Chronic prostatitis and small intestinal bacterial overgrowth: effect of rifaximin

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WEINSTOCK LB, GENG B, BRANDES SB. Chronic prostatitis and small intestinal bacterial overgrowth: effect of rifaximin. The Canadian Journal of Urology. 2011;18(4):5826-5830.

Introduction: *This pilot study determined the efficacy of rifaximin, a gut-directed antibiotic, in reducing chronic prostatitis (CP) and gastrointestinal (GI) symptoms in patients with CP type III. The prevalence of small intestinal bacterial overgrowth (SIBO) and irritable bowel syndrome (IBS) in patients with CP was also evaluated.*

Materials and methods: *Chronic prostatitis patients were recruited and screened for SIBO and IBS using the lactulose breath test (LBT) and Rome II criteria, respectively. Patients with a positive LBT result and Chronic Prostatitis Symptom Index (CPSI) score ≥ 15 received rifaximin 550 mg three times daily for 10 days. The CPSI score and global improvement of CP and GI symptoms were ascertained at screening (ie, 7 days before therapy), at baseline immediately before therapy (ie, day 0), and on days 14 and 28.*

Results: *Fourteen of 16 CP patients (88%) had a positive LBT result and were included in this therapeutic study (mean age, 41 years). Mean CPSI score significantly decreased from screening to day 28 (ie, 18 days after rifaximin treatment; $p = 0.043$). Mean abdominal pain and bloating scores were also significantly reduced on day 28 versus baseline ($p = 0.010$ and $p = 0.003$, respectively). Chronic prostatitis patients with IBS and SIBO had a statistically significant response as well.*

Conclusions: *Data from this pilot study suggest that SIBO and IBS are common in CP and that patients with CP and SIBO may benefit from rifaximin therapy. Further studies are warranted.*

Key Words: chronic prostatitis, small intestinal bacterial overgrowth, antibiotic, rifaximin, lactulose breath test, CPSI score

Introduction

Chronic prostatitis (CP) is an idiopathic syndrome characterized by pelvic pain, increased urinary frequency and urgency, and sexual dysfunction.[1] Patients with CP type III do not exhibit signs of bacterial infection,[2] although levels of inflammatory cytokines (ie, interleukin 6, interleukin 1β, tumor necrosis factor α)[3,4] are significantly increased in the seminal plasma of patients with CP type III versus healthy controls and have been shown to correlate with CP symptoms.[5] The presence of these inflammatory cytokines may result in the recruitment of leukocytes and the sensitization of local neurologic pain mechanisms;[6] however, participating factors underlying augmentation of cytokine levels remains unknown.

Because of the lack of known pathophysiology for CP, effective treatments for CP are lacking.[7] Therapies such as α-blockers,[7] finasteride,[8] corticosteroids,[9] and quinolone antibiotics[7] are often used for CP but are generally unsatisfactory because of the lack of efficacy or elicitation of adverse events. Identification of a novel pathophysiologic mechanism would broaden the therapeutic options for CP and enhance treatment development. The use of rifaximin as a therapy for CP was contrived because of the success of rifaximin therapy in interstitial cystitis, another chronic pelvic pain syndrome,[10] and the efficacy of rifaximin in eradicating small intestinal bacterial overgrowth (SIBO).[11,12]

Accepted for publication March 2011

Acknowledgments

This investigator-initiated study was funded by Salix Pharmaceuticals, Inc. Editorial assistance was provided under the direction of Dr. Weinstock by MedThink Communications with support from Salix Pharmaceuticals, Inc.

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Small intestinal bacterial overgrowth is an increase in bacterial concentration in the small intestines that leads to systemic inflammation and abdominal pain.[13] This disorder is common in patients with abdominal pain disorders such as irritable bowel syndrome (IBS),[14,15] and its eradication by gastrointestinal (GI)-targeted antibiotics such as rifaximin has shown success in treating GI symptoms.[11,12,16] The present pilot study evaluated the efficacy of rifaximin for the reduction of CP and GI symptoms in patients with CP type III and examined the association among CP type III, SIBO, and IBS.

Materials and methods

Patient population

Patients with CP type III (including types IIIA and IIIB) were recruited from April 2007 to June 2009 via referrals from urologists in St. Louis, MO, who were informed about the study through the mail. Patients were screened by a nurse coordinator using the diagnostic criteria for CP and the National Institutes of Health Chronic Prostatitis Symptom Index (CPSI) score.[17] Further, all patients had negative cultures of expressed prostatic secretions and had prostatitis symptoms lasting ≥ 3 months. In addition, patient records were reviewed to confirm the diagnosis of CP type III.

