Rifaximin treatment for the irritable bowel syndrome with a positive lactulose hydrogen breath test improves symptoms for at least 3 months

P. Meyrat*, E. Safroneeva† & A. M. Schoepfer‡

*Private Practice for Gastroenterology and Hepatology, Solothurn, Switzerland.
†Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.
‡Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois/CHUV, Lausanne, Switzerland.

Correspondence to:
Dr P. Meyrat, Private Practice for Gastroenterology and Hepatology, Dornacherhof 11, CH-4500 Solothurn, Switzerland.
E-mail: gastro.meyrat@hin.ch
Dr A. M. Schoepfer, Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois/CHUV, Rue de Bugnon 44, 07/2409, CH-1011 Lausanne, Switzerland.
E-mail: alain.schoepfer@chuv.ch

SUMMARY

Background
While rifaximin was able to improve symptoms in patients with irritable bowel syndrome (IBS) in phase III trials, these results are yet to be repeated in phase IV studies.

Aim
To evaluate the treatment response to rifaximin in IBS patients in a phase IV trial.

Methods
IBS patients underwent lactulose hydrogen breath testing (LHBT). LHBT-positive patients were treated with rifaximin for 14 days. Prior to treatment as well as at week 4 and 14 following the start of rifaximin treatment, patients completed a questionnaire assessing symptom severity on a Likert scale from 0 to 10.

Results
One hundred and six of 150 IBS patients (71%) were LHBT-positive and treated with rifaximin. As assessed at week 4 following commencement of the therapy, rifaximin provided significant improvement of the following IBS-associated symptoms: bloating (5.5 ± 2.6 before the start of the treatment vs. 3.6 ± 2.7 at week 4, P < 0.001), flatulence (5.0 ± 2.7 vs. 4.0 ± 2.7, P = 0.015), diarrhoea (2.9 ± 2.4 vs. 2.0 ± 2.4, P = 0.005) and abdominal pain (4.8 ± 2.7 vs. 3.3 ± 2.5, P < 0.001). Overall well-being also significantly improved (3.9 ± 2.4 vs. 2.7 ± 2.3, P < 0.001). Similar improvements in IBS symptoms were obtained at week 14. Eighty-six per cent of patients undergoing repetitive LHBT (55/64) tested negative at week 4.

Conclusions
We found a high percentage of LHBT-positive IBS patients. IBS-associated symptoms (bloating, flatulence, diarrhoea, pain) were improved for a period of 3 months following 2 weeks of treatment with rifaximin. We conclude that rifaximin treatment alleviates symptoms in LHBT-positive IBS patients.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic gastrointestinal condition of unknown aetiology and is characterised by the presence of abdominal pain and altered bowel function in the absence of clinical ‘alarm’ signs, such as anaemia or significant weight loss.1, 2 Currently, more than 10% of the general population suffers from IBS, leading to considerable healthcare expenditures.3, 4 The exact pathophysiology of IBS remains unknown; both central and peripheral mechanisms have been implicated in IBS pathogenesis.5 IBS patients may present with alterations in their intestinal microbiota6, 7 and they are tested significantly more frequently positive by lactulose hydrogen breath test (LHBT) when compared to healthy controls.8 The reported prevalence of the positive LHBT in IBS patients ranges from 14% to 78%.8 Authors of a systematic review and meta-analysis have calculated that a pooled prevalence of a positive LHBT or glucose hydrogen test is 54% (95% CI: 32–76%) or 31% (95% CI: 14–50%) respectively.8 The pooled odds ratio for any positive hydrogen test in IBS patients compared to healthy subjects was 3.45 (95% CI: 0.9–12.7) or 4.7 (95% CI: 1.7–12.95), depending on the criteria used for defining a positive readout of a test.8

