Treatment of Bacterial Overgrowth in Patients With Irritable Bowel Syndrome

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ABSTRACT

Background: Rifaximin is an effective treatment of irritable bowel syndrome (IBS) with small intestinal bacterial overgrowth (SIBO), yet long-term management has not been well studied. Patients with functional bowel symptoms were characterized by lactulose breath test (LBT), and a comprehensive approach to long-term SIBO therapy was employed.
Methods: On day 0, eligible patients completed a baseline symptom questionnaire and were offered rifaximin 1200 mg/d for 10 days followed by tegaserod 3 mg nightly (long-term) plus 1 month of zinc 220 mg/d and a bifidobacteria-based probiotic once daily. Two months later, patients were administered a follow-up questionnaire regarding symptoms at the time of completion of rifaximin therapy and their current symptoms.
Results: 161 of 212 patients with an abnormal LBT met Rome II criteria for IBS. High-methane producers were more likely to have constipation. After completion of rifaximin treatment, ≥50% improvement from baseline was reported by 72% of patients for abdominal pain, 67% for flatulence, 62% for bloating, 58% for constipation, 56% for diarrhea, and 53% for fullness. Similar results were reported at 2 months. Global IBS symptoms at 2 months were reported by 60% of patients to be moderately or greatly improved. Moderately or greatly improved symptoms were more frequent among high-methane producers (83%) than high-hydrogen producers (56%) or high producers of both methane and hydrogen (44%).
Conclusions: Rifaximin treatment followed by adjunctive therapy was associated with sustained improvement in patients with IBS and SIBO. High-methane producers experienced more frequent constipation and reported greater clinical response compared with high-hydrogen producers.

INTRODUCTION

An estimated range of 10% to 85% of individuals with irritable bowel syndrome (IBS) have small intestinal bacterial overgrowth (SIBO) diagnosed by an abnormal lactulose breath test (LBT) result.[1–5] Disruption of the normal small bowel bacterial population secondary to dysmotility in IBS may result in gas, bloating, flatulence, and altered bowel function.[6] Antibiotic eradication of SIBO, with recent studies correlating normalization of the LBT result, has resulted in symptomatic improvement in IBS.[1–3,7–15] Persistence of an underlying motility disorder of the migrating motor complex in IBS is thought to be responsible for SIBO and symptom relapse.[6,16] Intestinal permeability has been demonstrated to be a persistent problem in postinfectious IBS and may have a role in the inflammatory and hypersensitivity components of IBS.[6,17–18]

Treatment of bacterial overgrowth and IBS with a nonabsorbable antibiotic followed by subsequent prokinetic and intestinal permeability therapy has not been evaluated. The objective of the current study was to assess functional bowel symptoms and characterize patients according to LBT results. This study assessed the response to medical therapy directed at acute treatment and the prevention of recurrence of SIBO.

METHODS

Patients

Patients visiting a private, suburban gastroenterology clinic from June to October 2005 were eligible for treatment with study medication if they had functional bowel symptoms that met

all Rome II criteria for IBS diagnosis[19] and if they had an abnormal LBT result, as defined by Pimentel et al.[3] Patients were excluded if they had active organic gastrointestinal disease (eg, celiac disease, pancreatic insufficiency, Crohn's disease, and ulcerative colitis) on the basis of medical history, physical exams, testing with tissular transglutaminase and total immunoglobulin A for celiac disease, and colonoscopy at study entry.