Patients were excluded if they were dependent on narcotics, had used antibiotics or probiotics within 6 weeks of the study, or had undergone intestinal surgery with the exception of appendectomy or cholecystectomy. Patients were also excluded if they had known systemic causes of SIBO other than IBS (ie, rheumatoid arthritis, scleroderma, end-stage renal disease, diabetes, hyperparathyroidism, gastric surgery, chronic liver disease, celiac disease, and Crohn's disease) or if they had an alternative urological condition diagnosed by a urologist. The investigation was approved by a human studies committee (Sterling IRB, Atlanta, GA), and informed consent was provided by all patients.

Study design

Patients underwent a screening visit 7 days before initiation of rifaximin therapy. At this visit, patients were assessed for IBS, positive lactulose breath test (LBT) result, and severity of CP and GI symptoms. Patients also underwent similar baseline assessments immediately before the beginning of antibiotic therapy (ie, day 0). Patients with CP who had a positive LBT result ≤ 180 minutes after lactulose ingestion and a CPSI score ≥ 15 were administered rifaximin (Xifaxan; Salix Pharmaceuticals, Inc, Morrisville, NC, USA) 550 mg three times daily (t.i.d.) for 10 days. Patients were then followed for 18 days (ie, total study duration of 28 days).

Study assessments

Lactulose breath test: Patients with CP had an LBT at screening and on study day 14. Breath samples were collected before and every 20 minutes for 180 minutes after the patient ingested 10 g of lactulose mixed in 250 mL of water. Hydrogen and methane content of the samples was analyzed by gas chromatography (QuinTron DP Plus MicroLyzer; QuinTron Instrument Company, Milwaukee, WI, USA). A positive result was defined as an increase of ≥ 20 ppm from baseline in hydrogen, methane, or both gases within ≤ 180 minutes after lactulose ingestion. Results of LBT tests were also examined in a post hoc analysis using an increase of ≥ 20 ppm from baseline in hydrogen, methane, or both gases within ≤ 100 minutes as the criterion for a positive LBT result. Additionally, patients with flatline LBT results (ie, an increase of no more than 5 ppm of hydrogen above a baseline less than 3 ppm of hydrogen and the absence of methane production for 180 minutes) were considered to have a positive result. Flatline results were considered positive because this response may be attributed to the production of hydrogen sulfide.[18] Lactulose breath test results were compared with previously published data in healthy controls (ie, individuals who did not have GI symptoms, CP, or other diseases or disorders) that used criteria for LBT abnormality identical to those used in the present study.[19]

Irritable bowel syndrome: Patients were diagnosed with IBS at screening using Rome II criteria (ie, abdominal discomfort for ≥ 3 months/year with altered bowel habits and form and with some relief of discomfort with the passage of bowel movements).[20] Patients with IBS were asked to complete the IBS-Quality of Life (IBS-QoL) questionnaire at screening and on day 14.

Chronic prostatitis symptom severity: Symptoms of CP were assessed at screening, at baseline, and on days 14 and 28 using the CPSI score.[17] Additionally, prostatitis global response (PGR) was ascertained using a Likert scale in which patients rated improvement in CP symptoms as follows: 0, none; 1, mild; 2, moderate; or 3, marked. Patients with mild, moderate, or marked improvement were considered to be clinical responders.

Gastrointestinal symptom severity: Severity of abdominal pain and bloating was assessed at screening, at baseline, and on days 14 and 28 using a Likert scale in which responses to each question were as follows: never

affected; 0, not at all bothered; 1, hardly bothered; 2, somewhat bothered; 3, moderately bothered; 4, a good deal bothered; 5, a great deal bothered; or 6, a very great deal bothered.

Adverse events: Adverse events were reported on days 14 and 28 in response to the question, "Have you experienced any side effects?"

Statistical analysis

Descriptive statistics, including standard deviations, were used to summarize results at screening, at baseline (ie, day 0), and on days 14 and 28. Changes in CPSI, GI symptom severity (ie, abdominal pain and bloating), and IBS-QoL scores from screening or baseline to days 14 or 28 were also summarized for all variables using descriptive statistics; within-group changes were assessed using a 2-tailed, paired *t* test.

Results

Patient demographics

Of 16 CP patients screened, 14 patients with a positive LBT result were included in the study, Table 1. The data value for 1 CPSI score was missing for a single patient. All patients who received rifaximin (n = 14) completed therapy, although 1 patient withdrew from the study on day 17 because of exacerbation of CP symptoms.

Healthy controls from a previous study were used in this study for comparison and consisted of 10 men and 18 women (mean age, 45.3 ± 12.8 years).[19] All were healthy, did not have chronic GI symptoms or any other diseases, did not smoke, and were not taking selective serotonin reuptake inhibitors. One control was considered obese (body mass index > 30 kg/m^2).

