Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth

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SUMMARY
Background: Few controlled studies assessing choice and duration of antibiotic therapy for small intestinal bacterial overgrowth are available.
Aim: To assess efficacy, safety and tolerability of different doses of rifaximin, a broad spectrum non-absorbable antibiotic, for intestinal bacterial overgrowth eradication.
Methods: We enrolled 90 consecutive patients affected by small intestinal bacterial overgrowth. The presence of small intestinal bacterial overgrowth was based on the occurrence of a rise of H\textsubscript{2} values >12 p.p.m. above the basal value after 50 g glucose ingestion. Patients were randomized in three 7-day treatment groups: rifaximin 600 mg/day (group 1); rifaximin 800 mg/day (group 2) and rifaximin 1200 mg/day (group 3). Glucose breath test was reassessed 1 month after the end of therapy. Compliance to the treatment and incidence of side-effects were also evaluated.
Results: No drop-outs were observed in the three groups. Glucose breath test normalization rate was significantly higher in group 3 (60%) with respect to group 1 (17%; \( P < 0.001 \)) and group 2 (27%, \( P < 0.01 \)). No significant differences in patient compliance and incidence of side-effects were found among groups.
Conclusions: Higher doses of rifaximin lead to a significant gain in terms of therapeutic efficacy in small intestinal bacterial overgrowth eradication without increasing the incidence of side-effects.

INTRODUCTION
Small intestinal bacterial overgrowth (SIBO) is a clinical condition characterized by a malabsorption syndrome because of an increase in micro-organisms to a level exceeding \( 10^5 \) bacteria/mL of jejunal juice.\(^1\) Glucose breath test (GBT) has been proposed as a sensitive and simple tool for the diagnosis of bacterial overgrowth, being non-invasive and inexpensive compared with the gold standard, which is represented by the culture of intestinal aspirates; specificity and sensitivity of GBT are acceptable for screening studies (77–100% and 67–98% respectively).\(^2–4\) The \( \text{H}_2 \) and \( \text{CH}_4 \) produced in the human body after glucose ingestion derive entirely from intestinal bacterial fermentation, therefore the appearance of an early increase in breath \( \text{H}_2 \) or \( \text{CH}_4 \) concentration indicates the presence of a small bowel bacterial overgrowth.\(^2–4\)

Antibiotic therapy is the cornerstone of the treatment of SIBO. Current SIBO treatment is based on empirical courses of broad spectrum antibiotics as few controlled studies with respect to choice and duration of antibiotic therapy exist at present.\(^1\)

A remarkable improvement in symptoms can be achieved in most patients.\(^1\) Overgrowth may occur either by a mix of aerobic and anaerobic flora or by purely aerobic flora. Therefore, the most effective antibiotic regimens generally include one or more drugs with activity against aerobic and anaerobic bacteria.\(^1\)
Rifaximin is a rifamycin derivative with antibacterial activity caused by inhibition of bacterial synthesis of RNA.\(^5\) It is active against Gram-positive and Gram-negative bacteria, including both aerobes and anaerobes.\(^6\) Less than 0.1% of the oral dose of rifaximin is absorbed.\(^6\) Rifaximin is available in Italy for the treatment of acute bacterial diarrhoea,\(^7\) portosystemic encephalopathy\(^8\) and small bowel bacterial overgrowth syndrome,\(^9\) and it is also licensed in many countries of Europe and other continents.

The aim of the present study was to assess the efficacy as well as safety and tolerability of different doses of rifaximin for the treatment of SIBO.

METHODS

This is a prospective, parallel-group, randomized trial. It was conducted between September 2003 and October 2004 in consecutive out-patients from the Gastroenterology and Internal Medicine Departments of the Gemelli Hospital, Catholic University of Rome.

Eligibility criteria

Patients underwent GBT for various chronic gastrointestinal symptoms, the most common being bloating, abdominal discomfort and diarrhoea. Consecutive patients with positivity to GBT were included in the study after giving written informed consent. The exclusion criteria were: age <18 years; use of antimicrobial agents within the previous 3 months; hypersensitivity to the antibiotics belonging to rifamycin and/or tetracyclin families; pregnancy or breast feeding; evidence of major concomitant diseases (including tumours and hepatic and/or renal insufficiency).

