Prevention of Travelers’ Diarrhea With Rifaximin in US Travelers to Mexico

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Background. Because bacterial pathogens are the primary cause of travelers’ diarrhea (TD), antibiotic prophylaxis is effective in TD prevention. This study assessed the efficacy and safety of the nonsystemic antibiotic rifaximin in preventing TD in US travelers to Mexico.

Methods. Healthy adult students traveling to Mexico received rifaximin 600 mg/d or placebo for 14 days and were followed for 7 days post-treatment. Stool pattern and gastrointestinal symptoms were recorded in daily diary entries. The primary end point was prevention of TD during 14 days of treatment measured by time to first unformed stool.

Results. A total of 210 individuals received rifaximin (n = 106) or placebo (n = 104) and were included in the safety population. Median age was 21 years (range, 18–75 y), and the majority of participants were female (65%). Efficacy analyses were conducted in a modified intent-to-treat population of 201 patients who received rifaximin (n = 99) or placebo (n = 102). Rifaximin prophylaxis reduced risk of developing TD versus placebo (p < 0.0001). A smaller percentage of individuals who received rifaximin versus placebo developed all-cause TD (20% vs 48%, respectively; p < 0.0001) or TD requiring antibiotic therapy (14% vs 32%, respectively; p = 0.003). More individuals in the rifaximin group (76%) completed treatment without developing TD versus those in the placebo group (51%; p = 0.0004). Rifaximin provided a 58% protection rate against TD and was associated with fewer adverse events than placebo.

Conclusions. Prophylactic treatment with rifaximin 600 mg/d for 14 days safely and effectively reduced the risk of developing TD in US travelers to Mexico. Rifaximin chemoprevention should be considered for TD in appropriate individuals traveling to high-risk regions.

An estimated 40% of the 50 million individuals traveling from industrialized to developing countries each year develop travelers’ diarrhea (TD). This acute infectious illness is characterized by the passage of 7 to 13 watery stools over 2 days, accompanied by one or more additional enteric symptom.1–3 Based on microbiologic evaluation, enteric bacterial pathogens are thought to cause approximately 80% of TD cases, with strains of enterotoxigenic Escherichia coli (ETEC) and enteroaggregative E coli (EAEC) responsible for the majority of cases.1–5 Invasive bacterial pathogens including Shigella and Campylobacter contribute to approximately 4% to 20% of TD cases.5–7

Although TD is often self-limiting, lasting on average for 4 days, the negative consequences of acquiring this illness can be substantial, including disruption of travel plans and increased risk for development of postinfectious complications,8 such as postinfectious irritable bowel syndrome (PI-IBS)9–14 and inflammatory bowel disease (IBD).15 Antibiotic chemoprophylaxis provides substantial protection from TD and prevents potentially severe complications.16

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However, the guidelines recommended by the National Institutes of Health consensus panel in 1985 discouraged the routine administration of systemic antibiotics as chemoprophylaxis for TD because of the potential adverse effects associated with administration and concern that overprescribing could contribute to the growing epidemic of antibiotic resistance.17

The ideal chemoprevention agent would achieve the efficacy of systemic antibiotics without the potential adverse effects and antibiotic resistance associated with these agents. Rifaximin (Xifaxan®; Salix Pharmaceuticals, Inc., Morrisville, NC, USA) is a gut-selective, nonsystemic antibiotic18 that has a low risk for development of clinically relevant antibiotic resistance.19 It is indicated for the treatment of TD caused by noninvasive strains of *E. coli*2 and has demonstrated efficacy in treating TD in clinical studies.20 In addition, a randomized, double-blind, placebo-controlled trial in US travelers to Mexico (*n* = 210) demonstrated that chemoprophylaxis with rifaximin 200, 400, or 600 mg/d safely prevented the occurrence of TD in 72% of patients.21 In a separate study, rifaximin 600 mg/d effectively prevented experimental shigellosis in a challenge model conducted in healthy volunteers.22 These findings suggest that rifaximin 600 mg/d may be effective in preventing enteric infection caused by diarrheagenic strains of *E. coli* as well as invasive bacterial pathogens. The present phase 3 clinical study assessed the safety and efficacy of rifaximin 600 mg/d for 14 days in the prevention of TD in healthy US adults traveling to Mexico.