TABLE 1. **Patient demographics and disease characteristics**

Parameter	Patients (n = 14)
Mean age (SD), y	41.1 (12.3)
Race, n (%)	
White	11 (79)
Other*	3 (21)
Mean duration of CP (SD), y	3.8 (4.6)
Mean CPSI score† (range), n	25.1 (16-40)
Mean IBS-QoL score‡§ (range), n	84.7 (48-146)

CP = chronic prostatitis; CPSI = chronic prostatitis symptom index; IBS = irritable bowel syndrome; QoL = quality of life; SD = standard deviation.
*includes patients of Indian, Bosnian, and Iranian descent.
†CPSI score can range from 0 to 43.
‡IBS-QoL score can range from 34 to 170.
§scores were available only for patients with IBS (n = 7).

Lactulose breath test

At screening, 14 of 16 patients (88%) had a positive LBT result ≤ 180 minutes after lactulose ingestion, indicating the presence of SIBO. Ten patients had excess hydrogen production, 3 had a flatline response, and 1 had high levels of hydrogen and methane. Using the criterion of a positive LBT result ≤ 100 minutes after lactulose ingestion, 7 of 16 patients (44%) had a positive result. In comparison, previously published data demonstrated that 8 of 28 healthy controls (29%) had a positive LBT result ≤ 180 minutes and 3 of 28 (11%) had a positive LBT result ≤ 100 minutes after lactulose ingestion.[19] On day 14, 14% of patients had resolution of a positive LBT result ≤ 100 minutes after lactulose ingestion.

Chronic prostatitis symptom assessments

Mean CPSI score decreased from 25 ± 8 at screening to 22 ± 6 on day 14 ($p = 0.063$) and to 21 ± 10 on day 28 ($p = 0.043$). In CP patients with IBS, CPSI score was significantly reduced from screening on day 14 ($p = 0.050$) and day 28 ($p = 0.011$). Patients with CP, IBS, and a positive LBT result ≤ 100 minutes after lactulose ingestion had a mean reduction of CPSI score on day 14 ($p = 0.241$), which reached statistical significance on day 28 ($p = 0.034$).

Eight of 14 patients (57%) were considered to be clinical responders. In these patients, mean CPSI score was significantly reduced from 28 ± 9 at screening to 21 ± 8 on day 14 ($p = 0.016$) and to 20 ± 14 on day 28 ($p = 0.012$). The greatest improvement in PGR was marked in 3 of 8 patients (38%), moderate in 2 of 8 patients (25%), and mild in 3 of 8 patients (38%). In patients with a positive LBT result ≤ 100 minutes after lactulose ingestion who completed the PGR, the maximal improvement in PGR was marked in 1 of 6 patients (17%), moderate in 1 of 6 patients (17%), and mild in 3 of 6 patients (50%).

Gastrointestinal symptom assessments

Eight of 14 patients (57%) had chronic GI symptoms at screening. Mean abdominal pain ($p = 0.032$ versus screening; $p = 0.010$ versus baseline) and bloating ($p = 0.003$ versus baseline) scores were significantly reduced on day 28, Figure 1. In patients who had a positive LBT result ≤ 100 minutes after lactulose ingestion, there was a numerical improvement from baseline in mean abdominal pain score (3 ± 2) and

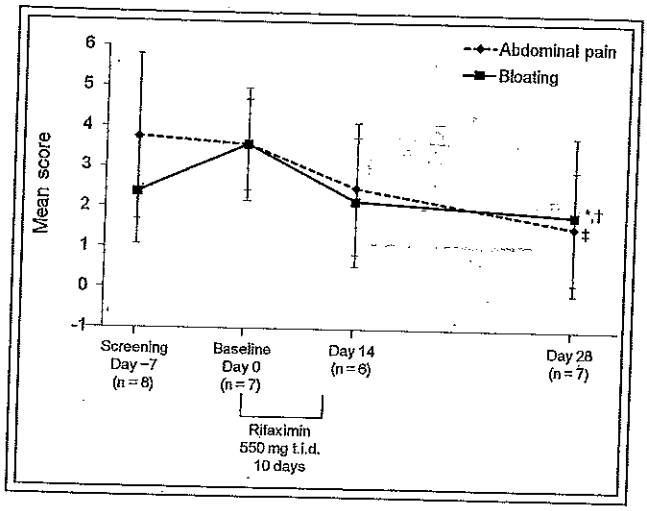

Figure 1. Improvement in abdominal pain and bloating after treatment with rifaximin 550 mg three times daily (t.i.d.) for 10 days.
*p = 0.032 versus screening.
†p = 0.010 versus baseline.
‡p = 0.003 versus baseline.

mean bloating score (3 ± 1) to day 14 (abdominal pain, 2 ± 2 [p = 0.519]; bloating, 2 ± 2 [p = 0.098]) and day 28 (abdominal pain, 2 ± 2 [p = 0.103]). In addition, mean bloating score was significantly improved from baseline to day 28 (p = 0.006).