The LHBT is one of the most commonly used breath tests that is based on measurement of hydrogen concentration in breath samples every 15 min (for up to 3 h) following the ingestion of 10 g of the non-absorbable sugar lactulose dissolved in water.9 According to the original definition of the positive LHBT, the rise of >20 ppm in hydrogen concentration occurring at least 15 min before a second rise in hydrogen concentration is believed to be indicative, among other phenomena, of rapid small bowel transit and/or small intestinal bacterial overgrowth (SIBO).10 A recent meta-analysis concluded that the breath test findings in IBS appear to be valid for SIBO diagnosis.11 However, the appropriateness of use of hydrogen breath testing in IBS as well as the choice of substrate that provides the best test characteristics is a subject of some controversy. In addition, it is also debated whether carbohydrate breath testing is an appropriate surrogate for diagnosing SIBO in IBS patients. SIBO has been conventionally diagnosed using jejunal fluid culture; the cultures are considered positive for SIBO if the total bacterial count is ≥10^5 colony forming units (CFU) of coliform bacteria per ml of jejunal fluid aspirate.9 The results of the early studies, where sampling of the small intestinal luminal contents was performed using an aseptic technique demonstrated an LHBT sensitivity and specificity of 68% and 44%,12 and 16.7% and 70%,13 arguing that breath- hydrogen testing may not be entirely adequate for SIBO diagnosis. However, difficulties in aspiration of jejunal fluid, potential for contamination during sampling, and the possibility of false negative results, especially when culturing for obligate anaerobes, are important limitations of this methodology.8 Therefore, many view indirect tests, such as breath tests, as a better alternative to this laborious method.11, 14

The use of systemic antibiotics for treatment of IBS has been reported with mixed results.15 Rifaximin is a semisynthetic derivative of rifamycin, which contains an additional benzimidazole ring that prevents rifaximin from being absorbed systemically (absorption 0.4% after oral administration).16 In vitro, rifaximin demonstrates activity against Gram-positive and Gram-negative, aerobic and anaerobic bacteria. This antibiotic has been approved by the Food and Drug Administration (FDA) for treating traveller’s diarrhoea and minimal hepatic encephalopathy. Several trials have demonstrated efficacy of rifaximin for treatment of global symptoms and bloating in IBS.17, 18 Validation of these findings in a phase IV trial is currently lacking. Therefore, we aimed to perform a study to assess the prevalence of positive LHBT and the treatment efficacy of rifaximin in a cohort of IBS patients in daily clinical practice.

MATERIALS AND METHODS

Patients

Consecutive outpatients with IBS diagnosis were prospectively enrolled into the study between January 2010 and September 2011. Patients provided written informed consent to be able to participate in this observational trial, and the study was approved by the local ethics committees. The study outline is demonstrated in Figure 1.

Inclusion criteria. Inclusion criteria for enrollment of patients into this study were as follows: fulfilment of the ROME III criteria, normal endoscopic and histological findings during both ileo-colonoscopy and oesophago-gastro-duodenoscopy (biopsies taken from terminal ileum, colon, duodenum, stomach), normal transabdominal ultrasound, normal haematological tests findings (hematogram, electrolytes, CRP, ASAT, ALAT, GGT, AP, bilirubin, lipase, creatinin, glucose).

Exclusion criteria. Presence of any ‘alarm’ symptoms, such as anaemia or weight loss, infectious diseases (positive results of microbiological workup of faecal samples...
for known infectious agents and faecal test for *Giardia lamblia* antigen), presence of endoscopic or histological alterations, which might be indicative of other disorders (e.g. celiac disease, inflammatory bowel disease, diverticulosis or diverticulitis) and contribute to IBS symptom generation, faecal calprotectin >50 μg/g of faeces, regular intake of aspirin and/or NSAIDs (≥2 tablets/week), diabetes, history of abdominal surgery involving the gastrointestinal tract.

