

High dosage rifaximin for the treatment of small intestinal bacterial overgrowth

E. SCARPELLINI, M. GABRIELLI, C. E. LAURITANO, A. LUPASCU, G. MERRA, G. CAMMAROTA, I. A. CAZZATO, G. GASBARRINI & A. GASBARRINI

Internal Medicine Department, Gemelli Hospital, Catholic University of Sacred Heart, Rome, Italy

Correspondence to:
Dr. A. Gasbarrini, Internal Medicine and Angiology, Catholic University of Sacred Heart, Gemelli Hospital, Largo A. Gemelli, 8; 00168 Rome, Italy.
E-mail: angiologia@rm.unicatt.it

Publication data

Submitted 12 October 2006
First decision 30 October 2006
Resubmitted 3 January 2007
Accepted 15 January 2007

SUMMARY

Background

Rifaximin is a broad spectrum non-absorbable antibiotic used for treatment of small intestinal bacterial overgrowth. Doses of 1200 mg/day showed a decontamination rate of 60% with low side-effects incidence.

Aims

To assess efficacy, safety and tolerability of rifaximin 1600 mg with respect to 1200 mg/day for small intestinal bacterial overgrowth treatment.

Methods

Eighty consecutive small intestinal bacterial overgrowth patients were enrolled. Diagnosis of small intestinal bacterial overgrowth based the clinical history and positivity to H₂/CH₄ glucose breath test. Patients were randomized in two 7-day treatment groups: rifaximin 1600 mg (group 1); rifaximin 1200 mg (group 2). Glucose breath test was reassessed 1 month after. Compliance and side-effect incidence were also evaluated.

Results

One drop-out was observed in group 1 and two in group 2. Glucose breath test normalization rate was significantly higher in group 1 with respect to group 2 both in intention-to-treat (80% vs. 58%; $P < 0.05$) and per protocol analysis (82% vs. 61%; $P < 0.05$). No significant differences in patient compliance and incidence of side effects were found between groups.

Conclusions

Rifaximin 1600 mg/day showed a significantly higher efficacy for small intestinal bacterial overgrowth treatment with respect to 1200 mg with similar compliance and side-effect profile.

Aliment Pharmacol Ther 25, 781–786

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a frequent clinical condition defined as an abnormally high bacterial population level in the upper small intestine, exceeding 10^6 organisms/mL. SIBO symptoms could be many and variably associated; abdominal pain or discomfort, bloating, diarrhoea and/or signs of malabsorption are the most common.¹ Recent findings suggest that SIBO is highly prevalent in patients with irritable bowel syndrome (IBS) and that SIBO decontamination is associated to a significant improvement of IBS symptoms.^{2, 3}

Glucose (GBT) and lactulose (LBT) breath test have been proposed as simple, inexpensive and non-invasive diagnostic tools for SIBO with respect to the gold standard (the culture of intestinal aspirates).⁴⁻⁶ Specificity and sensitivity of GBT (78–83% and 62–93%, respectively) are acceptable both for screening studies and clinical setting.⁴⁻⁶ Some authors suggested that LBT should be preferred as it may explore SIBO along the entire small bowel.³ However, it has been criticized by several researchers because of low accuracy (specificity and sensitivity 44–70% and 17–68%).⁶⁻⁸

Many antibiotics have been proposed in the last years for SIBO eradication. As overgrowth may occur either by a mix of aerobic and anaerobic flora or by purely aerobic flora, an effective antibiotic treatment should act against several bacteria species.⁹ Moreover, an ideal regimen should include drugs with low side-effect profile, that is a rare condition with common broad-spectrum absorbable antibiotics proposed for SIBO eradication.¹⁰⁻¹²

Rifaximin is a rifamycin derivative with antibacterial activity caused by inhibition of bacterial synthesis of RNA. Rifaximin is effective against both gram-positive and -negative bacteria, including aerobes and anaerobes. As <0.1% of its oral dose is absorbed, rifaximin administration is associated to a very low side-effect incidence.^{13, 14}

Results from a recent study by our group showed a significantly higher efficacy of a 7 days–1200 mg rifaximin therapy with respect to doses of 600 and 800 mg/die in SIBO treatment (60% vs. 17% and 27%, respectively); side effects were at all the tested dosages rare, mild, transient.¹⁵ Aim of this study is to test the hypothesis that higher rifaximin dosage (1600 mg) with respect to standard dosage (1200 mg) is associated to higher efficacy in SIBO treatment, without changing low side-effects profile.

MATERIAL AND METHODS

This is a prospective, parallel-group, randomized trial. It was conducted between October 2004 and March 2006 in consecutive out-patients from the Gastroenterology and Internal Medicine Department of the Gemelli Hospital, Catholic University of Rome.

