

Therapy of Travelers' Diarrhea With Rifaximin on Various Continents

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OBJECTIVE: Our aim was to compare the efficacy and safety of rifaximin, a virtually nonabsorbed antibiotic, 600 and 1200 mg per day, with placebo in patients with travelers' diarrhea.

METHODS: This was a multicenter, 1:1:1 randomized, parallel-group, double-blind study, conducted in Antigua, Guatemala; Guadalajara and Morelia, Mexico; and the coast of Kenya north and south of Mombasa. Adult patients with acute travelers' diarrhea were recruited; exclusion criteria included primarily medication that could influence the outcome. Subjects were treated for 3 days, three times daily; follow-up lasted 5 days. For each 24-h period, the subjects completed a diary card. Pre- and posttreatment stool, blood, and urine samples were assessed.

RESULTS: Among the 380 volunteers, median time to the last unformed stool was 32.5 and 32.9 h in both rifaximin groups, compared with 60.0 h with placebo ($p = 0.0001$). Also, secondary clinical outcome measures were favorably influenced by the active agent. No relevant side effects were reported.

CONCLUSION: Rifaximin is efficacious and safe for treatment of travelers' diarrhea at daily doses of 600 mg or higher. (*Am J Gastroenterol* 2003;98:1073–1078. © 2003 by Am. Coll. of Gastroenterology)

Infectious diarrhea in travelers is caused by bacterial pathogens in approximately 80% of cases. There are various evidence-based options for prophylaxis and therapy of travelers' diarrhea (TD) (1), but many among them are not practical. For instance, compliance with the recommendation to abstain from potentially contaminated food and beverage is low both among European and American travelers (2). Fastest relief of TD may be offered by the combination of antimotility and antimicrobial agents (3), although not all studies have shown an additive effect of the combination (4,

5). However, according to a survey conducted among more than 60,000 travelers who visited various destinations (2), up to more than 50% had included loperamide and less than 10% a quinolone in their travel kit, and a small minority used prophylactic antimicrobials (Steffen R, unpublished data). Travel health physicians, pharmacists, and travelers seem reluctant to prescribe and use such medication, being apprehensive mainly about cost, resulting resistance, and side effects.

Rifaximin, a virtually nonabsorbed, semisynthetic rifamycin derivative, has a broad antimicrobial spectrum that includes most gram-positive and gram-negative bacteria, both aerobes and anaerobes. Its characteristics have been described previously (6). Other nonabsorbed antimicrobials, such as bicozamycin (7) and aztreonam (8)—neither of which were marketed—were previously shown to be effective in the treatment of TD. Similarly, in a first small trial with TD patients, rifaximin was at least as effective as co-trimoxazole and showed significantly better outcome in shortening the duration of diarrhea when compared with two historical placebo groups (9). A larger study demonstrated that rifaximin was as effective as ciprofloxacin in the treatment of TD in U.S. students newly arrived in Mexico and international tourists in Jamaica (10). To broaden the experience with respect to safety and efficacy of rifaximin, and particularly to assess it as a therapeutic agent against TD acquired in various regions of the world, a multicenter study was initiated. The objective was to compare rifaximin 200 mg *t.i.d.*, 400 mg *t.i.d.*, and placebo.

MATERIALS AND METHODS

The protocol for this multicenter, randomized (1:1:1), parallel-group, double-blind, placebo-controlled study was reviewed and adopted by the ethical committees at the investigators' institutions in Zurich, Switzerland, Houston,

Texas, and Baltimore, Maryland, as well as by the local committees at the three study sites in Kenya (coast north and south of Mombasa), Mexico (Guadalajara and Morelia), and Guatemala (Antigua).

Male and female nonindigenous travelers—mainly tourists, or in Mexico, students from U.S. universities at least 18 yr of age (16–17 yr with parents' consent)—were invited to volunteer for the study if affected by acute diarrhea. All subjects were enrolled between May 1999 and July 2000, usually within 2 wk of arrival. Diarrhea was defined as three or more unformed stools in the 24 h prior to enrollment, with at least one additional sign of enteric infection: abdominal pain or cramps, nausea, vomiting, fever of at least 100°F or 37.8°C, macroscopic blood in the stools, fecal urgency, excessive gas/flatulence, or tenesmus. Exclusion criteria were symptoms lasting for more than 72 h, clinical findings suggesting moderate or severe dehydration, pre-existing unstable or clinically significant illness, use of antimicrobials with potential activity against enteric pathogens within the 7 days prior to randomization, more than two doses of a symptomatic antidiarrheal compound within 8 h preceding randomization, use of any symptomatic drug, such as aspirin or ibuprofen, within 2 h preceding randomization, hypersensitivity or allergy to rifaximin or other rifamycin-like compounds, previous participation in trials involving rifaximin, pregnancy, breastfeeding, and unwillingness to use adequate contraception in the course of the study.