**Methods**

**Lactulose hydrogen breath test (LHBT).** Patients were instructed to abstain from slowly digested foods, such as beans or high fibre cereals, for 24 h prior to the test. Patients had an overnight fasting period prior to the test. Patients were not on antibiotic treatment for at least 4 weeks prior to undergoing the LHBT. Patients were not on fibre supplements or laxatives 1-week prior to the test date and for the entire duration of the study. Patients were asked to brush their teeth both prior to providing the hydrogen baseline sample and following the lactulose ingestion to avoid rise in breath-hydrogen concentration within the first 10 min of the test as a result of carbohydrate fermentation by oropharyngeal bacteria. The test was performed using the breath-hydrogen analyser (Gastrolyser Breath-Hydrogen Monitor, Bedfont Scientific Ltd). Patients were administered 10 g of lactulose dissolved in 400 mL of water. Samples of end-expiratory air were collected every 15 min for the first hour (0, 15, 30, 45, 60 min) and every 30 min for the next hour. For this study, we have defined test results as positive when an increase in breath-hydrogen concentration of at least 12 ppm above basal level was observed within 60 min of ingesting lactulose on the condition that this early rise in hydrogen concentration preceded the second prolonged rise in hydrogen concentration by at least 15 min.

**Lactose breath test.** A lactose breath test (LBT) was performed in all patients 4 weeks prior to the LHBT. The LBT was performed using the breath-hydrogen analyser (Gastrolyser Breath-Hydrogen Monitor, Bedfont Scientific Ltd). In preparation for the test, patients were advised to follow the same guidelines, as those already described for the LHBT. Patients were administered a challenge dose of 50 g lactose dissolved in 400 mL of water. Samples of end-expired air were obtained at baseline, every 15 min for the first half hour and every 30 min for the next hour. A test result was considered positive when an increase in the concentration of hydrogen of at least 20 ppm compared to baseline was observed. Patients with positive LBT were advised by a registered dietician to adhere to a lactose-free diet and were on this diet when undergoing subsequent LHBT.

**Symptom questionnaires.** At baseline (week 0) and at week 4 and week 14 after the commencement of rifaximin treatment, patients completed a questionnaire that addressed the following items: bloating, diarrhoea, flatulence, abdominal pain and overall well-being. The symptom severity as well as changes in overall well-being were assessed on a 11-point Likert scale, where 0 corresponded to absence of symptoms or no reduction in overall well-being and 10 corresponded to most severe symptoms or severe reduction in overall well-being.

**Rifaximin.** Patients were treated with rifaximin (Xifaxan; Norgine Pharmaceuticals, Muttenz, Switzerland) for 14 days at a daily dosage of 800 mg (200 mg, four times daily). Rifaximin is not registered in Switzerland for treatment of IBS symptoms nor for treatment of travelers’ diarrhoea.

**Statistical analysis**

Clinical data were entered into a database (Microsoft Access 2000, Redmond, Washington, USA). All statistical examinations were performed using a statistical package programme (Stata, Version 12.1, College Station, TX, USA). Data distribution was analysed using Normal-QQ-Plots. Results of quantitative data are presented either as median plus interquartile ranges (for non-normally distributed data) or mean ± s.d. and range (for parametric data). Categorical data were summarised as the percentage of the group total. For quantitative data, differences

![Figure 1 | Study outline.](image-url)
between the groups were assessed using the Student’s t-test in case of parametric data and using the Wilcoxon rank-sum test in case of non-parametric data. Differences in frequencies for categorical data were assessed using the chi-squared test. The Kruskal–Wallis test was used for comparison of more than two independent samples. A P-value < 0.05 was considered to be statistically significant.

RESULTS

Clinical characteristics of the study population

The consort patient flow diagram is presented in Figure 2. A total of 150 IBS patients were included in the trial. The patients’ clinical characteristics, stratified according to the results of the LHBT, are illustrated in Table 1. Results of LHBT were positive in one hundred and six patients (71%). Patients were mostly female (76%). Concomitant lactose intolerance was found in 16% of IBS patients with negative LHBT and in 12% of IBS patients with positive LHBT. The majority (81%) of patients suffered from diarrhoea-predominant IBS. LHBT-positive IBS patients had an increased severity of bloating (5.5 ± 2.6 vs. 4.6 ± 3.0, P = 0.028) and diarrhoea (2.9 ± 2.4 vs. 2.2 ± 1.8, P = 0.026) when compared to IBS patients with negative LHBT.

