Effect of Adjunctive Loperamide in Combination with Antibiotics on Treatment Outcomes in Traveler’s Diarrhea: A Systematic Review and Meta-Analysis
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Clinical Infectious Diseases 2008;47:1007-14.

Background
A previous Cochrane Collaboration review established an effective advantage of antibiotic therapy, compared with placebo, for treatment of traveler’s diarrhea. The goal of the present study was to conduct a systematic review of the literature to establish the effect on treatment outcomes of using antimotility agents in conjunction with antibiotic therapy.

Methods
The meta-analysis was conducted through searches of electronic databases and pertinent reference lists (including other review articles) and consultation with experts in the field. Clinical trials on therapy of infectious diarrhea in adult populations that met eligibility criteria were studied. Data were extracted and verified by 2 independent investigators and were analyzed for outcomes of clinical cure at 24, 48, and 72 hours and time to last unformed stool. Study quality, heterogeneity, and publication bias were assessed. When appropriate, effect estimates among studies were pooled and sensitivity analyses were performed.

Results
Nine studies consisting of 12 different adjunctive loperamide antibiotic regimens were included for analysis. Among 6 paired studies comparing antibiotics alone versus antibiotics in combination with loperamide, the odds of clinical cure at 24 hours and 48 hours favored combination therapy, with summary odds ratios of 2.6 (95% confidence interval, 1.8-3.6; \( P=0.20 \), by \( x^2 \) heterogeneity statistic) and 2.2 (95% confidence interval, 1.5–3.1; \( P=0.20 \), by \( x^2 \) heterogeneity statistic), respectively, with no evidence of heterogeneity. Factors that possibly affect advantage of combination therapy over solo therapy included increased frequency of pretreatment diarrhea and higher prevalence of noninvasive pathogens.

Conclusion
Antibiotic therapy with adjunctive loperamide offers an advantage over antibiotics alone by decreasing the illness duration and increasing the probability of early clinical cure.

Comments:
This is the first systematic review that emphasizes on the effectiveness of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler’s diarrhea. The meta-analysis was conducted by searching of electronic databases. Only nine studies\(^1-9\) were randomized double-blind, placebo-controlled trials, and were eligible in this meta-analysis.
The populations of patients were the United States student travelling to Mexico in six studies, and the other populations were the United States military in three countries (Egypt, Thailand, and Turkey) in three studies. Clinical cure at 24, 48, and 72 hours and/or time to last unformed stool (TLUS) after initiation of therapy were the primary efficacy outcomes. Combination therapy has a tendency to improve clinical outcomes at 24 and 48 hours, in comparison with treatment with antibiotics alone [odds ratio (OR) 2.58, 95% confidence interval (CI) 1.84-3.62 and OR 2.15, 95% CI 1.50-3.09, respectively]. Moreover, combination therapy was able to reduce the time after treatment to last unformed stool, with a range of mean reductions duration of 2-23 hours. However, one study in Thailand failed to demonstrate any trend toward advantage with loperamide adjunctive therapy. These conflicting results may be due to different causative pathogens of traveler’s diarrhea in Thailand and other countries. The main common organisms of traveler’s diarrhea in Thailand are *Campylobacter* spp. and *Salmonella* spp., which are usually are invasive pathogens that are known to require longer courses of treatment and to better respond to azithromycin than ciprofloxacin. Therefore, anti-motility agent may not have an impact on improving symptoms, and may carry contributable risk of prolongation of the disease. In contrast, traveler’s diarrhea in the Caribbean, Central America is most frequently caused by enterotoxigenic *Escherichia coli* (ETEC). The diarrhea is usually less severe, and hence the addition of anti-motility agents may have increased treatment resolution because of clearance-prolongation effects.

There are several limitations in this study. This study was designed to use patients’ self-report regarding both improvement of diarrheal symptoms and adverse effects after treatment which was based on individual perception of unformed stool. Adjunctive treatment other than anti-motility agents including oral rehydration therapy, avoiding fatty food, and other medications (narcotics, activated charcoal etc.) may have a role in improvement of diarrheal symptoms. There were no data of these confounding factors in all nine studies. Moreover, all nine studies were conducted only in US students and military populations, indicating a common source outbreak of diarrhea among them. Hence, this meta-analysis could not apply to most traveler’s diarrhea in tourists which is usually not an common source outbreak of diarrhea.

In conclusion, traveler’s diarrhea caused by severe and invasive pathogens may not get benefit from an addition of anti-motility agent. In contrast, in traveler’s diarrhea that caused by less severe pathogens, adjunctive loperamide therapy may offer an advantage over antibiotics alone.

References

5. Ericsson CD, DuPont HL, Mathewson JJ, West MS,