Methods

Study Design

This phase 3, double-blind, randomized, multicenter, 3-week study investigated the efficacy of rifaximin in preventing TD in adults traveling to Mexico. Eligible participants were healthy US students aged ≥18 years attending school in Guadalajara, Mexico, who ingested the study drug within 72 hours of arrival in Mexico. Participants had not experienced diarrhea or received treatment with fluoroquinolones, macrolides, azalides, or trimethoprim-sulfamethoxazole 7 days before taking the study drug or antidiarrheal medications (eg, loperamide, bismuth subsalicylate) 24 hours before taking the study drug. Concomitant medications other than those listed above were permitted. Before the study began, individuals attended an orientation that included instructions on how to avoid diarrhea. Study participants received three tablets of rifaximin 200 mg once daily (ie, 600 mg/d) or a matching placebo for 14 days with a 7-day post-treatment follow-up. Clinical evaluations were conducted at screening (ie, baseline), during treatment (day 8), and at the end of the study (day 15, 16, or 17). Participants recorded the number of formed and unformed stools passed and enteric symptoms experienced on daily diary cards for the duration of the study. Individuals who withdrew from the study prematurely because of diarrhea or requested rescue medication were considered cases of TD. All participants supplied a stool sample at the end of the study regardless of TD acquisition. Individuals who developed TD during the treatment period discontinued the study medication and received rescue antibiotic therapy with levofloxacin, ciprofloxacin, or azithromycin. All individuals provided written informed consent. The study was conducted in accordance with ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. This trial is registered with the National Library of Medicine (www.clinicaltrials.gov) under NCT00742469.

Study Assessments

The primary efficacy end point was the relative risk of developing TD (three or more unformed stools within a 24-h period plus one or more symptom of enteric infection) based on the time to first unformed stool beginning the illness during 14 days of treatment with rifaximin or placebo. Secondary end points included: (1) incidence of TD resulting from all causes; (2) incidence of TD associated with isolation of diarrheagenic *E. coli* (ie, ETEC, EAEC); (3) incidence of TD associated with invasive bacterial pathogens (ie, *Shigella* spp, *Campylobacter jejuni*, *Salmonella* spp); (4) incidence of TD occurring in the 7-day follow-up period; (5) protection rates against TD, TD associated with diarrheagenic *E. coli*, and TD associated with invasive bacterial pathogens; and (6) number of participants with symptoms of enteric infection and mild diarrhea without TD (ie, more than two unformed stools within a 24-hour period plus one or more symptom of enteric infection).

Adverse events (AEs), defined as any event that started on or after the first day of treatment or worsened after treatment day 1, were recorded at clinical visits during treatment (day 8) and at the end of the study (day 15, 16, or 17) and coded using the *Medical Dictionary for Regulatory Activities* (MedDRA version 7.1). Hematologic and clinical chemistry parameters were evaluated at baseline and at the end of the study (day 15, 16, or 17).

Statistics

Sample size calculations were based on comparable sample sizes in a previous prophylactic study21 and by calculating a power of at least 95%, a significance level of 0.05, a 75% protection rate for those who received rifaximin, and a 55% protection rate for those who received placebo.

The intent-to-treat (ITT) population included all individuals who were randomized to treatment with rifaximin or placebo and received one or more dose of study medication. Because many bacterial pathogens associated with TD require ≤48 hours to cause disease,23 patients who developed TD during the
first 48 hours after initiation of rifaximin treatment were considered to have acquired infection before chemoprophylaxis was initiated. This approach was taken because patients were not able to begin prophylaxis upon entry into Mexico. The safety population included all individuals who were randomized to treatment with rifaximin or placebo, received one or more dose of study medication, and provided one or more post-baseline safety assessment. The primary and secondary end point analyses were conducted for the modified ITT population. The primary efficacy analysis compared the time to first unformed stool for rifaximin versus placebo applying Kaplan–Meier estimates and the Cox proportional hazards regression model (Wald test) with a two-sided \( t \)-test and a significance level of 0.05. Secondary end points were analyzed by applying Kaplan–Meier estimates, Cox proportional hazards regression models with 95% confidence intervals (CIs), and the Fisher exact test. Protection rates with 95% CIs were estimated using the following formula: protection rate = \( \frac{[P_R - P_L]}{P_R} \times 100 \), where \( P_R \) equals the number of individuals with diarrhea who received placebo and \( P_L \) equals the number of individuals with diarrhea who received rifaximin.

