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DYSBIOSIS IN THE SMALL INTESTINE: TOWARDS AN OPTIMAL THERAPY TO NORMALIZE THE GUT MICROBIOTA

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Abstract – *Objectives:* Rifaximin seems to be effective and safe in treating small intestinal bacterial overgrowth (SIBO), however, to date there is no consensus regarding the proper timing of therapy. The present study aims to provide preliminary data regarding the effects of rifaximin (600 mg/day for five days) in patients with SIBO.

Patients and Methods: We retrospectively analysed clinical records and baseline lactulose breath tests of 15 otherwise healthy patients with an established diagnosis of SIBO. 7 subjects were treated with rifaximin at the daily dose of 600 mg/day for 5 days per month (group 1). The other 8 subjects were treated with the same daily dose of Rifaximin, but for two monthly cycles of 5 days each (group 2). All the patients repeated the breath test after one month. The results of the breath tests performed at the baseline and after a month were compared to determine whether the different dosage of the therapy had had different effects.

Results: Comparing the results of breath tests performed at baseline and after one month, we found a significant lowering in expired H2 levels in patients who received rifaximin in two monthly cycles, while expired H2 levels remained stable in patients treated with only one monthly cycle of rifaximin. All the patients reported a clinical improvement.

Conclusions: The present study suggests that Rifaximin may be able to improve intestinal dysbiosis and gastrointestinal symptoms due to SIBO, with results that seem to be more evident when rifaximin is administered in two monthly cycles rather than one.

Keywords: Gut microbiota, Small intestinal bacterial overgrowth, Rifaximin.

INTRODUCTION

The human gastrointestinal tract hosts trillions of bacteria, with a symbiotic mutualistic interaction with the human body[1].

In physiologic conditions intestinal barrier mechanisms determine a gradient in bacterial abundance, with the highest bacterial concentration detectable in the colon. Inflammatory bowel disease, pancreatitis, diabetes, abdominal surgery and all the conditions of altered intestinal anatomy or motility can significantly impair these barrier mechanisms. Consequently, bacteria can colonize the small intestine, determining a

state of dysbiosis which is frequently accompanied by gastrointestinal symptoms ranging from bloating and flatulence to abdominal pain, diarrhoea and indigestion[2].

The combination of intestinal dysbiosis and gastrointestinal non-specific symptoms is known as small intestinal bacterial overgrowth (SIBO), a condition not yet completely understood and with hard-to-estimate incidence and prevalence rates.

In fact, low specificity of symptoms and frequent association with other diseases, together with the absence of sensible and specific diagnostic tests, make the diagnosis of SIBO a challenge to physicians.

The best diagnostic method for the diagnosis of SIBO is the small bowel culture[3]. However, it is a high-cost, invasive test, limited by potential sample contamination and inability to detect bacterial strains that require special culture conditions.

Carbohydrate breath tests based on the detection of hydrogen and methane produced by intestinal bacteria represent a cheap, simple and non-risky diagnostic tool to support the diagnosis of SIBO[4,5].

Lactulose is one of the most used substrates for breath tests to assess intestinal dysbiosis and to estimate oral-cecal transit.

Since lactulose physiological fermentation happens in the colon, an early increase of hydrogen excretion (within 90 minutes) suggests bacterial fermentation in the small bowel. Baseline high hydrogen excretion or double peak of hydrogen excretion after lactulose administration are also considered suggestive of SIBO[5].

Lactulose breath test sensitivity rates are reported to range between 31 and 68%, while specificity rates range between 44 and 100%[6].

Regarding the therapeutical approach to SIBO, lifestyle and dietary changes, associated with identification and correction of predisposing factors and pharmacological treatment, are required[5].

Many studies evidenced the role of antibiotics in the modulation of gut microbiota (GM) in the improvement of gastrointestinal symptoms[7]. Among antibiotics, rifaximin showed its eubiotic function on GM with significant clinical improvement in patients with SIBO, with good safety profile[8] and the advantage of low systemic absorption. However, still to define are proper timing of drug administration and therapy duration.

MATERIALS AND METHODS

The present study aims to provide preliminary data regarding the effects of rifaximin administered at the dosage of 600 mg/day for five days in patients with an established diagnosis of SIBO.

We retrospectively analysed clinical records of 15 otherwise healthy patients (8 males and 7 females) aged between 30 and 60 years old. All the patients complained gastrointestinal non-specific symptoms including chronic abdominal pain, abdominal distention, diarrhoea, flatulence, and nausea. None of the patients suffered from other pathologies known to affect gastrointestinal motility.