After signing the informed consent forms, the subjects were required to provide a stool, serum, and urine sample. Upon completion of the baseline assessment, they were given the trial medication and instructed to ingest a dose three times daily for 3 days and to complete a diary card every day. The first dose was taken under supervision of the study physician. A second visit with the on-site investigator was scheduled for day 4, that is, 24–48 h after the last drug dose, when they were required to submit a second stool, serum, and urine sample and to undergo a final physical examination. The total duration of participation in the study was 5 days (120 h).

Subjects who had taken less than five doses in the first 48 h were rated as noncompliant, as per inspection of the medication blister cards and the diary.

Stool samples provided before starting and then after ending therapy underwent gross observation for blood and mucus as well as microscopic evaluation for leukocytes at the regional laboratory affiliated with the study site. Each stool was cultured there for identification of the following enteric bacterial pathogens: *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Aeromonas*, *Vibrio*, *Plesiomonas*, and *Yersinia enterocolitica*. Five *Escherichia coli*-like colonies were isolated from each stool sample at the regional laboratory and transported to the central study laboratory at The University of Texas School of Public Health, Center for Infectious Diseases, Houston, on peptone stabs. At the central laboratory, enterotoxigenic *E. coli* was identified by production of heat labile (LT) or heat stable (ST) entero-

toxin or both by DNA hybridization/probe technique (11). Protozoal pathogens, including *Entamoeba histolytica*, *Cryptosporidium*, and *Giardia*, were identified as previously described in the central study laboratory at The University of Texas School of Public Health, Center for Infectious Diseases, Houston (11).

Similar to previous studies and following existing guidelines (12), the primary efficacy endpoint was the time elapsed from ingestion of the first dose of medication to passage of the last unformed stool (TLUS). "Wellness" (cure) was defined as 48 h with no unformed stools and no fever, or 24 h without watery stools, maximum two soft stools, and no clinical symptoms. Stools were defined as formed if they retained their shape, otherwise they were unformed (*i.e.*, soft if they took the shape of a container and watery if they could be poured).

Secondary endpoints included the number of subjects with improvement of diarrhea ($\geq 50\%$ reduction of bowel movements) during 24-h intervals, the number of unformed stools passed per time interval, the number of subjects who were declared "well," the number of treatment failures (clinical deterioration or worsening of symptoms, subject considered too ill to continue in a placebo-controlled study, or illness continuing after 120 h), and the number of subjects with microbiological cure, defined as a negative posttreatment culture with respect to the determined pretreatment etiologic agent.

Safety was assessed by analyzing adverse events as recorded on the diary cards or observed at the clinic visit, and by changes in vital signs and clinical laboratory tests (hematology, chemistry, and urinalysis) from pre- to posttreatment.

The sample size determination was based on a 0.025 level of significance for comparing each of the rifaximin groups with placebo (overall level of significance 0.05 for two pairwise comparisons), and an equal number of subjects required for each group. The sample size required to meet these parameters was estimated to be 90 subjects per group for a power of 0.90. To satisfy safety requirements for regulatory submissions, the sample size of 120 per group was selected. Only the intent-to-treat population (all randomized subjects) is described here, with statistical analyses carried out to determine the efficacy, but the results with the efficacy-evaluable population were very similar (data not shown). Consistent with guidelines, a safety population was defined, consisting of all randomized subjects who received at least one dose of study medication (13).

Statistical methods used for the analysis of TLUS included Kaplan-Meier methods, log-rank tests, and a proportional hazard model (Wald statistic) incorporating terms for treatment and site. The significance of differences between continuous variables was assessed by analysis of variance, and the Kruskal-Wallis test was employed when the data were not normally distributed. χ^2 testing was used for qualitative variables. All tests were two-tailed, and the overall level of significance was defined as $p \leq 0.05$.

