EDITORIAL COMMENTARY

Loperamide for the Treatment of Traveler’s Diarrhea: Broad or Narrow Usefulness?

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(See the article by Riddle et al. on pages 1007–14)

The meta-analysis by Riddle et al. in this issue of Clinical Infectious Diseases [1] focuses on the antidiarrheal drug loperamide hydrochloride and its efficacy when combined with antimicrobials to shorten illness in adults with traveler’s diarrhea. Loperamide is a piperadine derivative that slows intestinal motility because of its activation of μ-opiate receptors. By decreasing peristalsis and increasing anal sphincter tone, it increases intestinal transit time, thus retaining luminal contents and giving more time for reabsorption of secreted fluid. The drug has a less prominent effect through inhibition of intestinal secretion by its action on G1-linked receptors to counter increases in cyclic adenosine monophosphate caused by bacterial enterotoxins. It is available over the counter as a diarrheal remedy and has been recommended for traveler’s diarrhea for >25 years [2]. A newer form of the drug, loperamide oxide, was tested in Germany and was shown to be more effective than placebo against diarrhea [3]. Its advantage, as a prodrug that is changed to loperamide by anaerobic bacteria in the intestine, is to give more-prolonged and higher drug concentrations in the intestinal lumen, with less absorption into the blood, potentially causing fewer systemic adverse effects, such as CNS depression, than when loperamide hydrochloride is administered.

Clinical studies in the meta-analysis enrolled young US students or military personnel in prospective randomized trials in Mexico, Thailand, and Egypt. The most common microbial cause of diarrhea identified in study participants were enteroaggregative Escherichia coli, followed by Shigella species, Campylobacter species, Salmonella species, enteroinvasive E. coli, Giardia lamblia, Entamoeba histolytica, and Cryptosporidium species. Pathogenesis of traveler’s diarrhea occurs at the epithelial cell surface of the intestine, where enterotoxins cause fluid production or invasive pathogens elicit inflammation. Neural signals are transmitted from this surface to smooth muscle to increase peristalsis, giving rise to symptoms of cramps and frequent bowel movements. Traveler’s diarrhea is unique for a high attack rate because of a low level of immunity in travelers against prevalent pathogens in the food and water from the visited countries. Travelers are also a selected population of usually young, healthy adults who develop mild or moderately severe nondehydration illnesses that do not require hospitalization. They do not die as young children and malnourished inhabitants of developing countries sometimes do when infected with the same pathogens, and the travelers usually recover in a few days, even when treated with placebo [4]. Although initially not immune against local pathogens, travelers mount effective immune responses that are instrumental in their recoveries from self-limited illness. Absence of significant dehydration in most cases was demonstrated in a randomized trial of oral rehydration solutions in addition to loperamide, which showed no benefit of oral rehydration solutions to hasten recovery from symptomatic illness [5].

Trials in the analysis pertinently compared treatments of loperamide hydrochloride plus an antimicrobial drug with the same antimicrobial drug alone. Most of the analyzed studies reported that loperamide conferred a substantial benefit by reducing frequency of loose stools by approximately one-half and by shortening the average duration of diarrhea from \(\sim 1.5\) days to <1 day, with a range of mean reductions of duration of 2–23 h. How broadly applicable are these results to all diarrheal illness in travelers and other persons? Two studies in the analysis were partly discordant with regard to beneficial action: patients with Campylobacter infection in Thailand, where these infections showed fluoroquinolone resistance [6], and patients with Shigella infections in...
dents in Mexico, the mean and median loperamide. In 4 separate studies of sti
neity of enrolled patients' responses to active reporting of symptoms, is heteroge
other problem, perhaps related to subjec
tive, according to different perceptions of what constitutes an unformed stool. An additional fluid presented to it during se-
retion sites to reabsorb excess luminal fluid. Reduced peristalsis also diminishes fecal urgency and frequency of bowel move-
ments. It makes mild or moderately severe diarrhea even milder. A healthy distal co-
lon absorbs water and salt avidly and should be the major site of absorption of additional fluid presented to it during se-
cretory diarrhea. Shigella and Campylo-
bacter species cause primarily distal colitis, whereas enterotoxigenic E. coli affects the small intestine; therefore, impaired ab-
sorption in the colon may explain refractoriness of infection due to Shigella and Campylobacter when treated with loper-
amide [11]. Although loperamide should continue to be used by travelers, priority should be placed on selecting an appro-
riate antimicrobial to be combined with it. This selection will burden practitioners of travel medicine to be familiar with preval-
ent microbes in different countries and their antimicrobial susceptibilities.

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References

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