Dig Dis Sci (2010) 55:398–403
DOI 10.1007/s10620-009-0778-4

ORIGINAL ARTICLE

Evaluating Breath Methane as a Diagnostic Test for Constipation-Predominant IBS

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Received: 21 November 2008 / Accepted: 23 February 2009 / Published online: 18 March 2009

Abstract Studies suggest that subjects with IBS have altered gut flora. Among these findings, methane production is more commonly associated with constipation-predominant symptoms. In this study, we prospectively evaluated the role of methane as a diagnostic test. Consecutive Rome I positive IBS patients referred for a lactulose breath test were eligible to participate. After exclusion criteria, subjects completed a symptom questionnaire grading bloating, diarrhea, and constipation on a VAS scale (0–100 mm). Once completed, a physician interviewed the subjects and rated the subject accordingly, and also determined whether the patient had C-IBS, D-IBS, or neither. Subjects and physicians were blinded to the results of the breath test. The presence of methane in the breath test was compared to the results of the scoring by subjects and physicians. A total of 56 Rome I positive IBS subjects were enrolled. During breath testing, 28 subjects produced methane. Good agreement between physician's evaluation and the patient's was seen (diarrhea = 0.69; constipation = 0.69; bloating = 0.62). The severity of constipation was noted to be greater in the methane group (49.3 ± 28.7) than in the non-methane group (25.3 ± 31.47) ($P < 0.01$). In contrast, diarrhea was less severe in the methane group (12.3 ± 21.0) than the non-methane group (36.7 ± 32.4) ($P < 0.01$). Out of the 56 patients, 23 C-IBS subjects were identified by the physician. When methane was used to predict the assignment of C-IBS compared to non-C-IBS, it had a sensitivity of 91.7% and a specificity of 81.3% (OR = 47.7, CI = 9.4–232, $P < 0.00001$). In conclusion, methane is a potential diagnostic test for the identification of C-IBS and may guide treatment.

Keywords Irritable bowel syndrome · Breath testing · Constipation-predominant IBS · Methane

Abbreviations

IBS	Irritable bowel syndrome
C-IBS	Constipation-predominant IBS
D-IBS	Diarrhea-predominant IBS
LBT	Lactulose breath test
SIBO	Small intestinal bacterial overgrowth

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal condition worldwide, and as many as one in five adults carry the diagnosis in the US [1–6]. The diagnosis of IBS is generally based upon the presence of specific clinical symptoms in the absence of a structural or biochemical explanation for such symptoms. Therefore, the diagnosis of IBS is based on criteria applied after using a "diagnosis of exclusion" approach. The culmination of these efforts to develop clinical criteria for IBS are the Rome criteria [7–9]. These have now become powerful tools to facilitate enrollment in IBS clinical trials.

The newer versions of the Rome criteria go further in that Rome II defines subtypes of IBS based on their predominant symptom [8]. The most recognized subgroups are diarrhea- and constipation-predominant IBS (D-IBS and C-IBS, respectively). Defining subgroups became important in facilitating enrollment in clinical trials for symptom

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appropriate therapy [10–13]. In general, this classification helped dictate medical therapy for IBS. For example, identification of C-IBS patients implied they could benefit from agents that soften stool or accelerate transit [10, 11], while subjects with D-IBS might benefit from tri-cyclic antidepressants [14] or anti-kinetic agents [12, 13]. Although the identification of C and D-IBS was useful, this classification was based not on the pathophysiology of IBS, but rather the most dominant symptom.

While the pathophysiology remains unknown, recent research has implicated a significant role for altered small-intestinal flora in IBS [15–18]. The suggestion is that a large proportion of IBS patients have small-intestinal bacterial overgrowth (SIBO). The evidence for SIBO in IBS is now based on lactulose [15, 16] and glucose [17, 18] breath tests, and more recently, jejunal culture studies [19]. Alteration in gut microflora as a contributor to gastrointestinal symptoms in IBS is further supported by the successful improvement of IBS after antibiotics, even in randomized, placebo-controlled trials [20–23], although there is contradicting data [24]. The breath test may further define the IBS patient who might respond to antibiotics. For this, the Rome criteria have not been helpful.