Table 1. Study Population

Characteristics	Placebo	Rifaximin 600 mg/day	Rifaximin 1200 mg/day
Subjects recruited (ITT)	129	125	126
Exclusion* for			
Inclusion/exclusion violation	4	3	6
Lack of diary day 1 or 2	4	2	2
Lack of compliance (Rx < 2 d)	6	6	6
Efficacy evaluable population	119	116	114
Age (yr) (ITT)			
Mean \pm SEM	28.3 \pm 0.9	29.0 \pm 1.1	29.9 \pm 1.0
Range	16–69	18–72	18–66
Gender: male:female ratio	51:49	54:46	48:52

ITT = intent-to-treat population.

* More than one reason possible.

RESULTS

Among the 380 subjects enrolled (Table 1), most of whom were Caucasians, there were no significant differences with respect to demographic criteria. Similarly, no significant differences were registered with respect to baseline disease characteristics, including duration of pretreatment illness (median 30.0–31.8 h in the three groups), number of unformed stools (median 5, range 3–25), proportion of concomitant symptoms, such as abdominal pain/cramps (86.4%–91.5%), urgency (86.0%–87.3%), excess gas/flatulence (76.8%–79.8%), nausea (53.2%–59.2%), tenesmus (31.0%–35.7%), fever (20.6%–24.8%), and vomiting (9.3%–16.0%). Also, the initial stool examination showed no significant between-group differences when leukocytes, gross blood, and pathogens were compared. Vital signs, height, and weight were similarly distributed across treatment groups, and the same applied for pretreatment and concomitant medications.

Median TLUS was 60.0 h in the placebo group, 32.5 h in the rifaximin 600-mg group, and 32.9 h in the 1200-mg group ($p = 0.0001$ for each of the two active medication groups *vs* placebo) (Figure 1). Both in the placebo and in the two rifaximin groups, TLUS was markedly longer in Kenya compared with the two Latin American study sites; rifaximin 1200 mg shortened TLUS most effectively in two of the three sites (Table 2).

Wellness (clinical cure) was declared within 120 h in 79.2% and 81.0% of subjects in the low- and high-dose rifaximin groups, respectively, compared with 60.5% in the placebo group ($p = 0.001$ for each active treatment group *vs* placebo). Treatment failures were observed in 45 (34.9%) subjects in the placebo group, compared with 20 (16.0%) of those with rifaximin 600 mg and 21 (16.7%) with rifaximin 1200 mg daily ($p = 0.001$).

An improvement was significant in the rifaximin 600 mg groups *versus* placebo in the 24–48-h and 48–72-h inter-

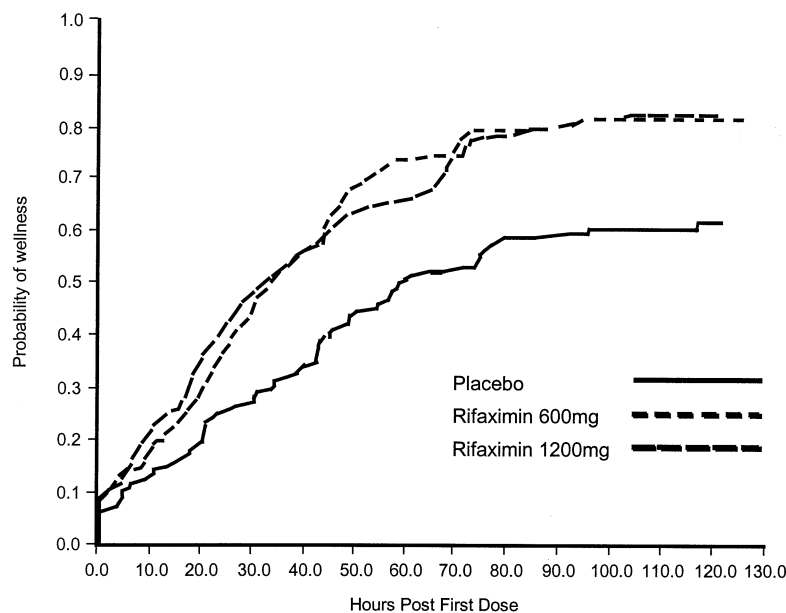
**Figure 1.** Probability of TLUS for the intent-to-treat population.

