Efficacy of *Lactobacillus* GG as a Diarrheal Preventive in Travelers

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Traveler's diarrhea can be a debilitating problem for individuals on international trips. Retrospective and prospective studies have shown the incidence of traveler's diarrhea to range from 15–56%.[1,2] A placebo-controlled, double-blinded study in Finnish travelers found that the probiotic *Lactobacillus* GG decreases the incidence of traveler's diarrhea.[3]

Lactobacillus GG, initially isolated from healthy humans, is remarkable in its ability to resist acid and bile degradation and to adhere to the intestinal mucosa.[4] To assess the efficacy of *Lactobacillus* GG in preventing diarrhea in American tourists, a study was conducted at the Travel and Immunization Center of the Long Island Jewish Medical Center (LIJMC).

Methods

Adult patients at the LIJMC Travel and Immunization Center between December 1993 and March 1995 who were traveling to developing countries for periods of 1–3 weeks were invited to participate in a double-blinded, randomized, placebo-controlled study. The study was approved by the Human Subjects Review Committee at LIJMC, and written informed consent was obtained from each subject. Patients were excluded if they were under the age of 18, unable to take pills or capsules, had an underlying immunosuppressive disorder or a history of inflammatory bowel disease. After informed consent, individuals were randomized to receive either *Lactobacillus* GG powder in capsules or a placebo containing ethyl cellulose powder in identical capsule form. The daily dose of *Lactobacillus* GG was approximately 2×10^9 bacteria. The travelers were instructed to take the capsules with cold water, once daily, starting 2 days prior to departure and continuing throughout the trip. In addition, all patients were instructed to drink only bottled or boiled water and to avoid salads, fruits and fresh vegetables. The patients were given a treatment course of antibiotics (ciprofloxacin at 500 mg twice a day orally) and loperamide to take in the event of a diarrheal illness. They were instructed not to take loperamide if symptoms of dysentery developed.

At enrollment, patients were asked to complete a form which included data on prior and current health status; medications; chronic diseases; past history of vaccinations, travel-related illness, inflammatory bowel disease or lactose intolerance; and the usual number of bowel movements per day. They were also given a diary card to take with them on their trip.

After their trips, patients returned their diary card and were contacted by telephone, mail, or office visit to determine if diarrhea occurred while they were away. If so, they were asked the number of stools per day, the duration of the diarrhea, other associated symptoms (fever, tenesmus, pain, nausea, vomiting, blood in the stool), medications taken for the treatment of diarrhea, and any other added medications. In addition, we asked travelers about compliance with taking the study medications.

Diarrhea was defined as three or more loose bowel movements per day associated with abdominal cramping in patients whose normal number of bowel movements were two or less.

Compliance was defined as taking the prescribed study medication as directed. We did not assess compliance regarding bottled water and avoidance of fresh fruit and vegetables. Days on which the traveler failed to take the assigned drug were excluded from the analysis.

For the purpose of statistical inference, the unit of analysis was the patient rather than the day. The dependent variable in the analysis was the proportion of days

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that a traveler had diarrhea (three or more loose stools). In this sense, every individual episode of diarrhea was not treated as a separate event. Instead, the number of days a participant reported diarrhea was divided by the number of days at risk (i.e., number of travel days) and a score was constructed for each patient to represent percent incidence of diarrhea. This approach was used to lessen the possible skewing of results if one or two patients had multiple episodes of diarrhea.

The question of whether the study drug impacted on the proportion of days a traveler experienced diarrhea was assessed by a two-tail *t*-test with alpha set at 0.05.

Results

Four hundred individuals were initially enrolled in this study. Two hundred and forty-five patients met the criteria for inclusion in the analysis (i.e., they took the prescribed study medication, returned the completed diary after the trip, and reported a "normal" prior stool rate of two or fewer per day). Of the 155 travelers excluded, 114 never took the medication (62 placebo, 52 study drug), 28 took a partial course (14 placebo, 14 study drug), and 13 had their trip canceled (5 placebo, 8 study drug). Of the 245 patients included, 126 received the study drug and 119 the placebo. This sample included 128 males and 117 females, ranging in age from 17–80 years with a mean of 50. The two treatment groups were similar in past medical illness, age, gender and destinations. For each patient, we computed a summary score based on all valid travel dates which were defined as follows: the individual took the pills on the current and the prior day and did not take supplemental antidiarrheal pills on the current day. Using these criteria, we collected data from a total of 2743 travel days.