Irritable bowel syndrome

Irritable bowel syndrome was present in 7 of 16 CP patients (44%) screened. Of the 14 patients with a positive LBT result ≤ 180 minutes after lactulose ingestion, 50% had IBS. Of patients with a positive LBT result ≤ 100 minutes after lactulose ingestion, 4 of 7 patients (57%) had IBS.

Mean IBS-QoL score decreased from 85 ± 37 at screening to 61 ± 21 on day 14 (p = 0.086). In patients who had IBS and a positive LBT result ≤ 100 minutes after lactulose ingestion, mean IBS-QoL score decreased from 65 ± 28 at screening to 49 ± 15 on day 14 (p = 0.223).

Adverse events

One patient experienced self-limited diarrhea.

Conclusions

Chronic prostatitis type III may be the result of sensitization of nerves near the pelvic area, thereby causing pain, urinary symptoms, and sexual dysfunction.[1] Irritable bowel syndrome is similarly associated with GI sensitization, and the comorbidity of IBS and CP observed in this study suggests that the two conditions may share a similar pathophysiology. The incidence of IBS in CP patients was six times greater than the prevalence of IBS in the general US population (ie, 7%).[21] Furthermore, 50% to 57% of CP patients with SIBO also had IBS, suggesting that all three conditions may be linked.

In the present pilot study, 88% of CP patients had SIBO as indicated by a positive LBT result ≤ 180 minutes. A post hoc analysis of LBT results using more recent criteria for LBT abnormality (ie, an increase of ≥ 20 ppm from baseline in hydrogen, methane, or both gases ≤ 100 minutes after lactulose ingestion) demonstrated that 44% of CP patients had SIBO. Using a possible false positive rate of 11% (ie, according to previously published data, 3 of 28 healthy controls [11%] had positive LBT result ≤ 100 minutes),[19] the net effect may be that 33% of CP patients had SIBO. To our knowledge, this is the first study to demonstrate the presence of SIBO in CP patients. The presence of SIBO in these patients may explain the ability of quinolones[22] and macrolide[23] antibiotics to improve CP symptoms because studies have shown that macrolide antibiotics stimulate GI transit[24] and quinolones eliminate SIBO.[25] In the present open-label study, treatment with rifaximin 550 mg t.i.d. for 10 days resulted in statistically significant improvement in CPSI and GI scores from pretreatment values. In addition, after conclusion of the study, six CP patients who had IBS were retreated with rifaximin because of incomplete symptom relief (n = 4) or relapses in CP symptoms during the following year (n = 2). Three of these patients (50%) had marked improvement of CP and IBS symptoms, and partial improvement was seen in 2 of the 6 patients (33%). Taken together, these data suggest that the modulation of intestinal flora may be an effective treatment strategy for some CP patients, especially those who have comorbid GI symptoms.

The findings from this pilot study should be considered with the following caveats. First, the prevalence of GI conditions may be biased because patients were referred from urologists who were aware of the theoretical basis of the study. Second, it is possible that the effects of rifaximin observed in this study were a placebo effect as a result of the open-label nature of the study. In addition, the small size of the study (ie, 14 patients) may have unduly attributed to a significant response to rifaximin. For example, in some cases, statistical significance was observed on days 14 and 28 versus screening but not versus baseline. Thus, larger studies are necessary to confirm our preliminary findings. The efficacy of rifaximin therapy also may have been compromised by the inclusion of patients without SIBO according to the more stringent criterion (ie, positive LBT result

≤ 100 minutes after lactulose ingestion). Furthermore, the sensitivity of the LBT remains debatable, although there is no gold standard to diagnose SIBO and the use of LBT is common.[26] In addition, adequate eradication of SIBO may have been prevented by the use of a short course of rifaximin rather than the long term antibiotics that are sometimes administered in SIBO therapy. Antibiotics are only one component of comprehensive therapy for SIBO, which may also include dietary modifications, probiotic therapy, and stimulation of motility in the small intestine.[13,27]

This pilot study demonstrated the efficacy of rifaximin in reducing both GI and CP symptoms. The observed association of CP with IBS and SIBO suggests that further studies to examine potentially shared pathophysiologies of these conditions, such as systemic cytokine levels, should be undertaken. Given that rifaximin is a well-tolerated nonsystemic antibiotic, the current data suggest that rifaximin may provide a new management option for CP; however, a double-blind placebo-controlled study to determine the efficacy of rifaximin for the treatment of CP is necessary.

Disclosure

Dr. Leonard B. Weinstock is on the speaker's bureau for Salix Pharmaceuticals, Inc. Dr. Bob Geng has no conflicts of interest to declare. Dr. Steven B. Brandes is on the speaker's bureau for Pfizer, Inc, and American Medical Systems. □

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