Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole


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**Abstract. – Background and Objectives:** Few controlled trials on antibiotic therapy for small intestinal bacterial overgrowth are available at present. Aim of the study was to assess efficacy, safety and tolerability of rifaximin with respect to metronidazole for the treatment of small intestinal bacterial overgrowth.

**Material and Methods:** We enrolled 142 consecutive patients with diagnosis of small intestinal bacterial overgrowth. Diagnosis of small intestinal bacterial overgrowth based on the clinical history and the positivity of glucose breath test. Patients were randomised to two 7-day treatment groups: rifaximin 1200 mg/day and metronidazole 750 mg/day. Glucose breath test was reassessed 1 month after. Compliance and side-effect incidence were also evaluated.

**Results:** One drop-out was observed in rifaximin group. Five drops-out occurred in metronidazole group. The glucose breath test normalization rate was significantly higher in the rifaximin with respect to the metronidazole group (63.4% versus 43.7%; \(p<0.05\); OR 1.50, 95% CI 1.14-4.38). The overall prevalence of adverse events was significantly lower in rifaximin with respect to metronidazole group.

**Discussion:** Rifaximin showed an higher SIBO decontamination rate than metronidazole at the tested doses, both with a significant gain in terms of tolerability. Either the present study or recent evidencies suggest that rifaximin represents a good choice for the management of patients affected by SIBO.

**Key Words:** Bacterial overgrowth, Glucose breath test, Rifaximin, Metronidazole.

**Abbreviations**

SIBO: small intestinal bacterial overgrowth

CFU: colony-forming unit

GBT: glucose breath test

\( \text{H}_2 \): hydrogen

IBS: irritable bowel syndrome

**Introduction**

Small intestinal bacterial overgrowth (SIBO) is a common clinical syndrome due to an increased level of bacteria exceeding the presence of more than \(10^5\) CFU/mL of intestinal aspirate or of colonic-type species within the small bowel\(^1,2\).

SIBO symptoms could be many and variably associated: abdominal pain or discomfort, bloating, diarrhoea and/or signs of malabsorption are the most common\(^1,2\). Recent findings suggest that SIBO is highly prevalent in patients with IBS and that SIBO decontamination is associated to a significant improvement of IBS symptoms\(^3,5\).

The culture of jejunal aspirates, regarded by many as the gold standard for the SIBO diagnosis, has several limitations such as the potential for contamination by oropharyngeal bacteria during intubation, and the fact that SIBO may be patchy and thus missed by a single aspiration. In addition, it is too much invasive, expensive and difficult and too little reproducible to be proposed as a routine diagnostic test for SIBO in the clinical practice, especially for patients with non-specific symptoms or those requiring repeated testing\(^1,2\).

The GBT is considered a simple tool for SIBO diagnosis, since it is non invasive, highly reproducible and expensive when compared to the culture of jejunal aspirates. In addition, the specificity and the sensitivity of GBT are acceptable for screening studies (77-100% and 67-98% respectively)\(^6,8\). The \( \text{H}_2 \) produced in the human body after glucose ingestion derives entirely...
from intestinal bacterial fermentation. The appearance of an early increase in breath H\textsubscript{2} concentration suggests the presence of SIBO\textsuperscript{6-8}.

An effective antibiotic decontamination regimen should include one or more drugs with activity against both aerobic and anaerobic bacteria since SIBO may occur either by a mix of aerobic and anaerobic flora or by purely aerobic flora in a minority of cases\textsuperscript{1,2,9-11}. Empirical courses of broad-spectrum antibiotics are widely used at present for SIBO decontamination, since few well-conducted trials have been performed up today to verify which is the best antibiotic regimen\textsuperscript{1,2,11,12}.

Metronidazole is effective against Gram-negative and Gram-positive anaerobic bacteria such as \textit{Bacteroides}, \textit{Fusobacterium} and \textit{Peptostreptococci}\textsuperscript{13}. These characteristics make it potentially useful for the treatment of small bowel bacterial overgrowth as confirmed by literature data\textsuperscript{14}.

Rifaximin is a rifamycin derivative with antibacterial activity caused by inhibition of bacterial synthesis of RNA\textsuperscript{15}. It is active against gram-positive and gram-negative bacteria, including both aerobes and anaerobes\textsuperscript{15-17}. Less than 0.1\% of the oral dose is absorbed\textsuperscript{16}. Rifaximin at a dosage of 1200 mg per day for 1 week is associated to a significant gain in terms of therapeutic efficacy in SIBO contamination without increasing the incidence of side-effects with respect to lower dosages (600 and 800 mg per day for the same treatment period)\textsuperscript{18}.