Fourteen geographic areas were represented, with the largest numbers of patients traveling to Asia (n=76), East Africa (n=37), South America (n=31), the subcontinent of India (n=30), and Central America (n=19). Additional areas that were represented included the Middle East, West Africa, and North Africa.

For the sample as a whole, the average incidence of diarrhea was reported as 5.6% per day at risk (95% confidence interval (CI) 3.7–7.5%). In our sample, the rate varied somewhat from region to region with a relatively high risk observed in South America (14% based on 14 persons) and a relatively low risk observed in Central America (1% based on 12 persons). However, the comparisons between regions are based on small numbers of cases and therefore are not necessarily representative of a larger population.

Lactobacillus GG was effective at reducing the incidence of diarrhea. The risk of having diarrhea on any given day was 3.9% for patients receiving study medication, as compared with 7.4% for patients receiving placebo (p=.05). Equivalently, the relative risk of diarrhea for persons on study medication was 53% (3.9%/7.4%), with a protection rate of 47% (7.4%–3.9%/7.4%). The difference was tested by analysis of variance. There was no evidence that the impact of *Lactobacillus GG* varied as a function of age or gender.

The protective effect appeared to be more pronounced in patients with a prior history of traveler's diarrhea. In this group, the risk was 16.7% for patients on *Lactobacillus GG* as compared to 29% for patients on placebo. The subsample included only 22 patients, making further analysis on this group inappropriate.

Side effects attributable to *Lactobacillus GG* were few: two patients reported abdominal cramping.

Discussion

At the present time, options for preventing traveler's diarrhea are limited. Pepto Bismol (bismuth subsalicylate) is considered the agent of choice. Unfortunately, it needs to be taken frequently; therefore, compliance may be a problem. Prophylactic antibiotics are generally not recommended, except in exceptional circumstances such as in individuals with inflammatory bowel disease, those who are immunosuppressed, or those who may have to accept foods while traveling which they normally would avoid (i.e., businessmen and politicians).[5,6]

A safe, well-tolerated agent such as *Lactobacillus GG* would be of significant benefit to international tourists. This unique *Lactobacillus GG* strain is acid and bile resistant. Not only does it adhere to human ileal cells but it also produces an antimicrobial substance. It has been shown to colonize the intestinal tract during oral antibiotic administration. Additionally, it may alter the balance of the intestinal flora and has been successfully used in the treatment of antibiotic-associated diarrhea.[4,7,8,9] Other studies have found that oral administration of yogurt with *Lactobacillus GG* decreased colonic bacterial enzymes (beta-glucuronidase and nitrate reductase) which are involved in the formation of free radicals and carcinogens in the colon.[9,10,11] *Lactobacillus GG* has been shown to enhance local immune defenses and has been used in the treatment of relapsing, antibiotic-associated *Clostridium difficile* colitis without significant side effects.[9] In our study, *Lactobacillus GG* was well tolerated, with the exception of two patients who had to discontinue therapy because of abdominal cramping.

In the Finnish study, *Lactobacillus GG* was used to prevent traveler's diarrhea with protection rates of 11.8–39.5%.[3] Our study in American travelers confirmed the Finnish findings. The response to medication for traveler's diarrhea is usually excellent, with resolution

of signs and symptoms after a few doses of quinolone plus loperamide. Many healthy patients are reticent to take any substance as a daily prophylaxis unless the disease being prevented is potentially life threatening. In clinical trials, Pepto Bismol (bismuth subsalicylate) at a dose of 4.2 g per day (of liquid) or 2.1 g/day (as a tablet) resulted in protection rates of 62 and 65% respectively.[12,13] At lower doses (1.05 g/day), protection was 35–40%.[13,14] Travelers may choose to treat symptoms when they arise rather than to take daily medication. However, for travelers on business trips or with a past history of travel-associated diarrhea, *Lactobacillus GG* may provide a safe alternative for prevention.

In conclusion, individuals traveling to the regions described in this study are running a risk of developing diarrhea of approximately 7.4% per day. It appears that *Lactobacillus GG* can reduce this risk to approximately 3.9% per day. Additionally, the data suggest that *Lactobacillus GG* may be more effective in preventing diarrhea in patients with a previous history of traveler's diarrhea.

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