**Results**

A total of 210 individuals received treatment with rifaximin (\( n = 106 \)) or placebo (\( n = 104 \)) and were included in the ITT and safety population. Seven participants in the rifaximin group and two participants in the placebo group met the definition of TD within 48 hours of receiving the first dose of study medication and were excluded from the ITT population to form a modified ITT population (99 patients received rifaximin and 102 patients received placebo).

Within the ITT and safety population, demographic and baseline characteristics of both treatment groups were similar (Table 1). More individuals in the rifaximin group completed the 14-day treatment phase (88 of 106 patients; 83%) compared with those in the placebo group (83% of 106 patients; 88 of 102 patients). The percentage of participants who did not develop TD was similar between rifaximin and placebo groups (76% vs 79%, respectively). The percentage of participants who took concomitant medications during the study was similar in the rifaximin and placebo treatment groups (76% vs 79%, respectively).

Primary and secondary end point analyses were evaluated for the modified ITT population. For the primary end point, prophylactic treatment with rifaximin 600 mg/d for 14 days significantly reduced the risk of developing TD versus placebo (\( p < 0.0001 \); Figure 2). Specifically, at the end of the 14-day treatment period, the cumulative occurrence of TD was 15% in the rifaximin group (15 of 99 patients) compared with 47% in the placebo group (48 of 102 patients). The hazard ratio indicated that the relative risk of developing TD was 0.27 (95% CI, 0.15–0.49) for the rifaximin group, equivalent to approximately one occurrence in four for individuals in the rifaximin group.

Secondary end point analyses demonstrated that a significantly smaller percentage of individuals who received rifaximin developed TD (20%) compared with those who received placebo (48%; \( p < 0.0001 \); Figure 3). A smaller percentage of individuals who developed TD in the rifaximin group received rescue therapy compared with placebo (14% vs 32%, respectively; \( p = 0.003 \)). Additionally, a smaller percentage of individuals who received rifaximin developed TD associated with diarrheagenic E. coli (ETEC or EAEC) compared with placebo (9% vs 18%, respectively), although the difference was not significant (\( p = 0.098 \)). TD was not associated with invasive bacterial pathogens (Campylobacter, Shigella, or Salmonella) in any individual. The percentage of individuals who developed TD associated with unidentified pathogens was significantly lower in the rifaximin versus placebo group (11% vs 30%, respectively; \( p = 0.01 \)). A greater percentage of individuals who received rifaximin completed the 14-day treatment period without developing TD (76%) versus those who received placebo (51%; \( p = 0.0004 \)). The percentage of patients who experienced mild diarrhea but did not develop TD was similar between rifaximin and placebo groups (29% rifaximin vs 21% placebo). During the 7-day post-treatment period, the percentage of participants who developed TD was similar for rifaximin (16%) versus placebo (15%).

The protection rates achieved with rifaximin prophylaxis were similar for TD (58%; 95% CI, 35–73) and TD requiring rescue antibiotic therapy (56%; 95% CI, 23–75; Table 2). Nine individuals in the rifaximin group versus 18 individuals in the placebo group developed TD associated with diarrheagenic E. coli, yielding a protection rate of 48% (95% CI, 9 to 76).

Within the safety population, consisting of 210 total participants, 174 (83%) reported one or more AE

**Table 1**: Demographics and baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rifaximin (( n = 106 ))</th>
<th>Placebo (( n = 104 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), ( y )</td>
<td>24 (18–75)</td>
<td>23 (18–57)</td>
</tr>
<tr>
<td>Male : Female, ( n )</td>
<td>40 : 66</td>
<td>34 : 70</td>
</tr>
<tr>
<td>Race, ( n )†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91 (86)</td>
<td>95 (91)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (8)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mean time in Mexico‡ (range), ( d )</td>
<td>1.4 (0–3)</td>
<td>1.5 (1–4)</td>
</tr>
</tbody>
</table>

*† Assessed to provide background demographic information on study subjects. Classifications were those listed herein. A participant categorized his or her race based on options defined by the study sponsor.

