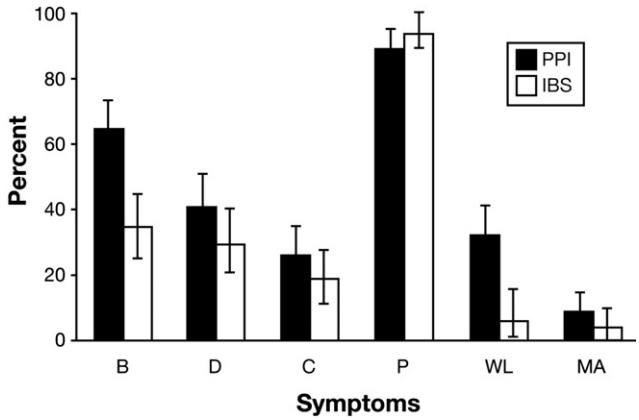

Figure 5. Types of SIBO-related symptoms in PPI and IBS groups. B, bloating; C, constipation; D, diarrhea; MA, macrocytic/megaloblastic anemia (hemoglobin <11 g/dL; mean globular volume >98 fmol; red blood cell count <4,000,000/μL); P, lower abdominal pain (of any degree during the last month); WL, weight loss (>10% during the last 6 months).

of the metabolic acivity of enteric bacteria because mammalian tissues do not generate hydrogen. They are noninvasive, easy to perform, sensitive enough, and highly specific for SIBO diagnosis.[6,7] GHBT was preferred to the lactulose-based test for its higher, although marginal, sensitivity,[6] by minimizing interference from colonic bacteria, and its easier practical interpretation. In this transversal open-label study, SIBO as assessed by GHBT, has been shown to be more frequent in patients on long-term treatment with PPIs than in IBS control and healthy control subjects, in a statistically significant way. This remained true also if 12 ppm was used as the cutoff level.

Other breath test-based studies have reported higher rates of SIBO in IBS patients[12–14] (50%–60% vs 24%), while a study based on culture of jejunal aspirate found a frequency of SIBO of 4% both in patients and control subjects.[15] When a mildly increased bacterial count ($>5 \times 10^3$/mL) was considered in the latter study, SIBO was found to be more common in IBS patients than in control subjects (43% vs 12%; $P = .002$).[15] These discrepancies may be due to methodological and instrumental differences. Moreover, while many studies have excluded the patients using PPIs, none of the studies have explicitly reported the prevalence of PPI exposure in IBS versus healthy control groups, making it very difficult to assess whether PPI exposure could have played any role in influencing the results. This appears to be an important oversight, as PPI use is highly prevalent in patients with IBS. To our knowledge only 4 reports have corrected the results for PPI and found an increased OR of 3.52–7.19 for SIBO,[16,17] of 4.9 for diarrhea,[2] and 2.55 for enteric infections.[3]

Very recently a single study, using lactulose hydrogen breath test, reports no difference between subjects with "current" PPI use (46.2%) and IBS non-PPI patients (56.3%); however, no mention is made of the "duration" of PPI treatment.[18] Indeed, the evidence-based reviews have concluded so far that PPI-related bacterial overgrowth infrequently leads to clinically important disease.[19,20] However, these reviews have focused on overt infections such as *Shigella, Salmonella, Yersinia,* and *Clostridium difficile,* not merely hydrogen breath test positivity. It is conceivable that a broader spectrum of PPI effects exists, revealing an "iceberg phenomenon," with relatively rare events not always correctly recognized, and common, yet covert events below the waterline.[21]

The reason why PPI-related SIBO may be underdiagnosed may reside in the frequent symptoms overlapping, and consequently misleading diagnoses with IBS or other clinical conditions.

This study demonstrates that prevalence of PPI-related SIBO and severity of symptoms increase with the duration of PPI treatment: in other words the longer the duration of PPI therapy, the heavier the consequences of SIBO. This is particularly true after the first year of PPI treatment at standard dose. Bloating and weight loss are more frequent in PPI-related SIBO than in IBS-related SIBO. It is possible that malabsorption of nutrients and a protein-losing enteropathy can play a role.[22] The importance of normal gastric acidity is highlighted by experience in some patients with sclerodermia and reflux esophagitis in whom symptomatic malabsorption developed when PPI therapy was substituted for less effective H2-receptor antagonist therapy.[23] Eradication of SIBO with rifaximin at high dosage for 14 days is satisfactory, and slightly more successful in patients taking PPI for less than 12 months than in patients on more long term PPI treatment. This trend may be due to a more profound, or qualitatively different alteration in enteric microflora after 1 year of continuous PPI treatment.

Eradication of SIBO was more inferior in the PPI group than in the IBS group, although in a statistically nonsignificant way, probably because of the continuation of PPI treatment during antibiotic therapy.

In our study the overall eradication rate of SIBO (87%–91%) is somewhat higher than previously reported (60%–75%).[9,24,25] This is probably due to the longer duration of treatment with rifaximin at high dosage (14 days vs 8–10 days), and to the absence of important comorbidities in the present series. Tolerability of rifaximin was excellent, with only 2% of minor side effects with prompt remission after cessation of treatment.

We didn't assess the recurrence rate of SIBO after successful eradication. However, recent data indicate that relapse of SIBO is independently predicted by the use of concurrent PPI therapy.[16] In other words, so long as the risk factor for SIBO is present, the condition may recur despite temporary removal with antibiotics.

Taking into account that at a pH of 4 most bacteria are killed within 30 minutes,[26] we think that modalities of PPI long term treatment should be tailored according to 2 targets: tissue repair maintenance, and "physiological respect" for gastric pH in order to prevent bacterial transient contamination to shift toward permanent pathological colonization or overt overgrowth.

In this regard, *à la demand* or periodical or less aggressive treatments could result in a lesser SIBO development risk. More studies are clearly needed to test this hypothesis, considering other variables such as actual *H pylori* infection, which is known to increase the effect of PPI on pH elevation. It is worthwhile to remind us that PPIs, at standard effective dosage, almost completely abolish the gastric acid barrier, with an increase in bacterial density more than 1000-fold.[27]

Limitations of this study include observational transversal open-label study design, lack of differentiation between single PPIs, lack of assessment of effects of *H. pylori* status on the SIBO, and lack of predominantly methane-producing bacteria evaluation. Nonetheless we think that it has a major value for having evaluated the role of PPI long-term use in the development of SIBO in patients without influencing comorbidities, and IBS group "free" from PPI use, showing a clear action of PPI in SIBO pathogenesis.

In this setting and under these modalities, treatment with rifaximin has proven to be a clinically useful medication.

Clearly, further studies are needed to assess this complex problem from the etiologic and therapeutic point of view.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.