Eligibility criteria

Patients were enrolled and underwent Glucose breath test (GBT) for various chronic gastrointestinal symptoms (bloating, abdominal pain or discomfort, diarrhoea and constipation).

Enrolled subjects were defined as IBS patients when fulfilling Rome II criteria (ref). In addition, IBS patients were classified into three bowel habit subtypes according to Rome II criteria: (i) diarrhoea-predominant (IBS-D); (ii) constipation-predominant (IBS-C); (iii) alternating bowel habit (IBS-A).¹⁶

Consecutive patients with positivity to GBT were included in the study after informed consent.

Each patient underwent a preliminary physical examination and case history.

The exclusion criteria were: age <18 years; use of antimicrobial agents within the previous 3 months; hypersensitivity to the antibiotics; 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 1 day after the end of treatment.

Breath H₂ and CH₄ testing

Glucose breath test was performed under standard conditions. Patients should not have received antibiotics and laxatives in the month preceding the test. To minimize and give stable values of basal H₂ and CH₄ excretion, subjects were asked to have carbohydrate-restricted dinner on the day before the test and to be fasting for the next 12 h before the test. The day of GBT patients did a mouthwash with chlorhexidine 20 mL at 0.05%. Smoking and physical exercise were not allowed for the 12 before and during the test.

End alveolar breath samples were collected with a two-bag system immediately before and every 15 min for 2 h after the ingestion of a 200-mL water iso-osmotic solution with glucose 50 g. The two-bag system consists of a mouthpiece, a T-valve and two bags, the first collects dead space exhaled, the latter takes alveolar air. The breath samples were aspirated from the latter bag with a 30-mL plastic syringe and immediately analysed using a DP Quintron Gas-Chromatograph (Quintron instrument Company, Milwaukee, WI, USA).

Literature data showed that a methanogenic flora too is involved in SIBO. Adding the assessment of CH₄ excretion values could lead to a gain in terms of accuracy of GBT in SIBO diagnosis.¹⁷

According to the literature, GBT was considered as indicative of the presence of SIBO when: (i) an increase of H₂ levels over the baseline value was >12 p.p.m.^{5, 7} and/or (ii) CH₄ levels increased >100% with respect to the basal value.¹⁷

The GBT was repeated 1 month after the end of the therapy in all patients to assess SIBO eradication.

Outcomes

The primary outcome of the present study was GBT normalization rate using the two rifaximin regimens (1600 mg vs. 1200 mg/day).

Secondary outcomes were patient's compliance and incidence of side effects in the two 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 haematochemical parameters considered; (ii) 'adverse experiences', considered as clinical findings or patient complaints that were not present the day before the enrolment. Each patient was asked to complete daily dairy cards on which recording and graduating (1 = mild; 2 = moderate; 3 = severe) any 'adverse experience' during the treatment period and to return them at the post-therapy interview.

Randomization

Using a computer-generated number sequence, generated by a statistician, patients were randomly assigned to one of the two 7-day treatment groups with rifaximin (Normix 200 mg, Alfa Wasserman, Bologna, Italy):

(i) Rifaximin 1600 mg/day (two tablets at 8:00 AM, three tablets at 2:00 PM and two tablets at 8:00 PM; group 1: *n* = 40).

(ii) Rifaximin 1200 mg/day (two tablet t.d.s.; group 2: *n* = 40).

Data analysis

Both intention-to-treat (ITT) and per protocol (PP) analysis 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 GBT normalization rates and the incidence of side-effects, the χ^2 or Fisher's exact tests were used. Odds ratio (OR) for achieving GBT normalization with 95% CI was calculated. The statistical analysis was performed by using STATA 6.0.

RESULTS

Patients characteristics and overall compliance

Characteristics of the study groups are summarized in Table 1.

One drop-out occurred in group 1 and two in group 2, both for non-adherence to the protocol follow-up.

In the other patients of both groups, the compliance was excellent. More than 95% of them took all the prescribed number of tablets for the 7-day treatment.

GBT normalization rate

Glucose breath test normalization rate was significantly higher in the group 1 with respect to the group 2 in both ITT and PP analysis (Figure 1).

In ITT analysis, GPT normalization rate was 80% in the group 1 (32/40) with respect to 58% (23/40) in the group 2 (*P* < 0.05, OR 1.82, 95% CI 1.09–8.01).

In PP analysis, GPT normalization rate reached 82% in the group 1 (32/39) with respect to 61% (23/38) in the group 2 (*P* < 0.05, OR 1.83, 95% CI 1.05–8.48).

Side-effects profile

No abnormalities in the tested laboratory parameters were observed at the control performed the day after the end of the treatment week.

