

Results of small intestinal bacterial overgrowth testing in irritable bowel syndrome patients: clinical profiles and effects of antibiotic trial

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Abstract

Purpose: Small intestinal bacterial overgrowth (SIBO) may coexist with irritable bowel syndrome (IBS) and eradication therapy has been reported as effective in reducing IBS symptoms. Aims of this study were to: 1. Assess the clinical profiles of IBS patients, who underwent breath testing with a glucose substrate – glucose breath test (GBT); 2. Evaluate hydrogen and methane parameters in various IBS groups; 3. Assess the role of inhibition of gastric acid in contributing to SIBO; 4. Investigate efficacy and safety of non-absorbable antibiotic rifamixin for eradication and symptom relief.

Methods: 204 IBS patients met the ROME II criteria for IBS (170F & 34M; mean age 46.4; range 18-88) and underwent GBT. 8 of these patients with positive GBT were treated with rifaximin 200 mg, 4 times a day for 1 month and symptom assessments and GBT were repeated.

Results: 93 (46%) had a positive GBT. 68 (73%) of these 93 IBS-diarrhea dominant (IBS-D), 12 (13%) were constipation dominant (IBS-C) and 13 (14%) IBS with alternating bowel pattern. 48% of SIBO positive patients were receiving PPI therapy compared to 40% of IBS patients with negative GBT. 61 (66%) produced only hydrogen, 27 (29%) methane only, and 5 (5%) both-hydrogen and methane. There were more methane producers in IBS-C than IBS-D group (58% vs 28%) while IBS-D had more hydrogen formers (71% vs 42%).

8 patients with SIBO (7F & 1M; mean age 55, range 31-85) received rifamixin 800 mg/day. Repeat GBT was normal in 6 (75%), 1 patient (12.5%) normalized according to hydrogen cri-

teria but methane remained positive. Symptoms score improved in 7 (87.5%) patients and no adverse events were noted.

Conclusions: 1. SIBO was present in nearly half of this large cohort of IBS patients based on the results of GBT; 2. Chronic PPI use was not associated with SIBO; 3. Methane formers on the GBT are more likely to be constipated; 4. Rifaximin is effective in treatment of SIBO in IBS and controlled trials are warranted.

Key words: irritable bowel syndrome, glucose breath testing, rifaximin, proton pump inhibitors.

Introduction

Small intestinal bacterial overgrowth (SIBO) is a condition where there are excessive numbers of bacteria ($>10^5$ bacteria/ml in jejunal fluid), mainly colonic type species present in the lumen of the small bowel. It may be caused by variety of reasons, such as: i) Weak gastrointestinal motility with ineffective clearance permitting colonic flora to migrate proximally, ii) Surgery, such as resection of the ileocecal valve or creation of a blind loop during gastric by-pass predisposes to migration, retention and colonization of the bacteria in the proximal small bowel, and iii) Conditions which are less hostile for the growth of bacteria in the small intestine, e.g., less acidic from the use of proton pump inhibitors (PPI). This overgrowth of microbiota in the small intestine and accompanying malabsorption can cause symptoms such as, diarrhea or constipation, excessive gas production, bloating, and abdominal pain [1,2].

Noninvasive breath tests are widely used to diagnose SIBO. These tests analyze production of gases, which are generated by enteric bacteria and are exhaled after ingestion of a fermentable carbohydrate like glucose or lactulose. Most common detectable gases are hydrogen and methane, which are indicators of bacterial metabolism in gut. Cultures of the jejunal fluid demonstrating $>10^5$ organisms/ml is the current gold standard test for

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diagnosis of SIBO, however, it is usually not practical to carry out in clinical practice. Usually the first step in the treatment of SIBO is to suppress bacterial colonization in the small bowel with a course of broad-spectrum antibiotics. The management may also include therapy for promoting small intestinal motility using prokinetics and/or maintaining proper intestinal flora with probiotics [3].

Rifaximin is a rifamycin derivative with a broad antibacterial spectrum. Less than 0.5% of the oral dose is absorbed and therefore has very low risk of systemic toxicity, adverse events, and drug interactions [4].