In the context of gut flora, breath testing, and IBS, the discovery that methane excretion during breath testing is associated with C-IBS is now well established [20, 24–26]. Recent studies suggest that approximately 20% [25] of IBS patients have methane-production on breath test at a level >20 ppm, and that most of these subjects have C-IBS. Further work in this area has demonstrated that methane gas itself slows small-intestinal transit, implying that it may be responsible for the constipation [27]. To support this, a recently published sub-analysis of a double-blind study demonstrated that the determinant of improvement in constipation among antibiotic treated C-IBS subjects was not just treatment with neomycin but rather the elimination of methane by the administration of neomycin [28]. This suggests that methane production during breath testing may be a diagnostic test or even a biomarker of C-IBS. More importantly, it may be a test that, if positive, dictates a pathophysiologic cause of constipation in addition to the therapy a patient receives.

In this prospective study, we evaluated the diagnostic utility of methane on lactulose breath test (LBT) as a predictor of C-IBS, as defined by the Rome criteria.

Methods

Patient Population

Subjects were recruited from patients referred to the GI Motility Program for a LBT. They were excluded if they did not meet Rome I criteria [7] or had inflammatory bowel disease (IBD), celiac disease, autoimmune disease, or a history of gastrointestinal surgery. Subjects were not excluded for medication use, but were required to list all medications they were currently taking. Subjects were offered a compensation of $25 for their participation in this study. The study was approved by the Cedars-Sinai Medical Center institutional review board.

Primary Study Design

After obtaining informed consent, subjects were given a bowel symptom questionnaire involving rating the degree of symptoms for the preceding 7 days on a scale of 0–100 mm by using a visual analog scale (VAS). Symptoms included bloating, excess gas, diarrhea, constipation, abdominal pain, passage of mucous, sensation of incomplete evacuation, straining, and urgency. Since subjects were not educated on Rome criteria, they were simply asked to state which symptom was most bothersome to them (diarrhea, constipation, or both). Subjects were blinded to the results of the LBT until after completion of the questionnaire and subsequent physician evaluation. Immediately upon completion of the questionnaire, the questions were given to research staff.

After subjects completed and turned in their questionnaire, they were interviewed by a physician. The subject questionnaire was always completed first so that the physician interview would not lead subjects to the symptoms of interest in the study and avoid bias. During each interview, a physician took a history to allow them to rate their interpretation of the patient's levels of constipation, diarrhea, and bloating. The physicians were aware that the diagnosis was IBS. The physicians were asked to comment on whether they felt the symptoms met the criteria for C-IBS. The physicians were familiarized with the Rome definitions of C-IBS prior to starting the study to encourage adherence to standard definitions. During the interview, physicians were blinded to both the results of the subject's LBT and answers to the subject's symptom questionnaire.

Lactulose Breath Test

Subjects presented to the GI Motility Laboratory for LBT after a 12-h fast. Subjects were asked not to ingest any beans, nuts, soy, or large meals, and to limit dairy intake the day before the test. They also could not smoke the morning of testing. After a sample of their breath (end expiratory) was collected at baseline, subjects ingested 10 g of lactulose syrup (Pharmaceutical Associates, Inc., Greenville, SC) with 240 ml of water. Further breath samples were then obtained every 15 min for 2 h. The concentrations of breath hydrogen and methane were

measured and corrected for CO_2 content using a Quintron model SC gas chromatograph (Quintron Instrument, Co, Milwaukee, WI). Data were reported in parts per million (ppm). The measurements were then plotted graphically and analyzed. Any detection of methane above 5 ppm was considered a methane-producing subject. The remaining subjects were termed non-methane producing subjects.

Statistical Analysis

To determine the inter-observer consistency between patient-stated outcomes and physician stated outcomes, Spearman rank correlation and linear regression were used. Since these were VAS scores from 0 to 100, each rating was given a quartile assignment in the 0–100 rating to allow for a calculation of agreement using Cohen's kappa. The study population was divided into two based on the criteria for the presence of methane above. The methane producers and non-methane producers were compared. The severities of diarrhea, constipation, and bloating in both methane and non-methane producing subjects were compared via Wilcoxon rank sum test for both the patient's and physician's perspectives.

Furthermore, whether constipation or diarrhea was the predominant symptom from both perspectives was also analyzed. The number of subjects deemed to have C-IBS was compared between methane and non-methane producers to determine the sensitivity and specificity of this finding using the Chi-square method. Finally, the degrees of constipation, diarrhea, and bloating from both patient's and physician's perspectives were also compared to the production of methane on the LBT using linear regression.