The aim of the present study was to assess the efficacy, safety and tolerability of the non-absorbable antibiotic rifaximin with respect to the systemic antibiotic metronidazole in patients affected by SIBO.

**Material and Methods**

This prospective parallel-group randomized trial was conducted between February 2005 and August 2007 in consecutive out-patients from the Gastroenterology and Internal Medicine Departments of the Catholic University of Rome, Italy.

**Inclusion/Exclusion Criteria**

Patients referring to our centre for the presence of gastrointestinal symptoms (bloating, abdominal pain, flatulence and diarrhoea) since ≥ 6 months were evaluated.

Major organic gastrointestinal disorders were ruled out on the basis of: history collection; full physical examination; laboratory tests (total blood count, erythrocyte sedimentation rate, reactive C protein, stool examination for occult blood, ova and parasites, anti-transglutaminase antibodies); abdominal ultrasonography and colonoscopy when alarm symptoms were present (fever, gastrointestinal bleeding, weight loss, anemia, abdominal mass).

The Rome II criteria were used to verify the diagnosis of IBS or other functional bowel disorders\textsuperscript{19}.

The exclusion criteria were: previous antibiotic treatment associated to SIBO diagnosis; age <18 years; use of antimicrobial agents within the previous 3 months; hypersensitivity to the antibiotics used in the present study; pregnancy or breast-feeding; evidence of major concomitant diseases (including tumours and hepatic and/or renal insufficiency).

Exclusion criteria were: age <18 years; hypersensitivity to the antibiotics; pregnancy or breast-feeding; evidence of major concomitant diseases (including tumours and hepatic and/or renal insufficiency). Consecutive patients with positive GBT were included in the present study after informed consent.

The procedures followed were in accordance with the Helsinki Declaration of the World Medical Association.

**Laboratory Parameters**

Total blood cell count, liver and kidney function were assessed in all patients at enrolment and 3 days after the end of the treatment.

**Breath H\textsubscript{2} Testing**

GBT was performed under standard conditions. In the month preceding the test patients should not have received antibiotics or laxatives. To minimize basal H\textsubscript{2} excretion, patients were asked to follow a carbohydrate-restricted dinner on the day before the test and to fast for at least 12 hours. On the day of testing, patients did a mouthwash with 20 ml of chlorhexidine 0.05\%. Smoking and physical exercise were not allowed for 30 minutes before and during the test. End-alveolar breath samples were collected immediately before glucose ingestion. A dose of 50 g of glucose in the form of iso-osmotic solution was administered and samples were taken every 10 min for 2 hours respectively using a two-bag system. The two-bag system is a device consist-
Table I. Demographic and clinical characteristics of SIBO positive patients included in the two treatment groups (group 1=rifaximin; group 2=metronidazole). BMI, body mass index; IBS, irritable bowel syndrome; FAD, functional abdominal disorder.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 71)</th>
<th>Group 2 (n = 71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34 ± 9</td>
<td>35 ± 11</td>
<td>ns</td>
</tr>
<tr>
<td>Males (%)</td>
<td>35%</td>
<td>40%</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22 ± 6</td>
<td>22 ± 7</td>
<td>ns</td>
</tr>
<tr>
<td>IBS</td>
<td>45%</td>
<td>39%</td>
<td>ns</td>
</tr>
<tr>
<td>Functional abdominal bloating</td>
<td>21%</td>
<td>25%</td>
<td>ns</td>
</tr>
<tr>
<td>Functional abdominal pain</td>
<td>15%</td>
<td>14%</td>
<td>ns</td>
</tr>
<tr>
<td>Unspecified FAD</td>
<td>19%</td>
<td>22%</td>
<td>ns</td>
</tr>
</tbody>
</table>
treated with metronidazole with respect to those treated by rifaximin. In fact, 5 drop-outs occurred in the metronidazole group (one for the inability to maintain appointments and 4 for the occurrence of side-effects), with respect to 1 in the rifaximin group (for the inability to maintain appointments).

**GBT Normalization Rate**

The glucose breath test normalization rate was significantly higher in the rifaximin with respect to the metronidazole group in intention-to-treat analysis (63.4%, 45/71 versus 43.7%, 31/71; \( p < 0.05 \); OR 1.50, 95% CI 1.14-4.38). No significant differences were found between groups in per protocol analysis.