Lactulose breath test was used to assess the diagnosis of SIBO. According to the 2017 North American Consensus on Hydrogen and Methane-based Breath Testing[9], 10 g of lactulose were administered to perform the test[9].

Exhaled H2 levels were then collected every 15 minutes for 240 minutes. A rise of $\geq$ 20 p.p.m. in hydrogen was considered diagnostic for SIBO.

All the patients had performed a baseline lactulose breath test which resulted suggestive of SIBO. They all reported that they had avoided laxatives, prokinetics, antibiotics and protonic pump inhibitors in the four weeks preceding the test; they also assured that they had followed a low-fiber diet the day before the test.

After the baseline test execution, rifaximin was given to 7 patients at the daily dose of 600 mg (200 mg after each of the 3 meals), for 5 days per month (group 1). The other 8 patients were treated with the same daily dose of Rifaximin, but for two monthly cycles of 5 days each (group 2).

The subjects continued their usual diet, except for the elimination of alcoholic beverages, coffee in quantities greater than two daily cups, cold and carbonated drinks, and smoking.

All the patients repeated the breath test after one month.

The results of the breath tests performed at the baseline and after one month were compared to determine whether the different dosage of the therapy had had different effects.

All enrolled subjects provided their written informed consent. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local Ethic Committee.

STATISTICAL ANALYSIS

Matched samples were compared with the Wilcoxon-Mann-Whitney test, while the Mann Whitney U test was used to compare independent samples.

RESULTS

At the baseline, we found no significant difference between expired H2 levels in the two groups of study (Table I).

Comparing the results of breath tests performed at baseline and after one month in group 1, no significant difference in expired H2 levels was observed (Table II).

Comparing the results of breath tests performed at baseline and after one month in group 2, we found a significant lowering in expired H2 levels at minutes 30, 45, 60, 75, 90 and 105. No significant difference emerged comparing H2 emission at minutes 0, 15 and from minutes 120 to 240 (Table III).

Finally, comparing the results of the breath tests repeated after one months between the two groups, we observed that expired H2 levels registered after 30, 45, 60, 75, 90 minutes from the beginning of the test were significantly lower in group 2 with respect to group 1. No significant difference in expired H2 levels was registered from minutes 0 to 15 and from minutes 105 to 240 from the beginning of the test (Table IV).

Complete breath tests results are available in Figures 1 and 2.

All the patients reported an improvement in their symptoms, although with individual variability.

DISCUSSION

SIBO represents a not yet completely understood pathological condition, whose management requires a global approach to the patient. The integration of lifestyle changes, identification and correction of predisposing factors, pharmacological therapy, and long-term response maintenance represents the cornerstone of the treatment.

Regarding the pharmacological approach, rifaximin represents a first line strategy to restore intestinal microflora, with the advantage of very poor systemic absorption and bactericidal action on aerobic and anaerobic bacteria[10]. To date, however, no data are available on the optimal dosage and timing of therapy.

TABLE 1. EXPIRED H2 LEVELS (PARTS PER MILLION – PPM) AT BASELINE LACTULOSE BREATH TESTS.

	Group 1	Group 2	*p*-value
0′	3 (2-5.5)	4 (2.75-7.5)	0.23
15′	6 (4-8.5)	3 (7.5-10.5)	0.06
30′	7 (6-10)	10.5 (5.75-18.25)	0.69
45′	13 (7-21)	21.5 (13.5-35)	0.27
60′	15 (11-31.5)	29 (16.75-43.75)	0.22
75′	22 (11-36.5)	23 (20.25-33.75)	0.77
90′	22 (22-45)	29.5 (17.5-41)	0.68
105′	37 (24.5-51.5)	34.5 (20-39.5)	0.38
120′	34 (28-69.5)	35.5 (25-36.75)	0.38
135′	40 (28-58.5)	29,5 (25.25-44.5)	0.49
150′	49 (31.5-70.5)	33 (18.75-44.25)	0.09
165′	45 (28.5-57)	35 (26-39.5)	0.31
180′	35 (30-61.5)	31 (22.5-34.5)	0.23
195′	44 (26.5-51)	28 (22,75-31)	0.30
210′	41 (31.5-46.25)	25.5 (17.5-41)	0.42
225′	37 (32.25-40.25)	28 (21-35.25)	0.23
240′	37,5 (27-44.25)	24 (16.25-35)	0.26

TABLE 2. EXPIRED H2 LEVELS (PPM) AT BREATH TESTS PERFORMED AT BASELINE AND AFTER ONE MONTH IN PATIENTS WHO RECEIVED 1 MONTHLY CYCLE OF RIFAXIMIN 600 MG/DAY FOR 5 DAYS