‡ Prior to enrollment in study.
Seven individuals in the rifaximin group and two in the placebo group developed TD within 48 hours of ingesting the first dose of study medication and were excluded from the efficacy analyses. TD = travelers’ diarrhea.

The cumulative probability of developing TD was significantly lower with rifaximin versus placebo ($p < 0.0001$). TD = travelers’ diarrhea; TFUS = time to first unformed stool.

TD is a substantial health problem that individuals face while traveling to developing countries.2 Acquiring TD can have a substantial negative economic impact on the traveler and destination country and cause potentially serious postinfectious complications (eg, PI-IBS, IBD).8–15 Effective chemoprophylaxis may reduce the severity and duration of TD, and antibiotics are the most effective option for chemoprophylaxis because of the substantial contribution of bacteria to the development of acute diarrheal illnesses.16

Systemic antibiotics are extremely effective against enteric bacterial pathogens and provide substantial protection against TD. In a randomized, double-blind, placebo-controlled study of healthy volunteers traveling to Tunisia ($n = 53$), oral ciprofloxacin 500 mg/d for 7 days provided 94% protection against TD, and only 1 individual (4%) in the ciprofloxacin group developed TD versus 18 (64%) in the placebo group ($p < 0.0001$).24 In a double-blind, randomized study during the entire study, including treatment and follow-up periods (Table 3). No serious AEs or deaths were reported during the study, and no clinically relevant changes in laboratory parameters were observed.

**Discussion**

**Figure 1** Disposition of study participants. *Seven individuals in the rifaximin group and two in the placebo group developed TD within 48 hours of ingesting the first dose of study medication and were excluded from the efficacy analyses. TD = travelers’ diarrhea.*
Rifaximin for Travelers’ Diarrhea

Figure 3 Incidence of TD in individuals treated prophylactically with rifaximin 600 mg/d or placebo for 14 days. Fewer individuals who received rifaximin developed all-cause TD, TD treated with rescue antibiotic therapy, TD associated with diarrheagenic E coli, or TD associated with unidentified pathogens. TD = travelers’ diarrhea.

of US military personnel in Egypt (n = 222), 2 of 105 individuals (2%) who received oral norfloxacin 400 mg/d for 7 days developed TD versus 30 of 117 individuals (26%) who received placebo.25 Despite the demonstrated efficacy of systemic antibiotics, current guidelines discourage their administration for TD chemoprevention because of the increased risk of antibiotic resistance and potential for serious adverse effects.17

In the present study, healthy individuals treated prophylactically with the nonsystemic antibiotic rifaximin 600 mg/d for 14 days were less likely to develop TD, receive rescue antibiotic therapy for TD, or experience TD associated with diarrheagenic E coli. The overall protection rate of rifaximin in this study was 58% compared with that for bismuth subsalicylate (40%–65%),26 and systemic antibiotics (59%–94%).24,27–30 It is difficult to compare protection rates of therapies outside of head-to-head studies because of differences in study design, TD etiology, and the date of studies (because of changes in resistance patterns over time). Also, evaluation of the overall benefit of a prophylactic antibiotic takes into account not only the protection rate but also the potential for AEs and risk of antibiotic resistance. Rifaximin is well tolerated, with an AE profile similar to placebo,18 and rifaximin is unlikely to cause clinically relevant antibiotic resistance.19 This contrasts with systemic antibiotics, which may cause severe AEs, predispose patients to the development of other infections,3 and increase the risk of development of bacterial strains resistant to systemic antibiotics.31

In this study, a smaller percentage of individuals who received rifaximin developed TD associated with diarrheagenic E coli (ETEC or EAEC) compared with placebo, and patients in the rifaximin group were significantly less likely to develop TD attributable to unidentified pathogens (ie, pathogens other than ETEC, EAEC, Campylobacter, Salmonella, Shigella). Because the study was not adequately powered to detect statistical differences between individuals with TD of different etiologies, the clinical relevance of

Table 2 Occurrence of TD and protection rate with rifaximin versus placebo

<table>
<thead>
<tr>
<th>Diarrhea end point</th>
<th>Rifaximin (n = 99)</th>
<th>Placebo (n = 102)</th>
<th>Protection rate, † (% (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>20</td>
<td>49</td>
<td>58 (35 to 73)</td>
</tr>
<tr>
<td>Treated TD†</td>
<td>14</td>
<td>33</td>
<td>56 (23 to 75)</td>
</tr>
<tr>
<td>TD associated with diarrheagenic E coli</td>
<td>9</td>
<td>18</td>
<td>48 (−9 to 76)</td>
</tr>
</tbody>
</table>

CI = confidence interval; TD = travelers’ diarrhea.

Because bacterial pathogens associated with TD are known to have incubation periods longer than 48 hours, individuals who developed TD during the first 48 hours after the start of treatment were excluded from efficacy analyses per protocol. Seven individuals in the rifaximin group and two individuals in the placebo group fully met the definition of TD within 48 hours of the first dose of study medication.

†Defined as (proportion in placebo group minus proportion in rifaximin group)/proportion in placebo group multiplied by 100.

Table 3 Treatment-related AEs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifaximin (n = 106)</th>
<th>Placebo (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more reported AE, n (%)</td>
<td>81 (76)</td>
<td>93 (89)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>89 (84)</td>
<td>93 (89)</td>
</tr>
<tr>
<td>GI-related AE, n (%)</td>
<td>87 (82)</td>
<td>92 (88)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>76 (72)</td>
<td>86 (83)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>57 (54)</td>
<td>70 (67)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (26)</td>
<td>43 (41)</td>
</tr>
<tr>
<td>Defecation urgency</td>
<td>41 (39)</td>
<td>53 (51)</td>
</tr>
<tr>
<td>AE during follow-up period, n (%)</td>
<td>52 (49)</td>
<td>56 (54)</td>
</tr>
</tbody>
</table>

AE = adverse event; GI = gastrointestinal.

*Safety population.
these statistical analyses is difficult to ascertain. These data suggest that rifaximin prevents TD caused by noninvasive strains of *E. coli* and other pathogens, as has been shown in vitro. Although rifaximin has been shown to protect against TD caused by the invasive pathogen *Shigella*, this parameter could not be assessed in the present study because no cases of TD associated with invasive pathogens were identified.

The present findings support those of a smaller 14-day study in US travelers to Mexico that demonstrated that significantly more individuals who received placebo developed TD (54%) compared with individuals treated with prophylactic rifaximin 200 mg/d (12%), 400 mg/d (19%), or 600 mg/d (13%). The present work expounds on this study by demonstrating the efficacy and tolerability of rifaximin 600 mg/d as a single, once-daily dose in a larger treatment population (n = 106). The present study utilized a single 600-mg dose because a dose-related trend toward a greater level of post-treatment protection was found in the previous prophylaxis trial (25%, 14%, 9% of patients treated with 200 mg/d, 400 mg/d, or 600 mg/d, respectively, experienced diarrhea recurrence). In addition, once-daily dosing of rifaximin 600 mg provides a single dose that may prevent diarrhea caused by enterotoxigenic and enteroinvasive bacterial pathogens and that may be convenient for travelers.

The International Society of Travel Medicine has recently published evidence-based reviews on the topics of treatment and prevention of TD. In the prevention review, rifaximin is identified as a potentially useful preventive drug for certain high-risk travelers. The current study is the second of two phase 3 clinical trials supporting an indication for rifaximin as prophylaxis for TD. Although higher protection rates against TD have been reported for systemic antibiotics (80%–94%) compared with rifaximin (58%–72%), the low potential of antibiotic resistance and adverse effects associated with rifaximin suggests that rifaximin be considered a safe and effective alternative for chemoprevention of TD caused by noninvasive strains of *E. coli*.

**Acknowledgments**

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**Declaration of Interests**

H. L., D. P. has consulted with, received honoraria for speaking, and has received research grants administered through his university from Salix Pharmaceutical Corporation; he has received an honorarium for consulting and/or speaking with McNeil Consumer Healthcare and Merck Vaccine Division. C. D. E. has received honoraria from Salix for speaking and consulting. Z. D. J. has consulted with, received honoraria for speaking, and has received research grants administered through her university from Salix Pharmaceutical Company. W. P. F., A. S., and E. B. are employees of and hold stocks in Salix Pharmaceuticals, Inc. The other authors state they have no conflicts of interest to declare.

**References**

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