Aims of this study were to: 1. Assess the clinical profiles of IBS patients, who underwent breath testing with a glucose substrate – the glucose breath test (GBT); 2. Correlate hydrogen and methane production with various sub-groups of IBS; 3. Assess the role of inhibition of gastric acid in contributing to SIBO; and 4. Investigate efficacy and safety of rifaximin in eradicating SIBO and providing symptom relief from IBS.

Materials and methods

The study was completed in two phases:

Phase I

Subjects: 204 subjects (170 females, 34 males) who met the ROME II criteria for IBS were included in the study. All the subjects were being followed in the functional bowel diseases clinic supervised by one of the authors (RWM). The following procedures were performed in all patients

Clinical data: Demographic data and information regarding the dominant bowel movement pattern with IBS was recorded. Subjects were subsequently sub grouped based on the predominant bowel movement pattern into, IBS-constipation dominant (IBS-C), IBS-diarrhea dominant (IBS-D), and IBS with alternating bowel habits and predominance of gas and bloating (IBS-other). In addition subjects were also asked to comment on their PPI medication usage.

Breath testing: Hydrogen and methane excretion were measured using a glucose breath test (GBT). Patients were asked to have a low carbohydrate dinner on the day before and then fast for at least 12 hours before testing. Use of antimicrobial agents within the previous 4 weeks, pregnancy, and breastfeeding were exclusion criteria. Smoking and heavy physical exertion were not allowed 1 hour prior to the test. Just before sampling, patients used a mouthwash with 40 mL of 1% chlorhexidine. Two samples were obtained at baseline and then at 30, 45, 60, 75 and 90 minutes following ingestion of 50 g of glucose in 150 cc water (iso-osmotic solution). The results of the glucose breath test were analyzed and expressed as mean (+/- SD). For every patient the baseline and peak values for hydrogen and methane were recorded and their total excretion of either hydrogen or methane was calculated as an area under the time-concentration curve.

End expiratory breath samples were taken to ensure alveolar gas sampling using a commercial device (Gasampler Quintron, Milwaukee, WI), which allows the first 500 mL of dead space air to be separated from remaining alveolar air collected in

Table 1. Summary of glucose breath test results

	IBS - total	IBS-D	IBS-C	IBS other	Receiving PPI
GBT positive	93 (45.6%)	68 (73.1%)	12 (12.9%)	13 (14.0%)	45 (48.4%)
GBT negative	111 (54.4%)	81 (73.0%)	18 (16.2%)	12 (10.8%)	44 (39.6%)

Table 2. Specific gas production and IBS subgroups in SIBO patients

	H ₂	CH ₄	Both Gases	Total
IBS-D	48 (70.6%)	19 (27.9%)	1 (1.5%)	68 (100%)
IBS-C	5 (41.7%)	7 (58.3%)	0 (0.0%)	12 (100%)
IBS-other	8 (61.5%)	1 (7.7%)	4 (30.8%)	13 (100%)
Total	61 (65.6%)	27 (29.0%)	5 (5.4%)	93 (100%)

a gas-tight bag. Samples were analyzed immediately after collection. To detect hydrogen and methane in air samples, a gas chromatograph was used (Model DP, Quintron Instruments, Milwaukee, WI). The concentration of hydrogen and methane in the breath was expressed in parts per million (p.p.m.).

The GBT was considered as positive for SIBO if: 1) There was a hydrogen and/or methane peak >20 ppm when the baseline was <10 ppm; or 2) In cases where the patient started with baseline of >10 ppm a further increase of >12 ppm indicated a positive result.

Phase II

The following procedures were done in phase II of the trial:

Subjects: 8 subjects (7 females, 1 male) from the initial cohort of subjects who had a positive GBT were selected for this phase of the study after they agreed to take rifaximin to treat SIBO.

Antibiotic Treatment Protocol: Subjects were asked to take 200 mg of rifaximin four times a day for 4 weeks and were instructed to report any adverse events during the treatment.

Symptom Score: Symptom assessment, and an overall score were obtained by analyzing frequency of stools, abdominal pain, bloating and gas pre and post therapy with rifaximin.