The overall prevalence of adverse experiences was similar in the two treatment groups. A total of 14 adverse events, all of mild intensity, were reported in

	GROUP 1 (n = 40)	GROUP 2 (n = 40)	P
Gender (male/female)	16/40 (40%)	14/40 (35%)	ns
Age (mean ± s.d.)	33 ± 18	35 ± 20	ns
Body mass index	21 ± 8	22 ± 7	ns
Irritable bowel syndrome (IBS) patients	33/40 (83%)	30/40 (75%)	ns
IBS-D	14/33 (43%)	15/30 (50%)	ns
IBS-C	11/33 (33%)	11/30 (37%)	ns
IBS-A	8/33 (24%)	4/30 (13%)	ns

IBS-D, diarrhoea-predominant; IBS-C, constipation-predominant; IBS-A, alternating bowel habit.

Table 1. Demographic and clinical characteristics of small intestinal bacterial overgrowth-positive patients included in the two treatment groups

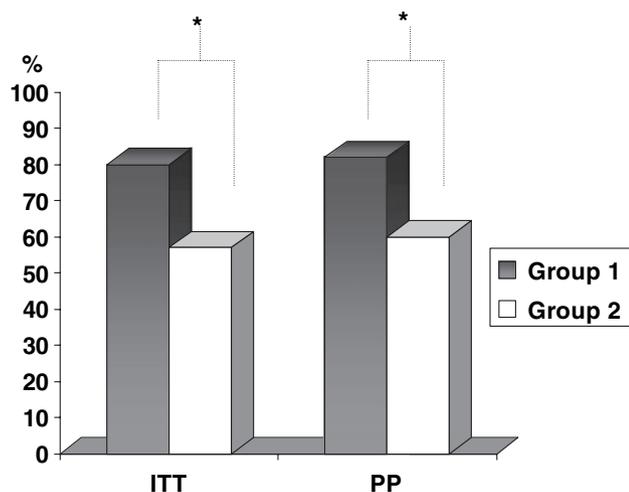


Figure 1. Glucose breath test normalization rates in group 1 (rifaximin 1600 mg/die) and in group 2 (rifaximin 1200 mg/die), in intention-to-treat (first column) and per protocol analysis (second column). * Statistically significant.

the 80 patients involved in the study (six in the group 1, eight in the group 2). The most frequent adverse experiences observed were constipation (five patients, two in the group 1 and three in the group 2) and dyspepsia (three patients, two in the group 1 and one in the group 2).

DISCUSSION

Several broad-spectrum absorbable antibiotic have been used for SIBO eradication: amoxicillin-clavulanic acid, metronidazole, fluoroquinolones such as norfloxacin and ciprofloxacin, among others.¹⁸ They are commonly associated to several side effects, often giving major discomfort to the patient: diarrhoea,

constipation, dizziness, weakness, cutaneous rash and dyspepsia.¹⁹

Efficacy profile in terms of high decontamination rate and clinical improvement is a major point, but the patients ask us for a particular attention to a safety and less 'side-effective' therapy.¹⁸

Some authors evaluated the therapeutic efficacy of non-absorbable antibiotics, such as neomycin and rifaximin, to decrease the potential side effects associated to systemic antibiotics.^{9, 14, 19} Both neomycin and rifaximin act topically in the gut lumen against bacterial overgrowth and seem to play a 'selective decontamination' of the intestinal microflora as they do not eradicate physiologically desirable lactobacilli.^{9, 14, 19}

In particular, rifaximin resulted to be a very interesting approach for SIBO therapy, getting together both good efficacy and low side-effect incidence.^{9, 19} It has a broad spectrum antibiotic efficacy against anaerobic intestinal bacteria, such as bacteroides, lactobacilli and clostridia, all frequently involved in metabolic alterations of SIBO patients.^{9, 19}

Rifaximin has been used in several studies with the aim of SIBO decontamination.¹⁵⁻²² Therapeutic schemes used are extremely different as regard for both doses and duration among the available studies.¹⁵⁻²²

Di Stefano *et al.*²⁰ compared the efficacy of a 1 week-1200 mg rifaximin course with respect to chlortetracycline in 10 patients with SIBO: GBT normalized in 70% of patients treated with rifaximin with respect to 27% in the chlortetracycline group. In a recent study by our group, the therapeutic efficacy of different doses of 1 week-rifaximin therapy was tested in a samples of 90 GBT-positive patients with chronic gastrointestinal symptoms: higher doses of rifaximin (1200 mg/day) led to a significant gain in term of GBT normalization rate with respect to doses of 600 and 800 mg/day.¹⁵

Data from the present study showed that a 1-week rifaximin course of 1600 mg/day is associated to a significant higher GBT normalization rate with respect to 1200 mg (82% vs. 61%) without changes in side-effect profile, candidating as the best therapeutic scheme for SIBO at present.