Laboratory parameters

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

Breath \(\text{H}_2\) testing

The GBT was performed under standard conditions. In the 30 days preceding the test, no patients had received antibiotics or laxatives. To minimize basal \(\text{H}_2\) excretion, subjects were asked to have a carbohydrate-restricted dinner on the day before the test and to be fasting for at least 12 h. On the day of testing, patients did a mouthwash with 20 mL of 0.05% chlorhexidine. Smoking and physical exercise were not allowed for 30 min before and during the test. End-alveolar breath samples were collected immediately before glucose ingestion. Then 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 h respectively using a two-bag system. The two-bag system is a device consisting of a mouthpiece, a T-valve and two collapsible bags, the first one collects dead space air, the second one collects alveolar air. From this bag the breath sample was aspirated into a 20 mL plastic syringe. Samples were analysed immediately using a model DP Quintron Gas Chromatograph (Quintron Instrument Company, Milwaukee, WI, USA). The test was considered as indicative of SIBO in the presence of an increase in \(\text{H}_2\) excretion >12 p.p.m. over the baseline value within 2 h.\(^3\) The GBT was repeated 1 month after the end of therapy in all patients in order to assess SIBO eradication.

Outcomes

The primary outcomes of the study were SIBO eradication rates using the three different rifaximin schemes.

Secondary outcomes were patient compliance and incidence of side-effects in the three therapeutic schemes. Compliance was assessed by a pill count of the drugs boxes returned the day after the last day of therapy administration. Low compliance was defined as more than 20% of pills returned. Side-effects were defined as the occurrence of (i) abnormalities in the main haematocchemical parameters considered; (ii) ‘adverse experiences’, considered as clinical findings or patient complaints that were not present in the 24 h immediately before the enrolment in the trial. At enrolment, each patient was asked to complete daily dairy cards on which recording and graduate (1 = mild; 2 = moderate; 3 = severe) any ‘adverse experience’ during the treatment period and then to return them at the post-therapy interview.

Randomization

Using a computer-generated number sequence, generated by a statistician, the patients were randomly assigned to one of following three 7-day treatment groups with rifaximin (Alfa Wasserman, Bologna, Italy).
1 Rifaximin 600 mg/die (one tablet t.d.s.; group 1: n = 30);
2 rifaximin 800 mg/die (two tablets at 8:00 AM, one tablet at 2:00 and 8:00 PM; group 2: n = 30); and
3 rifaximin 1200 mg/die (two tablets t.d.s.; group 3: n = 30).

Data analysis

Both per-protocol (PP) and intention-to-treat (ITT) analyses were performed. For the purpose of the analysis, the incidence of side-effects was considered as a binomial variable (present/absent). To detect differences in SIBO eradication rates and the incidence of side-effects, the chi-square or Fisher’s exact tests were used. Odds ratio (OR) for achieving SIBO eradication with 95% confidence intervals (CI) were calculated. P < 0.05 was considered to be statistically significant. The statistical analysis was performed using STATA 6.0.

RESULTS

Patients characteristics and overall compliance

Characteristics of the study groups are summarized in Table 1. No drop-outs were observed in the three groups.

Compliance with all the three rifaximin dosages was excellent. More than 95% of patients in all groups took the prescribed number of tablets for the 7-day treatment.

Breath $H_2$ testing normalization rates

Glucose breath test normalization rate was significantly higher in the group 3 (60.0%, 18 of 30 patients) with respect to the group 1 (16.7%, five of 30 patients; OR: 7.50; 95% CI: 2.24–25.06, P < 0.001) and the group 2 (26.7%, eight of 30 patients; OR: 4.12; 95% CI: 1.39–12.27, P < 0.01) in both ITT and PP analysis. No significant differences were observed between the group 1 and the group 2 in terms of GBT normalization rate (OR: 1.82; 95% CI: 0.52–6.38, P = N.S.; Figure 1).

Side-effects profile

No abnormalities in the tested laboratory parameters (total blood cell count, liver and kidney function) were observed at the control performed 3 days after the end of the treatment.

Details on the incidence of adverse events during the study period are reported in Table 2. The overall prevalence of adverse events was similar in the three groups. Eleven (12%) of the enrolled subjects had at

Table 1. Demographic and clinical characteristics of SIBO-positive patients included in the three treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 30)</th>
<th>Group 2 (n = 30)</th>
<th>Group 3 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>8/22</td>
<td>9/21</td>
<td>7/23</td>
</tr>
<tr>
<td>(male/female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>31 ± 14</td>
<td>34 ± 12</td>
<td>32 ± 10</td>
</tr>
<tr>
<td>(mean ± s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>21 ± 8</td>
<td>22 ± 6</td>
<td>20 ± 9</td>
</tr>
</tbody>
</table>

SIBO, small intestinal bacterial overgrowth; BMI, body mass index.