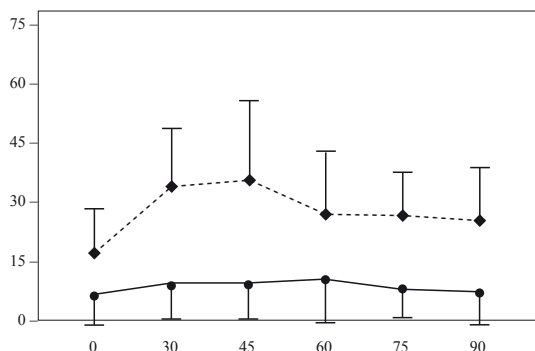
Breath Test: GBT was performed using the above protocol after the completion of the antibiotic treatment. A negative GBT signified the eradication of SIBO.

Results

Mean age of the subjects was 46 years, (range 18-88). 93 (46%) had a positive GBT. 68 (73%) were IBS-D, 12 (13%) had IBS-C and 13 (14%) IBS-other. 48% of IBS patients who had SIBO were receiving PPI therapy compared to 40% without SIBO negative GBT (*Tab. 1*).

With regards to the specific gas production: 61 (66%) produced hydrogen, 27 (29%) methane, and 5 (5%) both-hydrogen and methane (*Tab. 2*). There were more methane producers in

Figure 1. Hydrogen concentration in ppm (X-axis) detected in the breath test before (dashed line) and after (solid line) treatment with rifaximin. Y-axis represents time in minutes



IBS-C then IBS-D group (58% vs 28%) and more hydrogen formers in IBS-D (71% vs 42%).

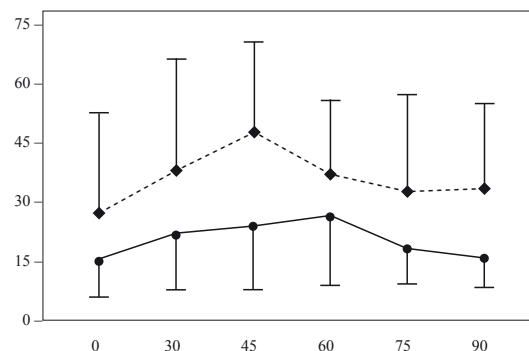
In the 8 subjects who were treated with rifaximin for SIBO, the mean age was 55 (range 31-85). Repeat GBT was normal in 6 (75%), 1 patient (12.5%) had a normal GBT according to hydrogen criteria but methane remained positive (Fig. 1 and 2). Improvement in overall symptom score was observed in 7 (87.5%) patients: 4 subjects had >75% improvement, 2 – 50-75%; 1 – 25-50% and 1 had no symptom improvement (<25% improvement). No adverse events were noted in any of the subjects.

Discussion

IBS is the most common functional bowel disease that affects up to 20% of the population. The criteria for the diagnosis is a symptom-based set of observations that are required because no consistent biological marker or unifying framework is available to explain the different symptoms and findings of IBS [5]. In addition to the degrees of constipation, diarrhea, or pain approximately 90% of the IBS patients also have a significant bloating component to their presentation [5]. This is usually associated with the perception of abdominal distention and recent data suggest that abnormalities in gas production and its transit through the small bowel can be present and could explain these symptoms. Whether SIBO contributes to some of the distressing symptoms such as gas and bloating in IBS remains an area of active investigation. In a study of 202 patients meeting Rome II criteria for IBS by Pimentel et al. abnormal breath test results suggesting SIBO was found in 78% [6]. In another study by the same group the incidence of an abnormal lactulose breath test was 84% vs 20% in the control of subjects who did not meet the Rome II criteria [7]. In a randomized placebo controlled trial using neomycin, there was a significant improvement in IBS symptoms in patients receiving neomycin compared to placebo [8]. Symptom improvement after antibiotics was more consistent in the group where SIBO was eradicated.

Up to 75% of their IBS patients had an abnormal lactulose test consistent with the presence of the SIBO [9]. The interpretation of the lactulose breath test is affected by the individual oral-cecal transit times. The lactulose breath test has the underlying principle that lactulose is a non-absorbed sugar that would arrive in the cecum and right colon and be metabolize into

Figure 2. Methane concentration in ppm (X-axis) detected in the breath test before (dashed line) and after (solid line) treatment with rifaximin. Y-axis represents time in minutes



hydrogen and in some cases methane depending on the specific bacteria species present. Separating SIBO in the distal ileum from cecal arrival time is usually not possible by the lactulose breath testing unless there is an identification of a subsequent second peak or second rise in hydrogen. When lactulose goes into the cecum and right colon there would be a second and substantially higher arise in hydrogen production, so-called second peak phenomenon. Unless the double-peak criteria is included, it is very difficult to interpret a lactulose breath test when the rise in breath hydrogen or methane begins 60 or later minutes after lactulose ingestion as it could also represent rapid small bowel transit [10].