Results

Patient Characteristics

A total of 56 subjects participated in this study, of which 28 produced methane gas on the LBT and 28 were classified as non-methane producers. Both groups were demographically similar (Table 1). No subjects were taking narcotic medications, and among drugs that might contribute to constipation, one non-methane producing subject was taking atenolol. Among methane-producing subjects, two subjects were taking β-blockers (one with atenolol and one with metoprolol).

Agreement Between Subject and Physician Symptom Characterization

There was generally good agreement between physician and subject rating of symptoms for the three symptoms of diarrhea ($R = 0.69$) (Fig. 1a), constipation ($R = 0.69$) (Fig. 1b), and bloating ($R = 0.62$) (Fig. 1c) in a linear regression analysis. Using a quartile comparison, the agreement between groups was also good ($\kappa = 0.62$ for constipation, $\kappa = 0.68$ for diarrhea and $\kappa = 0.55$ for bloating).

Table 1 Demographic comparison between methane and non-methane producing subjects

	Non-methane producer ($n = 28$)	Methane producer ($n = 28$)	P-value
Age	39.1 ± 13.1	45.4 ± 12.3	0.073
Female subjects [n(%)]	23 (82.1)	19 (67.9)	0.40
BMI	23.9 ± 4.8	23.5 ± 3.4	0.76

Comparison of Symptoms Between Methane and Non-methane Subjects

According to both patients' and physicians' perspectives, diarrhea was found to be more severe in non-methane patients, and constipation was found to be more severe in methane producing patients (Fig. 2a, b).

Comparison of C-IBS to Methane

Among the 56 patients in the study, after being interviewed by the physician, 24 subjects (43%) were given a diagnosis of C-IBS, 23 (41%) D-IBS and the remaining nine subjects (16%) were mixed or unsure. This determination was the basis for comparison of methane as a diagnostic test for C-IBS.

The primary outcome of this study was to evaluate the diagnostic utility of methane on LBT to predict C-IBS in a prospective manner. In Table 2, the dynamics of this testing are noted. The overall sensitivity of methane in predicting C-IBS was 91.7%. Furthermore, the odds ratio of having C-IBS if methane positive was 47.7 (CI = 9.4–232.0, $P < 0.00001$). Furthermore, while not reaching statistical significance, there was a correlation between the area under the curve and severity of constipation ($R = 0.36$, $P = 0.054$).

Discussion

In this study, we demonstrated that the detection of methane during lactulose breath testing is associated with constipation-predominant IBS. While the association of methane and constipation is not new, the use of methane detection as a diagnostic test for C-IBS is novel. These