	Baseline	After 1 month of treatment	*p*-value
0′	3 (2-5.5)	3 (3-3.5)	0.92
15′	6 (4-8.5)	3 (2.5-4)	0.11
30′	7 (6-10)	7 (7-8)	0.87
45′	13 (7-21)	6 (5-24)	0.51
60′	15 (11-31.5)	21 (9.5-23)	0.77
75′	22 (11-36.5)	26 (13-40)	0.93
90′	22 (22-45)	28 (21-41.5)	0.87
105′	37 (24.5-51.5)	22 (16-28.5)	0.07
120′	34 (28-69.5)	24 (18.5-42)	0.07
135′	40 (28-58.5)	23 (21.5-31.5)	0.06
150′	49 (31.5-70.5)	34 (16-35.5)	0.15
165′	45 (28.5-57)	33 (14-41)	0.22
180′	35 (30-61.5)	27 (17-40.5)	0.13
195′	44 (26.5-51)	24.5 (16.5-36.25)	0.46
210′	41 (31.5-46.25)	26.5 (17-30.75)	0.28
225′	37 (32.25-40.25)	25 (16-28.75)	0.19
240′	37.5 (27-44.25)	22 (14.5-22)	0.23

This study suggests that the administration of rifaximin (600 mg/day for 5 days) in two monthly cycles may have better outcomes in terms of hydrogen emission tested with lactulose breath test.

In fact, the repetition of the breath test after the administration of only one monthly cycle of rifaximin showed no differences in hydrogen emissions, while the repetition of the breath test after 2 monthly cycles of rifaximin showed a correction of the dysbiotic profile of the emitted gases.

This observation is in accordance with the tendency of the intestinal microbiota to return to basal characteristics after therapy discontinuation[11].

TABLE 3. EXPIRED H2 LEVELS AT BREATH TESTS PERFORMED AT BASELINE AND AFTER ONE MONTH IN PATIENTS WHO RECEIVED 2 MONTHLY CYCLES OF RIFAXIMIN 600 MG/DAY FOR 5 DAYS.

	Baseline	After 1 month of treatment	*p*-value
0′	4 (2.75-7.5)	2 (1-3.25)	0.13
15′	3 (7.5-10.5)	4 (2-4.25)	0.10
30′	**10.5 (5.75-18.25)**	**3 (1-4.75)**	**0.04**
45′	**21.5 (13.5-35)**	**2.5 (2-4.75)**	**0.001**
60′	**29 (16.75-43.75)**	**3.5 (2-4.25)**	**0.001**
75′	**23 (20.25-33.75)**	**3 (2.75-6.75)**	**0.002**
90′	**29.5 (17.5-41)**	**3 (3-7)**	**0.001**
105′	**34.5 (20-39.5)**	**3 (2-9)**	**0.002**
120′	35.5 (25-36.75)	6 (4.5-17.75)	0.08
135′	29.5 (25.25-44.5)	10 (3,75-27,25)	0.07
150′	33 (18.75-44.25)	16 (4.25-38.5)	0.25
165′	35 (26-39.5)	9 (2.5-33)	0.22
180′	31 (22.5-34.5)	20 (6-33.5)	0.32
195′	28 (22.75-31)	15 (11.5-27)	0.35
210′	25.5 (17.5-41)	23 (10.5-42)	0.84
225′	28 (21-35.25)	18 (11-37.75)	1.0
240′	24 (16.25-35)	19.5 (14-43.75)	0.94

TABLE 4. EXPIRED H2 LEVELS (PARTS PER MILLION – PPM) AT LACTULOSE BREATH TESTS PERFORMED AFTER ONE MONTH OF TREATMENT IN GROUP 1 AND GROUP 2.

	Group 1	Group 2	*p*-value
0′	3 (3-3.5)	2 (1-3.25)	0.25
15′	3 (2.5-4)	4 (2-4.25)	0.82
30′	**7 (7-8)**	**3 (1-4.75)**	**0.04**
45′	**6 (5-24)**	**2,5 (2-4.75)**	**0.04**
60′	**21 (9.5-23)**	**3.5 (2-4.25)**	**0.02**
75′	**26 (13-40)**	**3 (2.75-6.75)**	**0.006**
90′	**28 (21-41.5)**	**3 (3-7)**	**0.03**
105′	22 (16-28.5)	3 (2-9)	0.09
120′	24 (18.5-42)	6 (4.5-17.75)	0.09
135′	23 (21.5-31.5)	10 (3.75-27.25)	0.38
150′	34 (16-35.5)	16 (4.25-38.5)	0.64
165′	33 (14-41)	9 (2.5-33)	0.34
180′	27 (17-40.5)	20 (6-33.5)	0.34
195′	24.5 (16.5-36.25)	15 (11.5-27)	0.42
210′	26.5 (17-30.75)	23 (10,5 -42)	1
225′	25 (16-28.75)	18 (11-37.75)	0.81
240′	22 (14.5-22)	19.5 (14-43.75)	1