**Side-Effects Profile**

No abnormalities in the tested laboratory parameters were observed in the two groups at the control performed three days after the end of the treatment. Details on the incidence of adverse events during the study period are reported in Table II. The overall incidence of adverse events was 15.5% (22/142). The overall incidence of adverse events was significantly higher in the metronidazole with respect to the rifaximin group (22.5%, 16/71 versus 8.5%, 6/71; OR 1.59, 95% CI 1.15-8.61).

In the metronidazole group, 3 patients reported adverse events graduated as moderate and 4 patients abandoned the study because of the occurrence of severe adverse events. The 6 adverse experiences observed in the rifaximin group were all mild.

**Table II.** Adverse events during the study period in the two treatment groups (group 1=rifaximin; group 2=metronidazole).

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Group 1 (n=71)</th>
<th>Group 2 (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rush</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Bloating</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

**Discussion**

Empirical courses of broad-spectrum antibiotics are widely used at present in the clinical setting for SIBO decontamination\(^1,2,10-12\). This occurs for several reasons. Few literature data are available on the bacterial population contaminating the small bowel and its antibiotic sensitivity patterns\(^1,2,9\). On the other hand, although ideally the choice of antimicrobial agent should reflect in vitro susceptibility testing, this usually is impractical in the case of SIBO because many different bacterial species, with different antibiotic sensitivities, typically coexist\(^1,2,9\). In addition, few well-conducted clinical trials have been performed in order to assess the most effective and safe antibiotic regimen for SIBO decontamination\(^1,2\).

Metronidazole may be suitable for SIBO treatment since it is effective against Gram-negative and Gram-positive anaerobic bacteria such as *Bacteroides*, *Fusobacterium* and *Peptostreptococci*\(^13,14\). Castiglione et al\(^14\) showed a good therapeutic efficacy of both metronidazole and ciprofloxacin in terms of breath test normalization rate in patients affected by Crohn’s disease and evidence of SIBO.

However, all systemic antibiotics, also if endowed with a satisfactory efficacy profile, are associated to several side-effects such as diarrhoea, constipation, dizziness, weakness, skin rush and dyspepsia. The safety and tolerability of an antibiotic treatment are as important as its efficacy, especially in a disease as SIBO that is characterized by high recurrence rate and necessity of repeated antibiotic courses.

Non-absorbable antibiotics such as neomycin and rifaximin, both able to act against bacteria topically within the gut lumen, have been proposed for treatment of SIBO in order to minimize the potential side-effects of systemic antibiotics.

The neomycin treatment achieved the normalization of lactulose breath test in 20% of patients carrying SIBO with respect to 2% in the placebo group; no relevant side-effects and no drop-out were observed during the study\(^21\). The high binding (about 90%) of neomycin with faeces could explain the limited *in vivo* activity\(^21\).

Rifaximin has a broad-spectrum antibiotic efficacy, especially against anaerobic intestinal bacteria, such as *Bacteroides*, *Lactobacilli* and *Clostridia*, bacteria frequently responsible for metabolic alterations observed in SIBO patients\(^15-17\). Its toxicity is very low since it is not
Absorbed by the gut in a double-blind controlled trial, Di Stefano et al. compared the efficacy of rifaximin (1200 mg/die) with respect to clindamycin in the short-term treatment of SIBO. GBT normalized in 70% of patients treated with rifaximin compared to 27% of the clindamycin group. No side-effect occurred, thus confirming that rifaximin is a safe drug for SIBO treatment. In a recent study by our group, higher doses of rifaximin (1200 mg/day) led to a significantly higher therapeutic efficacy in terms of SIBO contamination with respect to doses of 600 and 800 mg per day. Moreover, at the tested doses, rifaximin was associated with uncommon, mild, transient side-effects and no drop-out was registered. Another advantage of rifaximin concerns antibiotic resistance: it has been demonstrated that resistant strains rapidly disappear from the gut thus allowing cyclic administration of rifaximin.

In the present study we tested efficacy, safety, and tolerability of rifaximin with respect to a systemic antibiotics such as metronidazole for SIBO decontamination. Rifaximin showed an higher decontamination rate compared to the absorbable antibiotic metronidazole, both with a significant gain in terms of tolerability.

In conclusion, the present data, both with available previous literature evidences, suggest that rifaximin may represent a good option for SIBO decontamination in consideration of its good GBT normalization rate, null toxicity, high tolerability. Future studies should be addressed to the management of SIBO patients refractory to the current rifaximin decontamination scheme and to verify its efficacy in the re-treatment of patients with SIBO recurrence.

References


2) Quigley E, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology 2006; 130(2 Suppl. 1): 78-90.


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