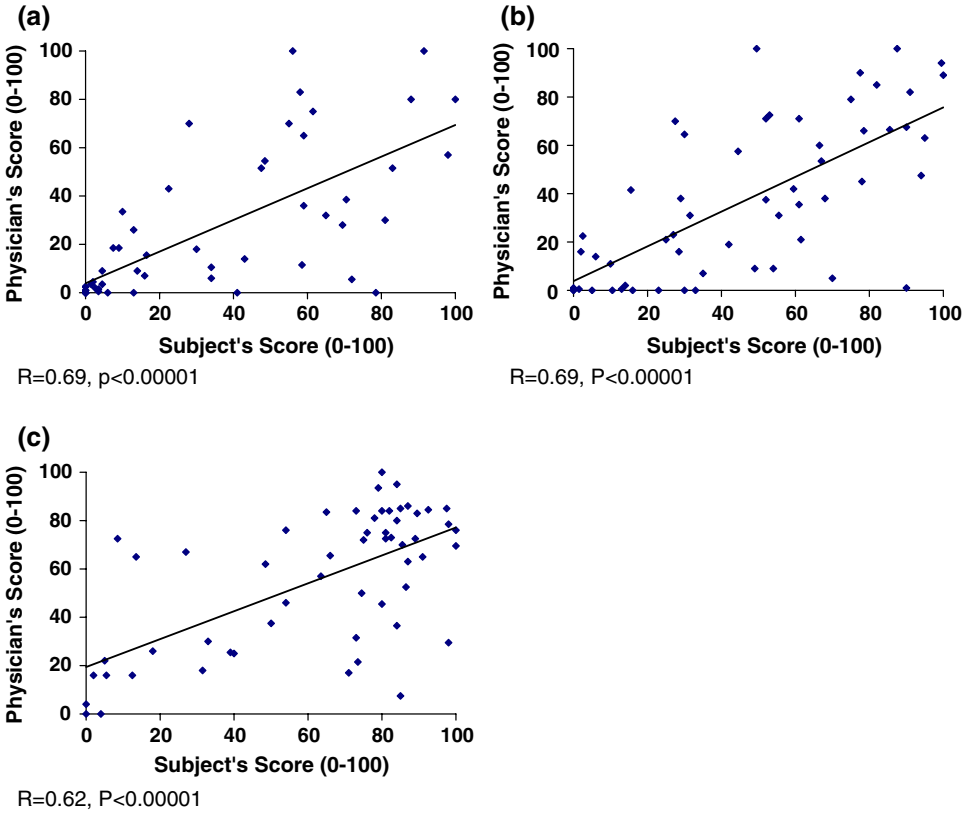

Fig. 1 Comparison of VAS symptom reporting between subjects and physicians. **a** Comparison of VAS for diarrhea between subject and physician, $R = 0.69$, $P < 0.00001$. **b** Comparison of VAS for constipation between subject and physician, $R = 0.69$, $P < 0.00001$. **c** Comparison of VAS for bloating between subject and physician, $R = 0.62$, $P < 0.00001$

results are also significant since using methane as a diagnostic methodology in IBS may more precisely direct therapy for C-IBS and even suggest pathophysiology.

In the last two decades, there has been a struggle to diagnose and understand the pathophysiology of IBS. Since there were no clear biomarkers for IBS, this condition was often referred to as a "diagnosis of exclusion". In response to this, and in order to better guide the field in the study of IBS, a consensus group formed to establish guidelines for the diagnosis of IBS, now termed the Rome criteria [7]. While not eliminating the need to exclude other disorders such as Crohn's disease, once other diseases are excluded these criteria help create a more uniform population to study. Even after applying the Rome criteria, IBS remained heterogeneous since the bowel patterns of IBS ranged from diarrhea to constipation. This led to a modified set of criteria in order to determine the predominant state of bowel function in IBS. As a result, IBS was designated as C-IBS and D-IBS [8]. This was a major leap in using diagnostic assignment to direct therapy. Since pharmacological agents (either available at the time or emerging) could treat constipation or diarrhea, this at least provided some guidance in the management of IBS. The only problem is that symptom-based criteria are not a biomarker for IBS, but rather, a characterization of the disease manifestations.

In the last 10 years, a new concept in the pathophysiology of IBS has emerged, suggesting that a proportion of IBS patients may have altered small intestinal flora. The initial studies indicated that IBS patients often had an abnormal LBT, suggesting the presence of SIBO [15–18]. While controversy remains surrounding the diagnostic reliability of the LBT [24], much of this controversy is based on the fact that there is no reliable technique for diagnosing bacterial overgrowth in humans [29]. However, a recent study determined that IBS patients do indeed have excessive numbers of coliform bacteria in the small intestine compared to controls although not greater than $>10^5$ cfu/ml [19]. To further support this concept, randomized, placebo-controlled studies using antibiotics to treat IBS have demonstrated benefit [20–23]. Two studies suggested that the improvement in functional symptoms after antibiotics is linked to a reduction of gut flora as evidenced by a reduction in gas production on the breath test [20, 21].

The growing evidence of altered gut flora in a subset of IBS subjects leads to some optimism for a potential biomarker of IBS. While general breath testing can be inconsistent [29], one consistent finding in studies of breath testing in IBS subjects is that methane production during this test is associated with constipation [20, 24–26]. Subjects with methane on breath testing have more severe constipation than subjects who do not produce methane. Other work has even demonstrated that the degree of methane production on breath tests predicts the degree of