Glucose on the other hand will identify bacterial overgrowth beginning in the proximal small bowel and extending to the proximal ileum. A positive result is a rise in the breath hydrogen above 20 ppm in the first 90 minutes. There are no false positive tests as could occur with the lactulose breath test. We therefore chose the glucose breath test technique to assess the incidence of SIBO in this large group of IBS patients who met the ROME II criteria. 46% of the patients in our cohort had a positive breath test for SIBO as opposed to 80 or 90% being reported by investigations relying on the lactulose breath test methodology. Nevertheless, the figure of 46% still indicates that a substantial number of patients previously regarded as pedestrian IBS patients have SIBO which could contribute to some of the symptoms of their condition [11].

We hypothesized that a contributing factor predisposing to SIBO is the loss of gastric acid in the stomach that usually provides a hostile environment in the small bowel for the growth of bacteria [12]. The use of PPI's could be one reason for low gastric acidity and in turn causing SIBO [12]. We therefore evaluated the risk of SIBO in IBS patients using PPI. Though, the rate of PPI use was slightly more in the IBS with SIBO, no definite correlation could be found. Other hypotheses that have been proposed include the previous history of gastrointestinal infection which would have initiated an imbalance of bacteria flora, or the migration of colonic flora into the small bowel because of impaired defense mechanisms in the small bowel, related to damage to the small bowel migrating motor complex apparatus (the housekeeper of the gut) induced by the gastrointestinal infection or hitherto present in IBS patients.

The focus of the second phase of our trial was to assess the efficacy of rifaximin therapy in reducing symptoms of

IBS and normalizing the GBT. Rifamixin was chosen for the study as it had a low probability for side effects with long-term use, given that it is a non-absorbable antibiotic. A dose finding study evaluating different doses of rifamixin showed that a higher dose (1 200 mg/day) was more efficacious in eradicating bacteria than the dose of 600 mg/day for 7 days. In our study we chose a dose of 800 mg/day for four weeks [13]. We hypothesized that the longer treatment period would result in greater SIBO eradication and a more sustained symptom free interval following treatment. The majority of the patients we summarized had been colonized for many months or even years based on the history of the presentation. We therefore felt that a higher eradication rate would be achieved by more sustained dosing. Indeed we achieved an eradication rate of 85% after four weeks, which is comparable to the response using a higher dose of rifaximin (1 200 mg/day) for 7 days. Whether another dosing cycle or a higher dose of rifaximin should be given to those not eradicated, the duration of the symptom free interval after antibiotic treatment or whether probiotic therapy should be added for maintenance of the SIBO free state are questions that remain to be answered.

Another interesting aspect of our study was the quantitation of hydrogen and methane proportions in the subsets of IBS patients. In normal subjects the elimination of hydrogen produced by bacteria fermentation in the colon depends on methanogenic and sulfate reducing bacteria that convert hydrogen to methane and hydrogen sulfide. These organisms are highly competitive so the stool of an individual contains high concentrations of only one of these two organisms. A study by Pimentel et al. [14] documented the excretion of methane alone in constipated IBS patients. Our data confirms that there is a predominance of methane production in constipated individuals. In IBS-D patient's hydrogen production is greater than methane. Methane production is also higher in patients in whom gas and bloating symptoms are dominant. Since some patients had a positive GBT only by the methane criteria, it is very important to measure both hydrogen and methane when a breath test for SIBO is performed.

One of the limitations of this study is diagnosing SIBO on the basis of a positive GBT and not performing the gold standard bacterial culture of the jejunal fluid as the latter technique is not performed at most institutions.

We conclude that a substantial number of patients with IBS have SIBO by using the GBT, which we believe is a more specific test than the lactulose breath test [15]. Hydrogen and methane are the predominant gases associated with IBS-D and IBS-C respectively. Rifaximin is effective in treating SIBO and improvement of IBS symptoms correlated with SIBO eradication. Optimal dosing regimens for rifaximin to eradicate SIBO and the-long term follow up of these IBS patients are subjects of further studies.

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