Table 2. Median TLUS (in Hours) at the Various Study Sites and According to the Pretreatment Stool

Study Site	n	Placebo	Rifaximin 600 mg/day	Rifaximin 1200 mg/day	<i>p</i>
Mexico	195	59.1	32.5	46.1	
Guatemala	100	49.0	28.9	23.3	
Kenya	85	74.3	42.7	30.3	
Total	380	60.0	32.5	32.9	0.0001*
Subgroups					
Leukocyte positive	60	N/A	45.1	36.7	0.067/0.003†
Leukocyte negative	315	57.0	32.5	30.1	0.0004/0.003†
Bacterial infection positive	163	58.6	28.4	30.3	0.001/0.06†
Bacterial infection negative	216	64.4	43.4	36.8	0.017/0.0004†
Parasitic infection positive	57	60.8	37.3	43.8	0.033/0.123†
Parasitic infection negative	313	60.0	32.2	28.5	0.033/0.123†

N/A = not available.

* Each rifaximin group vs placebo. Wald Statistic (proportional hazards model with terms for treatment group and site).

† Rifaximin 600 mg/day and rifaximin 1200 mg/day, respectively, vs placebo. Log-rank test (survival model).

vals. In the 24–48-h interval, improvement was noted in 87% of subjects in the rifaximin 600 mg group, compared with 72% in the placebo group ($p = 0.007$). In the 48–72-h interval, the rate of improvement was 91% for the 600-mg group, compared with 78% for the placebo group ($p = 0.008$). In the same intervals, the rate of improvement in the rifaximin 1200 mg group was higher than in the placebo group, but the significance level did not meet the planned 0.025 level for statistical significance. The mean number of unformed stools passed per time interval on day 1 was 3.8 for placebo and 3.1 for both active treatment groups, on day 2 it was 2.6 and 1.6, respectively, and on the last surveyed day 0.9 and 0.5, respectively ($p = 0.001$, repeated measures analysis of variance).

By decreasing order, the pathogens detected were enterotoxigenic *E. coli* (ETEC) ST, ETEC LT, ETEC LT/ST, *Cryptosporidia*, *Giardia lamblia*, *Salmonella*, and *Shigella* species. In Mexico and Guatemala, approximately half of the subjects had no pathogen identified pretreatment, whereas in Kenya at least 80% of subjects had one or more pathogens identified in the pretreatment stool.

The rate of microbiological cure based on those subjects with at least one pathogen at pretreatment was not significantly different across treatment groups. Just less than one fifth of subjects in each group had pathogens in their post-treatment stool sample that had not been detected in the pretreatment sample, the most common newly isolated entities being again ETEC LT, ETEC ST, ETEC LT/ST, and *Cryptosporidia*.

In subjects with leukocyte-negative stools, TLUS was significantly reduced by both active treatments (median 32.5 and 30.1 h in the 600- and 1200-mg groups, respectively, vs 57.0 h in the placebo group, $p = 0.003$ and $p = 0.004$ for both active treatment groups, respectively), whereas in the fewer subjects with leukocyte-positive stools, TLUS was only significantly reduced by rifaximin 1200 mg (median 36.7 h, median not achieved for placebo, $p = 0.003$, log-rank test) but not by rifaximin 600 mg (median 45.1 h, $p = 0.067$, log-rank test).

Median TLUS for subjects without parasitic infection was 32.2 h in the rifaximin 600 mg group and 28.5 h in the 1200 mg group versus 60.0 h in the placebo groups ($p = 0.0005$ and $p = 0.0002$ vs placebo, respectively, log-rank test). Insufficient data were generated for subjects with a parasitic infection to achieve significant results, but the trend was also in favor of the active treatment groups.

Study drug-related adverse events were reported by 90 subjects (69.8%) in the placebo group, 74 (59.7%) in the rifaximin 600 mg group, and 88 (69.7%) in the rifaximin 1200 mg group, without significant differences between groups. Most reported adverse events were GI-related, occurring in 61.1%, 50.8%, and 57.9% of subjects in the placebo, rifaximin 600 mg, and rifaximin 1200 mg groups, respectively. Worsening of enteric symptoms was also recorded as an adverse event, and this may account for the relatively high incidence of GI effects. The next most frequent and non-GI type adverse event was headache, which was reported for 19 (15.1%) subjects in the rifaximin 1200 mg group versus 10 subjects in each of the rifaximin 600 mg (8.1%) and placebo (7.8%) groups (not statistically significant differences). Fatigue was the only complaint reported more frequently (1.1%) in the rifaximin 1200 mg group ($p = 0.023$, Fisher exact test).

One single adverse event was reported as serious. It occurred in a subject taking placebo after the first day of treatment and was a case of severe diarrhea and cramps, for which the subject was hospitalized for one night. One patient receiving rifaximin 600 mg/day prematurely terminated medication after the first day of treatment because of feeling of malaise with lack of appetite. Both patients had an uneventful recovery.