Study Design and Procedures

This prospective, observational study was conducted at a private gastroenterology group practice. After an overnight fast, patients with functional bowel symptoms of abdominal pain, diarrhea, constipation, bloating, or flatulence visited the clinic on day 0 for symptom assessment and administration of the LBT. As part of the symptom assessment, patients were asked to indicate if they had experienced any abdominal pain, diarrhea, constipation, abdominal bloating, fullness after meals, flatulence, or belching during the previous 7 days. After patients completed the symptom assessment on day 0, the LBT was administered. After a baseline end-expiratory breath sample was obtained, patients drank 10 g lactulose powder (Kristalose™; Mylan Bertak Pharmaceuticals, Inc, Research Triangle Park, NC) in 240 mL water. Breath samples were collected at 15-minute intervals for the ensuing 180 minutes. Samples were analyzed for hydrogen and methane by gas chromatography (QuinTron DP Plus; QuinTron Manufacturing, Milwaukee, Wis).

On day 0, eligible patients completed a baseline symptom questionnaire and were offered rifaximin (Xifaxan®; Salix Pharmaceuticals, Inc, Morrisville, NC) 1200 mg/d for 10 days followed by tegaserod (Zelnorm®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) 3 mg nightly (prescribed for long-term use) plus 1 month each zinc 220 mg/d and a bifidobacteria-based probiotic (Flora-Q®; Kenwood Therapeutics, Fairfield, NJ) once daily. Approximately 2 months after day 0, patients were administered a follow-up questionnaire on which they were asked to indicate, for each functional gastrointestinal symptom present at baseline (ie, abdominal pain, diarrhea, constipation, abdominal bloating, fullness after meals, flatulence, and belching), the percentage of improvement immediately after finishing rifaximin treatment (ie, 10 days after day 0) and at the present time (ie, at the time the questionnaire was completed, approximately 2 months after day 0). In addition, patients were asked to rate their overall symptom improvement at the present time as greatly improved, moderately improved, mildly improved, or no improvement.

Endpoints and Data Analysis

The primary prospectively defined endpoint was the percentage of patients with moderately or greatly improved overall symptoms at 2 months after initiation of the treatment regimen. Other prospectively defined endpoints were (1) the percentage of patients with ≥50% improvement in the individual symptoms of abdominal pain, diarrhea, constipation, abdominal bloating, fullness after meals, flatulence, and belching among patients who had these symptoms at baseline; and (2) the mean percent improvement in individual symptoms of abdominal pain, constipation, bloating, flatulence, and diarrhea among patients with the symptom at baseline. These frequencies were calculated for symptoms at both 10 days and 2 months after initiation of the treatment regimen. Descriptive statistics were used to summarize data for patients with both baseline and follow-up data. Demographics, presence of baseline symptoms, and results for the study endpoints, with the exception of mean percent improvement, were summarized as a function of IBS diagnosis and as a function of breath test result (hydrogen-positive, methane-positive, methane/hydrogen-positive). Mean percent improvement was summarized as a function of breath test result only.

RESULTS

Patients and Breath Test Evaluations

Of 339 patients with functional bowel symptoms screened, 212 (63%) had an abnormal LBT result. In 11 (3%) of the 339 patients, the LBT produced a flatline response (ie, <5 ppm increase in hydrogen or methane over 180 minutes), an abnormal result reflecting hydrogen sulfide production. These patients were excluded from further evaluation. Among patients with an abnormal breath test result at baseline, an abnormal result was observed at 90 minutes in 75% of patients. The remaining 25% of patients required further breath analysis over the 180-minute period before an abnormal result was obtained. The majority of patients with an abnormal LBT result had a high-hydrogen result (75%). Of the 212 patients with an abnormal LBT result, 161 (76%) met Rome II criteria for IBS. Of these 161 patients, 82 (51%) returned evaluable follow-up data and were included in data summaries (Table 1). The mean time between initiation of treatment and completion of the follow-up questionnaire was 64.5 (± 41.8) days.

Baseline Symptoms

The most common symptoms at baseline among 82 patients who provided baseline and follow-up data were abdominal pain, bloating, and flatulence (Table 2). At baseline, 79% of patients complained of constipation, and 72% complained of diarrhea. Additionally, high-methane producers were more likely to have constipation (83%) than diarrhea (50%), whereas diarrhea and constipation were similarly common among high-hydrogen producers.