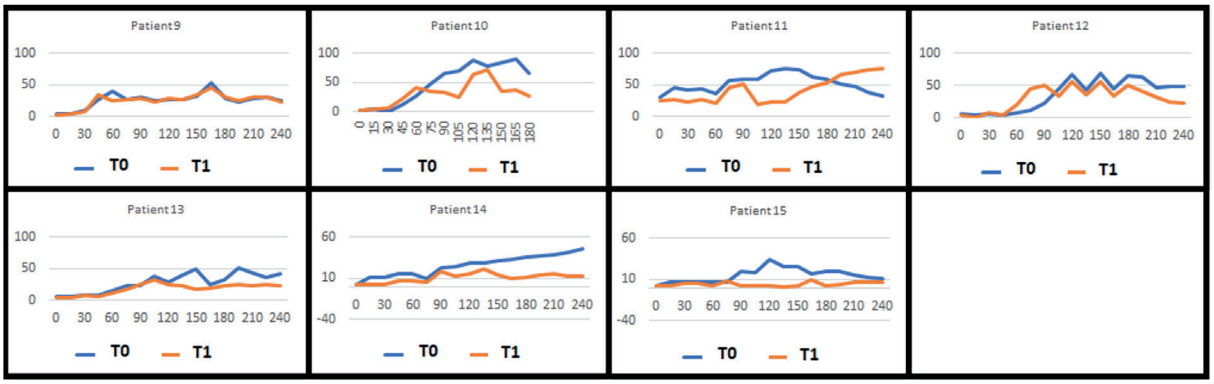

Figure 1. Baseline (T0) and after one month of treatment (T1) breath tests of patients treated with one monthly cycle of rifaximin (600 mg/day for 5 days)

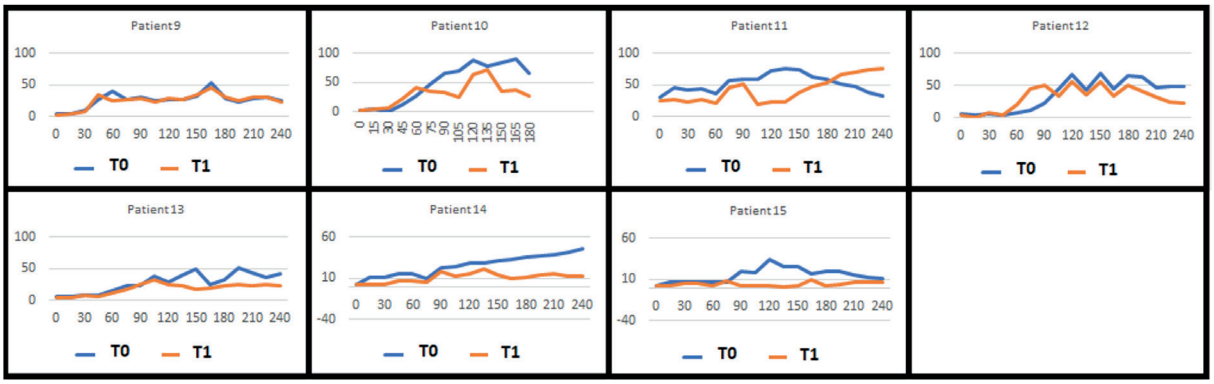

Figure 2. Baseline (T0) and after one month of treatment (T1) breath tests of patients treated with two monthly cycles of rifaximin (600 mg/day for 5 days)

Our study has several limitations; the retrospective design, the small sample and short follow up prevent from drawing definitive conclusions.

CONCLUSIONS

Overall, our study seems to suggest that Rifaximin may be able to improve intestinal dysbiosis and gastrointestinal symptoms due to SIBO, with results that seem to be more evident when rifaximin is administered in two monthly cycles rather than one.

In fact, all the patients reported clinical improvement, but breath test results seem to suggest a better outcome in patients treated with two monthly cycles.

Further investigation, focusing on larger cohorts of patients, with longer follow up and investigating also expired CH4 levels on breath test, are needed to better define this topic.

Conflict of interest

The authors declare no conflict of interest.

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