Two studies with a longer treatment duration have been published. Tursi *et al.*²¹ used a 10-day 800 mg rifaximin course (plus mesalazine at standard dosages) in 53 subjects with acute uncomplicated diverticulitis and positivity to LBT: a 98% breath test normalization rate was reported. Cuoco *et al.*²² showed an 82% decontamination rate after 14-day 1200 mg rifaximin course (followed by a 20-day cycle of probiotics) in 51 diabetic patients with IBS symptoms and LBT positivity suggesting SIBO. Clinical features of enrolled patients, the breath test used to assess SIBO, the use of other drugs in addition to rifaximin (probiotics, mesalazine) do not permit to compare such results with those reported above.^{21, 22}

Interestingly, irrespectively of tested doses and study duration, rifaximin resulted to be associated to

uncommon and mild side effects in all the cited studies.

At present, no data are available in literature concerning SIBO recurrence rate and treatment options for relapsing patients. Theoretically, SIBO decontaminated subjects are at high risk of SIBO recurrence basing on underlying predisposing conditions. For this reason, in the clinical practice, they need to be strictly followed-up in order both either to eliminate all these predisposing conditions or to assess and re-treat the eventual SIBO recurrence.

In conclusion, trials on large samples of SIBO patients appear to be necessary to define the long-term management of SIBO decontaminated patients both with the management of SIBO resistant to a first approach with the present rifaximin treatment scheme (using higher doses/longer therapy duration or switching to broad spectrum absorbable antibiotics).

ACKNOWLEDGEMENTS

Declaration of personal and funding interests: none.

REFERENCES

- Singh VV, Toskes PP. *Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. Curr Treat Options Gastroenterol* 2004; 7: 19–28.
- Pimentel M, Chow EJ, Lin HC. Normalization lactulose breath test correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003; 98: 412–9.
- Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 2000; 95: 3503–6.
- Lupascu A, Gabrielli M, Lauritano EC, *et al.* Hydrogen glucose breath test to detect small intestinal bacterial overgrowth: a prevalence case-control study in irritable bowel syndrome. *Aliment Pharmacol Ther* 2005; 22: 1157–60.
- Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol* 2002; 97: 1113–26.
- Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology* 1988; 95: 982–8.
- Kerlin P. Glucose-H₂ breath test for small intestinal bacterial overgrowth. *Gastroenterology* 1990; 98: 253–4.
- Corazza GR, Menozzi MG, Strocchi A, *et al.* The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. *Gastroenterology* 1990; 98: 302–9.
- Scarpignato C, Pelosini I. Experimental and clinical pharmacology of rifaximin, a gastrointestinal selective antibiotic. *Digestion* 2006; 73(Suppl. 1): 13–27.
- Corazza GR, Di Stefano M, Scarpignato C. Treatment of functional bowel disorders: is there room for antibiotics? *Digestion* 2006; 73(Suppl. 1): 38–46.
- DuPont HL. New insights and directions in travelers' diarrhea. *Gastroenterol Clin North Am* 2006; 35: 337–53.
- DuPont HL. Travellers' diarrhoea: contemporary approaches to therapy and prevention. *Drugs* 2006; 66: 303–14.
- Pelosini I, Scarpignato C. Rifaximin, a peculiar rifamycin derivative: established and potential clinical use outside the gastrointestinal tract. *Chemotherapy* 2005; 51(Suppl. 1): 122–30.
- DuPont HL, Jiang ZD, Okhuysen PC, *et al.* A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med* 2005; 142: 805–12.
- Lauritano EC, Gabrielli M, Lupascu A, *et al.* Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2005; 22: 31–5.
- Olden KW. Diagnosis of irritable bowel syndrome. *Gastroenterology* 2002; 122: 1701–14.
- Corazza GR, Benati G, Strocchi A, *et al.* The possible role of breath methane measurement in detecting carbohydrate malabsorption. *J Lab Clin Med* 1994; 124: 695–700.
- Van Citters GW, Lin HC. Management of small intestinal bacterial overgrowth. *Curr Gastroenterol Rep* 2005; 7: 317–20.
- Baker DE. Rifaximin: a nonabsorbed oral antibiotic. *Rev Gastroenterol Disord* 2005; 5: 19–30.

- 20 Di Stefano M, Miceli E, Missanelli A, *et al.* Rifaximin versus chlortetracycline in the short-term treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2000; 14: 551–6.
- 21 Tursi A, Brandimarte G, Giorgetti GM, *et al.* Assessment of small intestinal bacterial overgrowth in uncomplicated acute diverticulitis of the colon. *World J Gastroenterol* 2005; 11: 2773–6.
- 22 Cuoco L, Salvagnini M. Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin. *Minerva Gastroenterol Dietol* 2006; 52: 89–95.