≥50% Improvement in Functional Bowel Symptoms

After completion of rifaximin treatment (10 days after day 0), ≥50% improvement from baseline was reported by 72% of patients for abdominal pain, 62% for bloating, 67% for flatulence, 56% for diarrhea, 58% for constipation, and 53% for postprandial fullness (Figure 1). A similar pattern of results was reported for symptoms experienced at 2 months after beginning treatment regimen (Figure 1). For symptoms 10 days or 2 months after initiation of the treatment regimen, high-methane producers were more likely to report ≥50% improvement with adjunctive rifaximin therapy than high-hydrogen producers for all symptoms except diarrhea and belching (Figure 2).

Frequency of Moderately or Greatly Improved Symptoms

The percentage of patients reporting moderately or greatly improved overall symptoms at 2 months with adjunctive rifaximin therapy was 60% (Figure 3). Moderately or greatly improved overall symptoms were more frequent among high-methane producers (83%) than among high-hydrogen producers (56%) or high producers of both methane and hydrogen (44%) (Figure 3).

Mean Percent Improvement in Individual Symptoms

Among patients who responded to the questionnaire and had the relevant symptom at baseline (n = 82), mean percent improvement in symptoms at 10 days was 62% for abdominal pain, 53% for constipation, 52% for bloating, 53% for flatulence, and 62% for diarrhea. The corresponding percent improvements in symptoms at 2 months were 58% for abdominal pain, 50% for constipation, 52% for bloating, 51% for flatulence, and 55% for diarrhea. For each symptom, greater mean percent improvement was reported among high-methane producers (67%–84% at 10 days and 61%–82% at 2 months) than among high-hydrogen producers (46%–58% at 10 days and 43%–53% at 2 months).

DISCUSSION

The results of this observational study are consistent with a growing evidence base suggesting that SIBO contributes to IBS symptoms that are amenable to treatment with SIBO-eradicating antibiotics. In the current study and in previous studies,[1–3,7,20] the frequency of SIBO was high among patients presenting with functional bowel symptoms. Among 254 patients meeting Rome II criteria for IBS, 63% had an abnormal LBT result, reflecting the presence of SIBO. A similar percentage of patients with functional bowel symptoms not meeting Rome II criteria had an abnormal LBT result.[15]

This study corroborates previous findings that the LBT gas profile can predict symptom presentation,[21,22] although this observation should be interpreted cautiously given the small number of patients in high-methane subgroups in the current study. In individuals with IBS and SIBO, high-methane producers were more likely to have constipation than diarrhea. Methane has been shown to slow intestinal transit and to reduce postprandial plasma concentrations of serotonin, which mediates peristalsis.[23,24]

In this study, high-methane producers responded better to SIBO therapy than high-hydrogen producers. Moderately or greatly improved overall symptoms 2 months after initiation of comprehensive SIBO therapy were reported by 83% of high-methane producers compared with 56% of high-hydrogen producers and 44% of high producers of both methane and hydrogen. In addition, for individual symptoms, greater mean percent improvement was reported among high-methane producers than among high-hydrogen producers. Together, the results suggest that the LBT profile is clinically important both in predicting clinical symptoms (constipation-predominant vs diarrhea-predominant) and in predicting response to therapy. These possibilities warrant further investigation with a larger number of patients.

Treatment with rifaximin followed by adjunctive SIBO therapy was associated with substantial improvement of functional bowel symptoms in patients with a diagnosis of both IBS and SIBO. The percentage of patients reporting moderate or great improvement in symptoms approximately 2 months after initiation of the treatment regimen was 60%, a substantial response despite not having a comparative placebo arm. The degree to which rifaximin treatment alone accounted for the prolonged improvement in functional bowel symptoms observed in this study cannot be determined given the observational design and the subsequent administration of probiotic, zinc, and tegaserod. Nonetheless, eradication of SIBO by rifaximin and improvement of functional bowel symptoms, as demonstrated in both controlled and open-label IBS studies,[1,2,9,10] is consistent with the possibility that rifaximin contributed to symptom improvement in the current study.