We further analysed the initial symptom presentation in IBS patients with negative and positive LHBT and found that bloating was significantly more severe in IBS patients with positive LHBT aged less than 50 years old when compared with patients aged 50 years and older. These results are further illustrated in Table 2. No age-specific differences were observed with respect to the severity of diarrhoea, flatulence, abdominal pain and overall well-being.

Rifaximin treatment in IBS patients with positive LHBT decreased the severity of bloating, flatulence, diarrhoea, abdominal pain and improved overall well-being

The following items were assessed using a patient questionnaire: bloating, flatulence, diarrhoea, abdominal pain, and overall well-being. The clinical symptoms were assessed on a 11-point Likert scale at week 0 (prior to the commencement of rifaximin treatment), at week 4 and at week 14 following the start of rifaximin treatment. All 106 patients with positive LHBT underwent a 2-week treatment with rifaximin (800 mg daily). Thirteen LHBT-positive IBS patients dropped out of the study for the following reasons: Lack of adherence to the rifaximin treatment for 14 days despite good tolerance (n = 8) and side effects (n = 5).

The patients’ self-assessed symptom severity as well as reduction in overall well-being at week 0 (prior to commencement of the treatment), week 4 and week 14 following the start of rifaximin treatment is presented in Table 3 and Figure 3. A significant improvement in all the assessed items at week 4 and week 14 following the start of rifaximin therapy was observed. Of the 93 patients, who came for a week 4 follow-up appointment, 89 (96%) also came for a follow-up visit at week 14.

We also evaluated whether there was a difference in the IBS symptoms between a group of LHBT-positive IBS patients that only completed the symptom questionnaire (n = 29) at week 0 and week 4 following the start of the treatment and the group that not only completed a symptom questionnaire, but also underwent another LHBT (n = 64) at week 4 following the start of the treatment. The results of this analysis are shown in Figure 4. We found no difference with respect to the reported severity of bloating, diarrhoea, flatulence and abdominal pain at week 4 following the commencement of rifaximin treatment between the LHBT-positive IBS patients that only completed the symptom questionnaire when compared to the LHBT-positive IBS patients that completed the symptom questionnaire and underwent an additional LHBT. Therefore, it appears that symptom assessment alone is appropriate for follow-up evaluation of IBS patients.

In the cohort undergoing a second LHBT (n = 64), a negative LHBT was documented in 55/64 (86%) of patients. In the LHBT-positive IBS patients with documented missed eradication (n = 9), we did not observe any significant changes in the symptom severity.
The following side effects were observed in the patients undergoing rifaximin treatment: headache (n = 3/106, 3%), dry skin (n = 1/106, 1%), and nausea without vomiting (n = 1/106, 1%). A total of 13 out of 106 (12%) LHBT-positive IBS patients, who started rifaximin treatment, quit the therapy prematurely (eight patients did not adhere to the treatment regimen despite good tolerance and five patients interrupted the treatment due to the side effects as mentioned above).

**DISCUSSION**

We demonstrate that a high percentage of IBS patients test positive by LHBT, and that IBS-associated symptoms respond well to rifaximin treatment.
Collectively, the results of this analysis demonstrate that IBS patients frequently test positive using different hydrogen breath tests and that these patients are more likely to test positive using any test when compared to healthy control subjects.8

The prevalence of a positive LHBT in our study was 71%, which is comparable to results reported by Pimentel et al. (78%) and by Nucera et al. (65%).11, 19 In our study, bloating intensity was more severe in patients under 50 years of age when compared to that of patients over 50 years of age.8

Table 3 | Clinical characteristics of the LHBT-positive IBS patients who underwent a 2-week treatment with rifaximin

<table>
<thead>
<tr>
<th>Item</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 14</th>
<th>P-value week 0 vs. week 4</th>
<th>P-value week 0 vs. week 14</th>
<th>P-value week 4 vs. week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td>5.5 ± 2.6</td>
<td>3.6 ± 2.7</td>
<td>3.4 ± 2.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.366</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2.9 ± 2.4</td>
<td>2 ± 2.4</td>
<td>2.2 ± 1.8</td>
<td>0.005</td>
<td>0.008</td>
<td>0.312</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5.0 ± 2.7</td>
<td>4.1 ± 2.7</td>
<td>4.1 ± 2.2</td>
<td>0.015</td>
<td>0.006</td>
<td>0.446</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4.8 ± 2.7</td>
<td>3.3 ± 2.5</td>
<td>3.0 ± 1.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.058</td>
</tr>
<tr>
<td>Reduced overall well-being</td>
<td>3.9 ± 2.4</td>
<td>2.7 ± 2.3</td>
<td>2.4 ± 2.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.214</td>
</tr>
</tbody>
</table>

Results prior to the rifaximin treatment (week 0), at week 4 and at week 14 following the start of rifaximin treatment are shown. At week 4 and 14 following the start of a 2-week rifaximin treatment, a significant improvement of all clinical characteristics was observed.

Figure 3 | This figure presents the symptom severity (mean) before and after rifaximin treatment. A significant reduction in all the assessed items was observed.
observed in patients aged 50 years and older prior to the start of the study. We found a significant decrease in the intensity of bloating, diarrhoea, flatulence and abdominal pain following rifaximin therapy. Accordingly, the overall well-being significantly improved following the 2-week treatment with rifaximin. These positive therapeutic results are in accordance with the findings of the recently published phase III, double-blind, placebo-controlled TARGET trials.17 In these trials, IBS patients without constipation were assigned either to a group that received rifaximin (at a dose of 550 mg) or to a group that received placebo three times daily for 2 weeks. IBS patients were then followed for additional 10 weeks. In the group that received rifaximin, significantly more patients had demonstrated an improvement of global IBS symptoms (40.7% vs. 31.7%, \( P < 0.001 \) in the two studies combined), and had a response to treatment based on daily ratings of IBS symptoms, such as bloating, abdominal pain and stool consistency during the first 4 weeks after completion of the treatment when compared to the placebo group.17 Similar to our study, Sharara et al. used a daily dosage of 800 mg and documented a global improvement of IBS symptoms in 27% of patients receiving rifaximin when compared with 9.1% receiving placebo (odds ratio 3.70).20 A recently published meta-analysis on the efficacy and safety of rifaximin in treatment of IBS revealed that rifaximin is, indeed, more efficacious than placebo for global IBS symptom improvement [OR = 1.57, 95% CI: 1.22–2.01, therapeutic gain 9.8%, number needed to treat (NNT) = 10.2] and for improvement of bloating (OR = 1.55, 95% CI: 1.23–1.96; therapeutic gain = 9.8%, NNT = 10.1). Thereby, the therapeutic efficacy of rifaximin for IBS treatment is comparable to the one of tegaserod (NNT = 10), fibres (NNT = 11) and alosetron (NNT = 8).21–24 To evaluate the correlation between the clinical response to rifaximin treatment based on the use of self-assessed symptom severity questionnaire and the result of LHBT, 64 patients completed the symptom questionnaire and underwent an additional LHBT at week 0 and week 4 following a 2-week rifaximin treatment. We conclude that no difference with respect to clinical characteristics between those two groups of patients was observed and that symptom assessment alone is sufficient for evaluation of treatment effectiveness of LHBT-positive IBS patients.

Figure 4 | This figure compares the IBS-associated symptoms and overall well-being in patients having completed only the symptom questionnaire (\( n = 29 \)) and in IBS patients having completed the symptom questionnaire and having undergone an additional LHBT (\( n = 64 \)) following a 2-week rifaximin treatment. We conclude that no difference with respect to clinical characteristics between those two groups of patients was observed and that symptom assessment alone is sufficient for evaluation of treatment effectiveness of LHBT-positive IBS patients.
the two groups after 2-week rifaximin treatment was observed. As such, clinical monitoring appears to be sufficient for the follow-up of IBS patients, who tested positive using LHBT prior to undergoing rifaximin treatment.

There is conflicting evidence on the potential confounding role of proton pump inhibitor (PPI) use in subjects undergoing breath testing as a surrogate parameter for SIBO. Spiegel et al. proposed a model where PPI use would be associated with increased risk for SIBO (diagnosed by hydrogen breath tests as surrogate parameters) due to the elimination of gastric acid. Although Lombardo et al. found an increased incidence of SIBO as measured using glucose hydrogen breath testing in patients undergoing PPI therapy, Ratuapli et al. could not detect an association between PPI use and increased risk of SIBO. In our study, the fraction of patients taking PPI was relatively low. In addition, this fraction was similar between those IBS patients with positive and negative LHBT. As such, we conclude that PPI use does not appear to be a confounding factor in our cohort of IBS patients.

This study has several important strengths and limitations. This is the first phase IV study demonstrating that the prevalence of positive LHBT is quite high in IBS patients in daily clinical practice and that therapy with rifaximin is efficacious in alleviating IBS-associated symptoms not only in the short term, but also for at least 3 months following the completion of the treatment. Furthermore, our study demonstrates that lactulose hydrogen breath testing can be easily utilised in routine clinical practice and that clinical monitoring alone is sufficient and does not necessitate additional LHBT following completion of the therapy as effectiveness of the therapy can be evaluated using a questionnaire assessing clinical symptoms. One limitation of this study may lie in the fact that it was not designed as a placebo-controlled trial. Furthermore, we did not systematically assess methane levels. Methane-producing bacteria utilise hydrogen for methane production and may therefore be associated with false negative hydrogen breath tests. Methane-producing flora is especially important in constipation-predominant IBS patients. We think that the results on treatment efficacy of rifaximin are not skewed as constipation-predominant IBS patients account for only 6% of the entire population. There is an ongoing controversy regarding the test that allows for accurate diagnosis of SIBO and whether surrogate methods can detect SIBO. Culture of jejunal aspirates was once considered as a gold standard for SIBO diagnosis. However, currently, it has been recognised that this method has its limitation due to the restricted accessibility of the distal small intestine, potential for bacterial contamination during sampling, and the possibility of false negative results, when culturing for obligate anaerobes. However, the results of the studies, where sampling of the small intestinal luminal contents was carried out using an aseptic technique, indicate that the positivity rate of culture aspirates has surpassed that of LHBT. Importantly, when compared with cultures of jejunal aspirates, LHBT showed 68% sensitivity and 44% specificity for SIBO diagnosis as determined by Corazza et al., and 16.7% sensitivity and 70% specificity as determined by Riordan et al. As such, these studies questioned the utility of LHBT in diagnosing SIBO even in combination with other tests, such as bowel scintigraphy.

Although lactulose hydrogen breath testing appears as a procedure, that is, easy to carry out in an outpatient setting, LHBT results may not be indicative of SIBO, but rather be reflective of the accelerated oro-cecal transit, as demonstrated in a study of Yu et al., who performed combined oro-cecal scintigraphy and LHBT in a cohort of IBS patients. The authors argued that the time difference between the arrival of the head of the test meal in the cecum and positive readout of LHBT is sufficient to allow for fermentation of the test meal in the colon and expiration of the hydrogen gas, and that antibiotic treatment reduces IBS-associated bloating by suppressing colonic bacteria in the colon, rather than in the small intestine. Regardless of the exact mechanism, the results of this and other studies convincingly demonstrate that rifaximin treatment results in consistent improvement of IBS-associated symptoms, especially bloating, when compared to placebo. Alleviation of IBS-associated symptoms by means of rifaximin treatment has consistently been shown to be associated with a very low rate of side effects, which can be explained by the minimal systemic absorption of this antibiotic. Therefore, in our opinion, the use of rifaximin for management of IBS symptoms appears to be a viable therapeutic option in patients with IBS.

In summary, our study demonstrates that a considerable proportion of IBS patients test positive by LHBT and that IBS symptoms (bloating, flatulence, diarrhoea, pain) were significantly diminished and overall well-being improved following a 2-week treatment with rifaximin. The positive treatment response lasted for at least 3 months. Our results confirm the existing high prevalence of positive LHBT in IBS patients and indicate that the extent of favourable treatment response to rifaximin is similar to the ones reported in trials performed in tertiary referral centres.
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