DISCUSSION

This study, in which results were pooled across three study sites on two continents, demonstrates that rifaximin at both the 600 mg daily and 1200 mg daily dose levels significantly reduced the duration of posttreatment diarrhea (TLUS), the

primary efficacy parameter, when compared with placebo. Primary efficacy results were supported by significant improvement in the number of unformed stools per time interval and improved rates of wellness in the rifaximin groups compared with the placebo group. Treatment failure occurred in the placebo group at twice the rate in each rifaximin group. These findings are consistent with the two previous studies in which the effect of rifaximin on TD has been assessed (9, 10). Generally, there was no significant difference between the 600 mg and 1200 mg dosages, with a slight trend in advantage for the higher dose in two of three sites (mainly in Kenya, where a far higher bacterial and parasitic detection rate was observed).

The assessment of microbiological cure was confounded by the low number of pathogens identified in the pretreatment diarrhea sample at both Latin American study sites and the relatively high proportion of new isolated pathogens in the posttreatment stool samples. Although antibacterial therapy significantly shortens the illness, it may not render the posttreatment stool cultures negative for enteric pathogens; as previously observed, eradication or failure to eradicate the pathogen does not correlate with clinical improvement to antimicrobial therapy (14). These analyses thus were of limited usefulness. The eradication rates in the rifaximin groups and placebo were similar, but comparable to the findings of previous rifaximin studies in the same population (9, 10). Similar to previous studies, a relatively high rate of newly identified pathogens were identified in the posttreatment samples, supporting the idea that reinfection is common in that setting as the travelers continue to ingest contaminated food. Plasmid analysis can demonstrate whether reinfection occurs with different strains (15).

In this study in TD, rifaximin, similar to other potent antimicrobials, significantly shortened the duration of the illness. Whereas earlier studies of rifaximin in travelers were carried out mainly in Mexico, this study was conducted in three different regions of the world, giving a global orientation to the study and its results. Interestingly, despite an unusual high incidence of *Cryptosporidium* infection in Kenya, the clinical improvement of the rifaximin-treated subjects at this site was significantly superior to placebo-treated subjects, which may illustrate activity against this pathogen as previously observed (16). Additionally, the significant reduction of the illness duration achieved with the daily dosage of 1200 mg in subjects with fecal leukocyte-positive diarrhea suggest that rifaximin may be effective against invasive or inflammatory pathogens, similar to other virtually nonabsorbable antibiotics, bicozamide and aztreonam (7–9). This aspect should be investigated in a separate trial in a setting where this frequently occurs.

As expected for a poorly absorbed antimicrobial, rifaximin up to 1200 mg daily for 3 days was well tolerated by subjects with TD. No serious adverse events occurred in the active treatment groups. The most frequently reported adverse events were GI events or headache, as often seen in

acute diarrhea. Rates for adverse events were similar among treatment groups and, for some GI events, higher in the placebo group compared with the rifaximin groups. The higher incidence of fatigue in the 1200-mg group is surprising and without plausible explanation, particularly because this was not observed in a previous study with 1800 mg daily (9). No clinically significant changes from pretreatment to end-of-study evaluation were noted in the laboratory data, vital signs, or physical examination (data not shown).

Although no drug–drug interaction was formally evaluated in this trial, there is no indication that rifaximin would have significant drug interactions (*e.g.*, with antimalarials). The agent showed no potential to inhibit microsomal CYP450 isozymes at concentrations ranging from 2 to 200 ng/ml, and rifaximin, unlike rifampin, has no potential to inhibit or to induce human hepatic cytochrome P450 at anticipated clinical plasma concentrations. The lack of any significant induction between rifaximin and human cytochrome P450 is also consistent with an absence of any significant induction of drug metabolizing enzymes in the liver and the gastrointestinal tract of rats given the agent orally for 6 months (unpublished data).

In conclusion, rifaximin is a potent and well-tolerated agent, to be recommended for inclusion in the travel kit for treatment of TD. Having an effective drug that is exclusively used to treat bacterial diarrhea is preferred for managing enteric disease in the situation where a drug is important in the therapy of bacterial infections of the GI, urinary, and respiratory tracts, which is the case for the fluoroquinolones. If resistance develops from the selective pressure of widespread use of the quinolones, this would have public health significance. Also, a poorly absorbed drug should be safe to use in children and pregnant women, a problem with the current TD treatment regimens. More data are needed to judge the value of rifaximin in inflammatory or invasive illness.

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