The second phase of SIBO therapy in this study appears to have maintained symptomatic improvement. Long-term tegaserod was given in an attempt to improve the phase III abnormality of the migrating motor complex found in patients with IBS who have SIBO.[17] Zinc was prescribed for 1 month to help reverse defects in small intestinal permeability.[17,24] The bifidobacteria-based probiotic was prescribed to help repair the reported small intestinal permeability and immune defects characteristic of SIBO, IBS, and postinfectious IBS.[17,18,25]

The results of this study should be interpreted cautiously given the aforementioned observational design, which limits the ability to attribute improvements to the treatment regimen. In addition, because the follow-up questionnaire used to assess symptoms at the time of completion of rifaximin (ie, 10 days after day 0) took place approximately 2 months after day 0, recall bias might have affected patients' ratings of early symptom improvement. Patient compliance may also have impacted the results of the study (questionnaires were returned by 82 of the 161 treated IBS patients who had an abnormal LBT result). Furthermore, the extended intervals required to obtain breath test results could have impacted the study findings. An

estimated 25% of patients required the entire 180 minutes of breath analysis to achieve an abnormal result.

In this study, treatment of functional bowel symptoms with rifaximin and adjunctive SIBO therapy was associated with symptomatic improvement among patients with an abnormal LBT result and a Rome II diagnosis of IBS. These results support findings of a double-blind, placebo-controlled trial in which rifaximin 1200 mg/d for 10 days substantially improved global symptoms of IBS compared with placebo (37% vs 20%, respectively).[10] The current study is the first to evaluate comprehensive SIBO therapy in IBS directed at all defects attributed to SIBO pathophysiology (eg, bacterial excess, decreased motility, increased permeability, altered immunity). Benefits were sustained over a mean follow-up period of at least 2 months, and improvement was generally more marked among high-methane producers than high-hydrogen producers. This study supports further investigation of the potential benefits of SIBO therapy in functional bowel disorders.

Table 1. Patient Characteristics and Breath Test Results (n = 161)

Female, n (%)	134 (83)
Mean age (range), y	50 (10–85)[a]
Breath test result, n (%)	
High hydrogen	120 (75)
High methane	27 (17)
High hydrogen and methane	14 (9)

[a] *160 patients ≥ 18 y of age; 1 patient 10 y of age.*

Table 2. Baseline Symptoms in Patients with IBS and Abnormal LBT

Symptom	Patients, n (%)			
	Total (n = 82)	High Hydrogen (n = 55)	High Methane (n = 18)	High Hydrogen and Methane (n = 9)
Abdominal pain	82 (100)	55 (100)	18 (100)	9 (100)
Diarrhea	59 (72)	44 (80)	9 (50)	6 (67)
Constipation	65 (79)	44 (80)	15 (83)	6 (67)
Bloating	77 (94)	51 (93)	17 (94)	9 (100)

Fullness	66 (80)	43 (78)	15 (83)	8 (89)
Flatulence	72 (88)	47 (85)	16 (89)	9 (100)
Belching	46 (56)	31 (56)	8 (44)	7 (78)

IBS = irritable bowel syndrome; LBT = lactulose breath test.

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FIGURE LEGENDS

Figure 1. Majority of patients reported ≥50% improvement in all symptoms from baseline, except belching at 10 days, and belching and diarrhea 2 months after initiation of rifaximin treatment.

Figure 2. High-methane producers reported ≥50% improvement in baseline symptoms more frequently than high-hydrogen producers 10 days after initiation of rifaximin treatment for all symptoms except diarrhea and belching.

Figure 3. Percentage of patients reporting moderately or greatly improved symptoms 2 months after initiation of rifaximin treatment. Data are for patients with symptoms at baseline.