Table 2. Details of the incidence of adverse events during the study in the three treated groups

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Group 1 (n = 30)</th>
<th>Group 2 (n = 30)</th>
<th>Group 3 (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Overall</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
least one adverse event during the treatment period. No differences in the overall prevalence of adverse events were observed among the three groups. The complaints were mild in all cases and similar in the three groups. Weakness, headache, constipation, dizziness, insomnia were the adverse events reported.

DISCUSSION
As few controlled studies concerning choice and duration of the antibiotic therapy are available, current treatment options for SIBO eradication are based on empirical courses of broad spectrum antibiotics.\(^1\)

Attar et al. compared the efficacy of three different agents for the treatment of bacterial overgrowth-related diarrhoea (amoxicillin-clavulanic acid, norfloxacin and \textit{Saccharomyces boulardii}) showing that stools declined by 29\% and 45\% with amoxicillin-clavulanic acid and norfloxacin, yet negative H\(_2\) breath test percentages were 50\% and 30\%, respectively.\(^10\) A recent study by Castiglione et al. found satisfactory therapeutic efficacy of both metronidazole and ciprofloxacin in terms of SIBO eradication in patients affected by Crohn’s disease.\(^11\)

To minimize the potential side-effects because of systemic antibiotics, some authors evaluated the therapeutic efficacy of non-absorbable antibiotics such as neomycin and rifaximin, able to act topically in the gut lumen against bacterial overgrowth. In a recent study by Pimentel et al. on 111 irritable bowel syndrome (IBS) patients, treatment with neomycin, a non-absorbable aminoglycoside widely employed for gut decontamination especially in patients with portosystemic encephalopathy, 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 were observed during the study. No drop-out associated with the drug occurred.\(^12\) The high binding (about 90\%) of neomycin with faeces could explain the limited \textit{in vivo} activity.\(^13\) Moreover, in a recent animal study, neomycin has been shown to not cause significant changes in total aerobic bacterial count in faeces samples.\(^14\)

Rifaximin has a broad spectrum antibiotic efficacy, in particular against anaerobic intestinal bacteria, such as bacteroides, lactobacilli and clostridia, bacteria frequently responsible for metabolic alterations observed in SIBO patients.\(^5\) \(^6\) Rifaximin has the similar active characteristics of rifamycin, but it is not absorbed from gut, therefore it exhibits less toxicity.\(^5\) \(^6\) Corazza et al. tested rifaximin at different doses (800 mg/die and 1200 mg/die) in two groups of only six patients affected by SIBO as diagnosed by lactulose breath test: they found that the use of higher doses of rifaximin did not increase the therapeutic efficacy of the drug. Moreover, any side-effects occurred during the treatment period.\(^15\) In a double-blind controlled trial Di Stefano et al. compared the efficacy of rifaximin (1200 mg/die) with respect to chlortetracycline in the short-term treatment of SIBO. H\(_2\) glucose BT normalized in 70\% of patients treated with rifaximin vs. 27\% of patients treated with chlortetracycline. No patient showed any side-effect, confirming that rifaximin was a safe drug for SIBO treatment.\(^9\)

At the best of our knowledge, this is the only available study on a large population testing the therapeutic efficacy of different doses of rifaximin for SIBO eradication. Results from the present study show that higher doses of rifaximin (1200 mg/die) were associated with a significantly higher therapeutic efficacy in terms of SIBO eradication with respect to doses of 600 and 800 mg/day. Moreover, at the tested doses, rifaximin was associated with uncommon, mild, transient side-effects and no drop-out associated with the drug was registered among three groups.

On the basis of the available literature, the 7 days – 1200 mg rifaximin therapy is a good option in terms of efficacy and tolerability for SIBO treatment. Future researches should be addressed to evaluate the management of patients refractory to the present eradication scheme and to assess the efficacy of the same therapeutic approach in the retreatment of patients with SIBO recurrence.

ACKNOWLEDGEMENT
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REFERENCES
4 Corazza GR, Menozzi MG, Strocchi A, et al. The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture