Azithromycin Found to Be Comparable to Levofloxacin for the Treatment of US Travelers with Acute Diarrhea Acquired in Mexico

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Increased drug resistance among enteropathogens is an emergent problem in travelers’ diarrhea. This randomized, double-blind trial was conducted in Guadalajara, Mexico, during the summers of 1999–2001 to compare azithromycin with levofloxacin for the treatment of travelers’ diarrhea. A total of 217 US adults were randomized to receive a single oral dose of azithromycin (1000 mg; 108 persons) or levofloxacin (500 mg; 109 persons), with a follow-up period of 4 days. Three patients in each group dropped out of the study. The median time between initiation of therapy and passage of the last unformed stool (azithromycin group, 22.3 h; levofloxacin group, 21.5 h) and the number of unformed stools passed during the 4-day follow-up period (azithromycin group, 6.5; levofloxacin group, 5.5) were similar. Treatment failure occurred in 10 patients (9.5%) receiving azithromycin and 8 patients (7.5%) receiving levofloxacin. Possible minor, self-limiting adverse events occurred in 57 patients in each treatment group. Azithromycin was found to be a safe and effective alternative to levofloxacin for the treatment of acute travelers’ diarrhea in US adult travelers to Mexico.

Diarrhea is the most common travel-related condition among people who travel from industrialized regions to tropical and subtropical areas of the developing world, with incidences as high as 40%–55% [1–3]. Different microorganisms have been reported as etiologic agents of travelers’ diarrhea, and bacterial enteropathogens appear to be responsible in up to 80% of cases with an identified etiology [2–4]. The principal bacterial enteropathogens that cause travelers’ diarrhea are enterotoxigenic Escherichia coli (ETEC), enteroaggregative E. coli, Campylobacter jejuni, Shigella species, Salmonella species, Aeromonas species, Plesiomonas species, and non-cholerae species of Vibrio [2]. Because of the high prevalence of bacterial microorganisms, antimicrobial drugs have become the recommended therapy for this illness. Of these drugs, the fluoroquinolones have become preferred for travelers’ diarrhea in adults on the basis of their activity against each of these bacteria [5, 6]. However, an increasing number of fluoroquinolone-resistant enteropathogens have been reported, and this has become a significant problem in some parts of the world [7, 8]. This acquired resistance has prompted a search for alternative drugs.

Azithromycin, an azalide, has a long half-life and achieves a high intracellular concentration [9]. It has excellent in vitro activity against common bacterial enteric pathogens [10–13]. In addition, this drug has already been reported to be effective against travelers’ diarrhea in Southeast Asia, where C. jejuni is a common cause of diarrhea and where fluoroquinolone-resistant Campylobacter species are prevalent [14–17].

The present study was developed to examine the
safety and the clinical and microbiologic efficacy of a single oral dose of azithromycin for the treatment of travelers’ diarrhea. Azithromycin was compared with a single oral dose of levofloxacin, which is the active isomer of ofloxacin and has the same activity as the older fluoroquinolones against bacterial enteropathogens. Levofloxacin has the advantage of a longer half-life [18], which permits once-daily dosing. In other travelers’ diarrhea studies conducted by some of us [19, 20], the efficacy of a single 400-mg dose of ofloxacin has been documented. We currently use a single 500-mg dose of levofloxacin as standard treatment. We have had extensive clinical experience with this drug and dosage.

METHODS

Patients. The study was a double-blind, randomized clinical trial conducted during the summer months (June through August) of 1999–2001 in Guadalajara, Mexico, that involved US students attending summer programs of the University of Arizona and the University of San Diego [21]. Eligible subjects included men and women (age, ≥18 years) with acute diarrhea. Subjects were excluded if they were pregnant or breast-feeding, had an unstable medical condition, had taken antidiarrheal medication in the 24 h before enrollment or any number of doses of symptomatic therapy within 2 h before enrollment, or had received an antimicrobial drug with expected activity against enteric bacterial pathogens within the week before enrollment.

Written consent was obtained from each subject before enrollment. Subjects underwent screening procedures that included obtaining of a medical history and a brief physical examination. The study was reviewed and approved by the University of Texas–Houston Health Science Center Committee for the Protection of Human Subjects and the local regulatory authorities in the area where the study was conducted. A pretreatment stool was confirmed to be unformed by clinic personnel before enrollment of the subject. Eligible subjects were then randomized to receive a single dose of either azithromycin (1000 mg) or levofloxacin (500 mg). Double placebos were used to blind the study. Medications were randomized in blocks of 10 patients per group. Use of any antidiarrheal compounds, including aspirin, ibuprofen, and antiperistaltic agents, was prohibited during the study. Subjects were seen daily for 4 days at our clinics at the schools in Guadalajara. Subjects completed daily diary entries in which they reported clinical symptoms and signs, as well as the time and form of all stools passed during the 4-day observation period. Safety was assessed by means of physical examination and review of subjects’ symptoms recorded in daily diaries. A second stool sample was obtained for microbiologic assessment on day 4 or 5 after the administration of antimicrobial therapy.

Laboratory studies. Bacterial pathogens sought in our local laboratories included Shigella species, Salmonella species, C. jejuni, Aeromonas species, Plesiomonas species, Vibrio species, and Yersinia enterocolitica. Protozoal pathogens, including Entamoeba histolytica, Cryptosporidium species, and Giardia species, were identified using ELISA (Alexon). Five E. coli–like colonies were retrieved from MacConkey agar plates from each stool sample for all patients and were inoculated into individual peptone stabs. They were transported to Houston for further identification. ETEC was sought by looking for the capacity to produce heat-labile and heat-stable enterotoxin, using the DNA hybridization/probe technique [2].

Definitions. Acute diarrhea was defined as passage of ≥3 unformed stools in 24 h, with a duration of illness of ≤72 h. One or more signs or symptoms of enteric infection had to be present, including nausea, vomiting, abdominal cramps or pain, tenesmus, dysentery (i.e., passage of grossly bloody stools), or fecal urgency. Stool form was divided into 3 categories: “formed” (stool retained its shape), “soft” (stool took the shape of a container), and “watery” (stool could be poured). Both soft and watery stools were considered to be unformed. “Wellness” (cure) was defined as (1) passage of no unformed stools in a 48-h interval during which there was no fever, with or without other clinical symptoms; or (2) passage of no watery stools and ≤2 soft stools in a 24-h interval during which there was no fever or other clinical symptoms of enteric infection. Duration of posttreatment diarrhea was defined as the time from initiation of therapy until passage of the last unformed stool (i.e., “time to last unformed stool” [TLUS]), after which subjects were declared to be healthy. In determining the TLUS, presence of mild excessive gas or mild flatulence was not considered to be a symptom of continuing illness. Becoming rapidly healthy was defined as having a TLUS of 0 h. Treatment failure was defined as (1) clinical deterioration or worsening of clinical symptoms ≥24 h after therapy, compared with pretreatment symptoms and number of stools passed; (2) no improvement in clinical symptoms ≥24 h after therapy; or (3) continuing illness 72 h after therapy. Bacteriologic cure was defined as the absence of the pretreatment etiologic agent in the posttreatment stool sample, and bacteriologic failure was defined as the continued presence in the posttreatment stool sample of the etiologic agent. An adverse experience was defined as a clinical finding or patient complaint in the daily diary that was not present during the 24-h period immediately before enrollment in the trial.

The primary clinical efficacy end point was based on rapidity of resolution of diarrhea, as measured by TLUS. Secondary end points included the number of unformed stools passed and the number of subjects with clinical symptoms (i.e., nausea, vomiting, abdominal pain and cramps, excess gas/flatus, urgency, tenesmus, and fever) per time interval of study, the
number of subjects for whom treatment failed, the number of subjects with bacteriologic cure, and the occurrence of adverse experiences.

**Statistical analyses.** The objective of the analysis of TLUS was to demonstrate that the TLUS for azithromycin was not inferior to the TLUS for levofloxacin. A procedure described by Com-Nougue et al. [22] for establishing equivalence (non-inferiority) with survival-type data was used for the analyses. For analyses of improvement of diarrhea, continuing clinical signs and symptoms of enteric illness, wellness and treatment failure, bacteriologic cure, and incidence of adverse events, either the \( \chi^2 \) test or Fisher’s exact test was used. All comparisons of treatment groups were performed using 2-tailed tests, and \( P < .05 \) indicated statistical significance.

A sample size calculation was based on comparing the treatment groups with respect to the proportion of subjects who passed their last unformed stool by the end of the first 24 h of the study. For fluoroquinolones (levofloxacin), historical data indicate that the probability of passing the last unformed stool by the end of the first 24 h is 0.62. The sample-size calculation was based on an alternative probability of 0.30 for azithromycin, a .05 level of significance \( (\alpha = 0.05) \), a power of 0.80, and an equal number of subjects in each group. This is equivalent to assuming a median TLUS of 21 h for the levofloxacin group and 25 h for the azithromycin group (hazard ratio, 0.55). The final sample size of 200 patients provided >80% power for the specific alternative.

All statistical analyses were based on the intent-to-treat principle, meaning that all subjects other than those who left the study were included in the analysis of the treatment groups to which they were randomized. TLUS was summarized using Kaplan-Meier estimates. Subjects for whom the TLUS could not be calculated (because enrollment was terminated early as a result of treatment failure) were conservatively analyzed as having a TLUS of 97 h. Likewise, subjects who passed unformed stools in the 72–96-h (day 4) period for whom a TLUS could not be calculated because no day 5 data were collected were also conservatively analyzed as having a TLUS of 97 h. Data from subjects for whom the TLUS could not be calculated because they terminated enrollment early as a result of an adverse event were censored at the time of the last available information about unformed stools.

**RESULTS**

Of the 217 subjects enrolled in the study, 108 were randomized to receive azithromycin and 109 to receive levofloxacin. A total of 105 and 106 subjects in the azithromycin and levofloxacin groups, respectively, completed the trial. Three subjects in each group were lost to follow-up and did not return their daily diaries.

The azithromycin and levofloxacin groups were comparable with regard to mean age (25.4 vs. 25.3 years), sex (male sex, 45.7% vs. 44.3% of subjects), mean number of unformed stools passed 24 h before enrollment (6.3 vs. 6.1), and clinical symptoms (nausea, 69% vs. 70% of subjects; vomiting, 16% vs. 15%; abdominal pain, 89% vs. 88%; excess intestinal gas, 71% vs. 74%; and fever, 12% vs. 14%). The median durations of diarrhea before receipt of treatment were 33.0 h and 32.0 h for the azithromycin and levofloxacin groups, respectively.

The results of laboratory studies of pretreatment stool specimens and pretreatment enteropathogen detection rates were similar in the azithromycin and levofloxacin groups: fecal leukocytes were present in 36% and 26% of subjects, respectively; ETEC was identified in 51% and 55%, respectively; and a mixture of other pathogens (Shigella species, Salmonella species, and Cryptosporidium species, with or without ETEC coinfection) was identified in 13% and 18%, respectively.

In figure 1, the cumulative percentages of subjects who remained ill during the study are presented over the 3 days for which TLUS could be calculated for the 2 treatment groups. The 2 curves are similar.

As shown in table 1, the median TLUSs for the 2 treatment groups were not significantly different. Of the 105 subjects who received azithromycin, 10 (9.5%) were determined to have had treatment failure (9 continued to have diarrhea at the end of the 4-day follow-up period, and 1 withdrew from the study on day 2 because of worsening of diarrheal illness). In the levofloxacin group, 8 (7.5%) of 106 subjects (7 at the end of the study and 1 during day 3) were determined to have had treatment failure. A higher proportion of subjects who received levofloxacin became rapidly healthy (21% vs. 8%; \( P = .0108 \)), as defined by a TLUS of 0 h; otherwise, the treatment groups were equivalent with respect to TLUS.

For both groups, the mean number of unformed stools passed during each of the 4 days of observation is shown in figure 2. The bar graph reveals that a similar mean number of stools were passed each day in the 2 treatment groups, with no significant differences found \( (P > .1) \). Likewise, the total number of unformed stools passed during the 96-h observation period did not differ \( (P > .1) \). The clinical symptoms occurring after therapy was initiated were similar in the 2 groups.

In table 2, the microbiologic outcome after therapy is presented. A pathogen was detected in 68 (65%) of 105 subjects in the azithromycin group and 71 (67%) of 106 subjects in the levofloxacin group. The principal pathogen identified was ETEC, which was present in 55 (52%) of 105 subjects who received azithromycin and 57 (54%) of 106 subjects who received levofloxacin. Of subjects for whom a pretreatment bacterial pathogen was detected, 6 subjects in the azithromycin group and 7 subjects in the levofloxacin group did not provide
Figure 1. Comparative effectiveness of azithromycin (105 subjects) or levofloxacin (106 subjects) for treatment of travelers’ diarrhea (percentage remaining with diarrhea after initiation of therapy).
patients with travelers’ diarrhea have been previously reported in Southeast Asia [14–17]. The present study provides evidence that azithromycin is effective in therapy for travelers’ diarrhea in another region of the world (Guadalajara), where there are different causative agents [25, 29]. Our study also shows that this azalide is effective against the subgroup of cases of travelers’ diarrhea caused by ETEC, the most prevalent bacterial pathogen identified in this location [25], as well as in many other regions of the world. Because of the small numbers of other bacterial enteric pathogens isolated (especially Shigella, Salmonella, and Campylobacter species), our study does not allow us to be certain of the efficacy of azithromycin against these invasive pathogens. However, we are confident of the value of azithromycin in invasive forms of diarrhea, on the basis of the findings of therapeutic trials performed in Bangladesh [31] and Southeast Asia [14, 30, 32].

Patients treated with levofloxacin appear to have a slightly faster clinical response than do azithromycin-treated patients: more levofloxacin recipients in our study had durations of posttreatment diarrhea (TLUSs) equaling 0 h (21% vs. 8%). Only a much larger study could determine whether this trend is clinically important.

Although the results were not statistically significantly different, we also found that levofloxacin had a slightly higher microbial eradication rate than azithromycin for diarrhea caused by any bacterial enteric pathogen identified (69% vs. 58%) or by ETEC identified (61% vs. 55%). The pathogen eradication rate for single-dose therapy in this study was lower

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Table 1. Duration of posttreatment diarrhea, number of unformed stools passed, and rapid achievement of wellness and failure to achieve wellness (time between initiation of therapy and passage of the last unformed stool [TLUS], 0 h) after treatment with azithromycin or levofloxacin among US students who acquired diarrhea in Guadalajara, Mexico.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
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<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Levofloxacin</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(n = 105)</td>
<td>(n = 106)</td>
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<tr>
<td>TLUS, median h</td>
<td>22.3</td>
<td>21.5</td>
<td>.16</td>
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<tr>
<td>Mean no. of unformed stools</td>
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<tr>
<td>In the first 24 h of the study</td>
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<td>2.9</td>
<td>&gt;.1</td>
<td></td>
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<tr>
<td>At 96 h</td>
<td>6.5</td>
<td>5.5</td>
<td>&gt;.1</td>
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<tr>
<td>No. (%) of subjects who rapidly became healthy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (8)</td>
<td>22 (21)</td>
<td>.0108</td>
<td></td>
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<tr>
<td>No. (%) of patients who had treatment failure</td>
<td>10 (9.5)</td>
<td>8 (7.5)</td>
<td>.6079</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as a TLUS of 0 h.

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Figure 2. Mean number of unformed stools passed during the study after treatment with azithromycin (105 subjects) or levofloxacin (106 subjects)
than we have seen with 3 days of fluoroquinolone therapy, which has ranged from 88% to 98% [25, 33]. We have seen lower rates of pathogen eradication with other antimicrobial regimens, such as treatment with rifaximin for 3 days (74%) [33]. We do not feel that this difference is important. The objective of antimicrobial therapy for treatment of travelers’ diarrhea is shortening illness and returning travelers to normal activities. Whether enteropathogens persist in or are eradicated from stool appears not to predict the clinical benefits of antimicrobial therapy [34].

More than one-half of the patients in both treatment groups presented with minor adverse events, as defined in Methods. However, these were self-limited and transient and did not lead to withdrawal from the study. We have seen similar rates of minor adverse experiences in other trials, and most of these events (e.g., nausea, vomiting, abdominal pain, tenesmus, fecal urgency, and flatulence) appear to be related to the underlying diarrheal disease.

We found that single oral doses of azithromycin and levofloxacin were as effective as fluoroquinolones given for 3–5 days for the treatment of travelers’ diarrhea, as has been found in other studies [24–27]. Single-dose therapy offers 3 advantages to international travelers for self-treatment of diarrhea: ease of administration, improved compliance, and lower cost. Azithromycin has additional safety considerations. It is already approved for other uses in children, and it is a category B drug in pregnancy [23], both of which are contraindications for fluoroquinolones [35]. We feel that the present study shows that single-dose azithromycin is a safe and effective alternative to fluoroquinolones for the self-treatment of acute travelers’ diarrhea.

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**References**