A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Rifaximin for the Prevention of Travelers’ Diarrhea in US Military Personnel Deployed to Incirlik Air Base, Incirlik, Turkey

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Background. Infectious diarrhea is an important problem among travelers and deployed US military overseas causing substantial morbidity due to acute illness and may result in burdensome postinfectious sequelae.

Methods. The nonsystemic antibiotic rifaximin was evaluated for prevention of travelers’ diarrhea (TD) in a US military and civilian adult beneficiary population in a randomized, double-blind, placebo-controlled clinical trial. In all, 100 volunteers deployed to Incirlik Air Base, Turkey, received rifaximin 1,100 mg once daily or placebo for 2 weeks, and participants were followed daily for 2 weeks.

Results. In an intention to treat analysis (n = 95), TD (based on subjects meeting case definition or early treatment) developed in 6.3% (3 of 48) of the rifaximin group compared with 19.2% (9 of 47) in the placebo group (Fisher’s exact test \( p = 0.07 \)). Rifaximin provided 67% (95% confidence interval, −13% to 91%, \( p = 0.07 \)) protection against TD. Rifaximn 1,100 mg once daily was well tolerated with no observed differences in adverse events, whether solicited or unsolicited among the two treatment groups.

Conclusions. Rifaximin may represent an option among military personnel on deployment for prevention of TD with supportive future studies that consider deployment length, settings, and operational situations where widespread use of chemoprophylaxis may increase force health protection without undue risk during critical deployments.

Historically and in modern times, infectious diarrhea among deployed US war fighters has posed a significant health threat despite advances in field preventive measures.1–3 Rifaximin, a nonsystemic, gut-selective antibiotic, indicated in the United States for the treatment of TD caused by noninvasive strains of Escherichia coli, has the potential to address a number of the current concerns associated with the burden and management of infectious diarrhea in specific deployment settings. Given the high operational tempo as well as potential complication of giving multiple doses of antibiotics along with other chemoprophylactic regimens (eg, doxycycline for malaria), a single high dose daily (QD) regimen was evaluated for TD prevention in a deployment setting.

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Methods

Subjects were military beneficiaries traveling from the United States, with most staying at Incirlik Air Base, Incirlik, Turkey, for 14 days. Subjects were eligible for inclusion in this study if all of the following criteria were met: ≥18 years of age, in good health, and if female, met criteria for non-childbearing potential, or had a negative urine pregnancy test at screening and agreed to use a medically approved method of birth control. Exclusion criteria were as follows: antibiotic use within 7 days, antidiarrheal medication within 24, hypersensitivity or allergy to rifaximin or rifampin, acute diarrhea during the 7 days prior to enrollment, or within 24 hours after ingesting initial dose of study drug. Treatments were randomly assigned to consecutive numbers by using an allocation ratio of 1:1 in blocks of four for either oral rifaximin 1,100 mg QD (two 550 mg tablets) or matching placebo QD for 14 days. Salix Pharmaceuticals, Inc. (Morrisville, NC, USA) provided the interventional products in sequentially...
labeled bottles. Subjects were instructed to take study drug every morning with breakfast, and missed doses were to be taken with the following meal.

TD was defined as the coexistence of acute diarrhea (≥3 unformed stools within a 24-h period) and one or more of the following signs or symptoms of enteric infection: abdominal pain or cramps, moderate to severe increase in intestinal gas, nausea, vomiting, fever (≥37.8°C), fecal urgency, tenesmus, or gross blood and/or mucus in the stool. Stools were defined as formed (retained shape), soft (assumed shape of container and could not be poured, but would not hold form if placed on a surface; often had a custard or pudding-like consistency), or watery (could be poured). Additionally, subjects who had diarrhea and took a medication specifically for relief from the symptoms of diarrhea were categorized as having TD.

Enteric symptoms were assessed via daily subject diary entries and weekly clinic visits. Adherence was assessed during weekly follow-up visits through pill counts and interview. In addition, safety was assessed by monitoring adverse events. Excluding preestablished weekly visits, subjects could go to the clinic at any time of the day throughout the study on an informal basis. Stool specimens were collected for the purpose of conducting etiological agent analyses; however, only five acute specimens were submitted, and, therefore, results of these analyses will not be reported herein.

A target enrollment of 100 subjects with 50 subjects randomly assigned to each treatment arm was based on the relative risk of developing TD based upon analysis of time to first unformed stool (TFUS), an estimated 40% attack rate from prior studies at Incirlik,4,5 and a hazard ratio reported in a previous study of rifaximin for the prevention of TD in travelers to Mexico.6 Participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. A protocol deviation in assignment of study drug storage cabinet which resulted in nonsequential assignment of study drug.

The primary efficacy end point was the relative risk of TD during 14 days of treatment with rifaximin relative to placebo based upon the TFUS (defined as the number of hours from the first dose of study drug to the first of three occurrences of an unformed stool within 1 d meeting the definition of TD) associated with TD using the Cox proportional hazards model with a two-sided test at a significance level of 0.05 (Stata Version 10, StataCorp, College Station, TX, USA). Subjects who terminated for reasons other than treatment failure or who completed the entire 14-day treatment period without meeting the definition of TD were noted as having a censored TFUS as of the last available daily subject diary information.

The study protocol was approved by the NAMRU-3 Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects, and all subjects provided written informed consent.

Results

Between July 2007 and February 2008, 100 subjects were randomized to receive rifaximin 1,100 mg (n = 50) or placebo (n = 50) once daily for 14 days. There were no differences between treatment groups in baseline demographics. The median age was 36 years, 88% were males, and 73% were whites. One subject in the rifaximin group developed TD 4 hours after initiating treatment and was excluded from analysis. One volunteer in the rifaximin group and three volunteers in the placebo group were lost to follow-up. The remaining 95 subjects were included in the intention to treat analysis where 6.3% (3 of 48) of the rifaximin group developed TD compared with 19.2% (9 of 47) in the placebo group (Fisher’s exact test p = 0.07; Table 1). Based on a time-to-event analysis (Figure 1), it was observed that the rifaximin group resulted in a hazard ratio of 0.29 [95% confidence interval (CI) 0.08 to 1.09; p = 0.07] and resulted in an estimated protective efficacy of 67% (95% CI 13% to 91%; Fisher’s exact test p = 0.07).

Table 1 Efficacy of rifaximin in prevention of TD, intention to treat analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifaximin (n = 48)</th>
<th>Placebo (n = 47)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD, n (%)</td>
<td>3 (6.3)</td>
<td>9 (19.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Developed TD</td>
<td>3 (6.3)</td>
<td>7 (14.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Developed treated TD</td>
<td>0 (0)</td>
<td>2 (4.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Terminated early with no diagnosis of TD, n (%)</td>
<td>2 (4.2)</td>
<td>3 (6.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>Developed mild diarrhea without TD, n/n (%)*</td>
<td>9/45 (20.0)</td>
<td>8/38 (21.1)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Excludes subjects meeting TD definition.
Among 13 subjects (4 rifaximin, 9 placebo), adherence to self-dosing could not be ascertained \((n = 11)\), and 2 failed to adequately complete their daily diary, and outcomes were obtained by report during weekly visit. There were no observed differences in adverse events, whether solicited or unsolicited among the two treatment groups (data not shown).

Discussion

In Turkey where diarrheagenic *Escherichia coli* are the major pathogens,\(^4,5\) the rate of protection against TD with rifaximin observed in this study (67%) was similar to that observed in a prior study by DuPont and colleagues\(^6\) among student travelers to Mexico. The design of this study is unique from previous rifaximin prophylaxis trials because of the higher rifaximin daily dose (1,100 mg) administered. A safe and effective QD dosing regimen of rifaximin would be more convenient and potentially more cost effective versus a twice daily (BID) or three times daily (TID) dosing regimen. Although unclear, one wonders if a higher QD rifaximin dose of 1,100 mg might also have a residual protective impact seen with more frequent daily dosing regimen at lower rifaximin doses (eg, 200 mg BID or TID). Alternatively, QD scheduling at any dose may not be as effective as BID dosing given the possibility of a therapeutic trough with QD dosing, although in the DuPont and colleagues\(^6\) study, efficacy was observed with rifaximin 200 mg QD dosing.

This study has important limitations including inadequate power due to lower than anticipated attack rate, limited microbiological outcomes, nonsequential treatment allocation, as well as issues of adherence ascertainment and to a lesser extent daily diary completion among enrollees. Despite these deficiencies, there was no discernable effect of the nonsequential treatment allocation on primary outcomes, although such an effect cannot be ruled out. Furthermore, restricting analysis to those for whom adequate adherence and outcome ascertainment could be assessed resulted in no appreciable change in the primary outcome with an estimated protective efficacy 71% (−34% to 94%; Fisher’s exact \(p = 0.14\)).

Given the potential harms of long-term daily antibiotics in a population at risk for trauma-associated infections (including enteric trauma) and impact on individual and community microbiome, it is uncertain that antimicrobial chemoprophylaxis would offer a practicable solution during most extended military deployments (which historically have averaged about 3–6 mo). However, there are a number of relevant settings including port visits, in special operations forces, or in the initial phase of deployment settings where risk of TD is highest and the consequences of heat injury are frequent, where chemoprophylaxis may offer an acceptable solution. Further studies to explore the efficacy and safety of TD chemoprophylaxis in these populations and settings are warranted.

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References