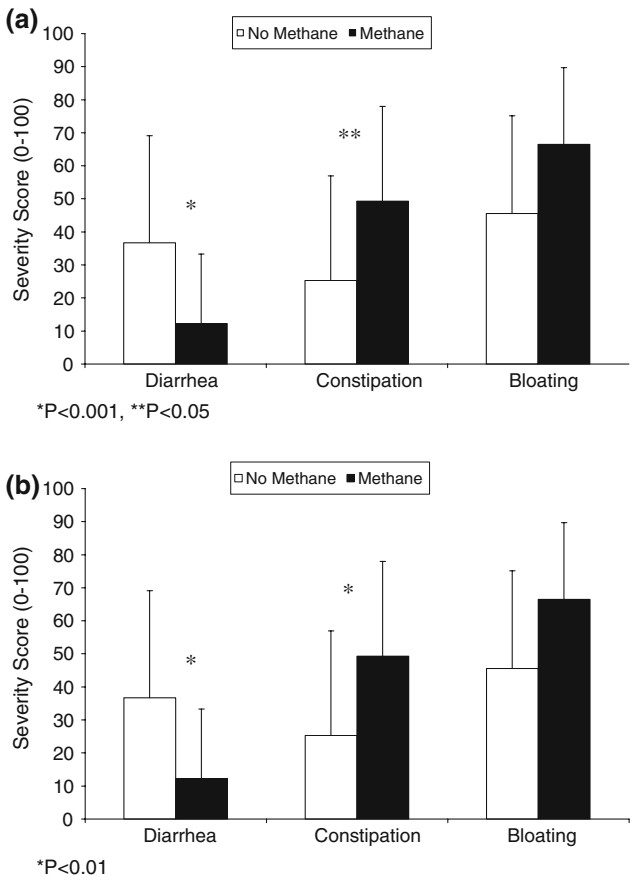

Fig. 2 Comparison of severity of symptoms between methane and non-methane producing subjects. **a** Comparison of severity based on subject's scoring, $*P < 0.001$, $**P < 0.05$. **b** Comparison of symptoms based on physician scoring, $*P < 0.01$

Table 2 Comparison of sensitivity and specificity of methane as a determinant of C-IBS

	C-IBS present	Not C-IBS	Total
Methane producer	22	6	28
Non-methane producer	2	26	28
Total	24	32	56

Sensitivity = 0.92; Specificity = 0.81; Positive predictive value = 0.79; Negative predictive value = 0.93

constipation [30]. In a recent study, infusion of methane into the small intestine of dogs produced a near 70% slowing of intestinal transit [27]. This result suggests that the methane production in the gut could be actively contributing to the constipation in IBS. The data further lends optimism to the idea that the detection of methane on breath testing in humans may be a good biomarker of constipation, at least in IBS. Even more convincing of the benefit of such a biomarker is a recent study that demonstrated an improvement in C-IBS when treated with neomycin [28]. In this study, the entire determinant of the improvement of constipation rested on the success of neomycin in eliminating the methane production.

Despite the finding of methane as a marker of C-IBS, there has never been a head-to-head comparison of methane on breath testing and the Rome criteria. In this study, we investigated the strength of methane detection as a diagnostic test for C-IBS based on Rome criteria. This was a blinded study since neither the physicians nor the patients knew the results of the breath test during evaluation. The study again confirmed the association between methane and constipation symptoms and severity. In this prospective study, methane as a diagnostic test was very strong in predicting C-IBS. It demonstrated a sensitivity of 91% and specificity of 81.3%.

This and the growing body of findings related to methane and constipation suggest that methane is indeed a good biomarker for C-IBS. While Rome criteria provide a general guide to the clinician based on the assignment to C-IBS, in most cases this guidance relates to using any generic treatment for constipation such as laxatives or prokinetics [31]. This would be no different than obtaining a simple history of constipation and thus empiric treatment of constipation. What methane production may afford is a result that directs specific therapy. For example, based on the data above, a single breath sample would detect methane and in the setting of constipation, guide one to use neomycin as therapy for the constipation.

While these data are enthusiastic in their suggestion of methane as a biomarker of constipation, better controlled studies are needed just in subjects with methane to determine the ideal antibiotic or treatment response to eliminate methane and afford an improvement in symptoms.

In conclusion, this study demonstrates that methane on breath test in subjects with IBS is highly sensitive in identifying subjects with C-IBS based on conventional Rome criteria. Since methane may be a biomarker for the pathophysiology of that constipation, it may be a good diagnostic test to guide therapy.

Acknowledgments This work was supported by Beatrice and Samuel A. Seaver Foundation.

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