**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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**CRD summary**  
This review found that adding loperamide to antibiotic therapy for the treatment of traveller's diarrhoea reduced illness duration and increased the probability of early clinical cure. The review included small, low-quality trials that were mostly conducted in Mexico. Limitations mean that the reliability and generalisability of the authors' conclusions are uncertain.

**Authors' objectives**  
To assess the effectiveness of loperamide in conjunction with antibiotics compared to antibiotics alone for the treatment of traveller's diarrhoea.

**Searching**  
MEDLINE, EMBASE, ACP Journal Club, Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register were searched for articles published in English between 1966 and 2007. Reference lists of identified studies were reviewed and experts in the field were contacted.

**Study selection**  
Randomised controlled trials (RCTs) that compared an antibiotic plus anti-motility agent to an antibiotic alone for the treatment of traveller's diarrhoea in adults presenting with acute diarrheal disease were eligible for inclusion. In the included studies, the participants were US students travelling in Mexico or US military personnel working in Egypt, Thailand or Turkey. The mean age was 24 years. Patients presented a mean of 36 hours after symptom onset, having had a median of six stools in the previous 24 hours. All studies excluded participants with bloody and/or mucoid stools. Across all studies combined, the causative pathogen was identified in 57 per cent of cases, with Escherichia coli, Shigella and Campylobacter the most common.

In all studies the anti-motility agent was loperamide, given as an initial 4 mg followed by 2 mg after each loose stool. The mean number of additional doses, where reported, was two. A variety of antibiotics with differing regimes were used.

Studies had to assess at least one of the following: clinical cure at 24, 48 and 72 hours; and time to last unformed stool after initiation of therapy. The definition of clinical cure varied between studies, but included the resolution of diarrhoea and associated symptoms.

The initial study selection was performed by two reviewers and confirmed by two unmasked reviewers, including one of the reviewers who performed the initial selection.

**Assessment of study quality**  
Two reviewers independently assessed the quality of the included studies using the Chalmers criteria (the maximum score was not reported). Discrepancies were resolved by discussion.

**Data extraction**  
Two reviewers independently extracted the data onto a previously piloted form. Discrepancies were resolved by discussion.

Odds ratios and mean time to last unformed stool were extracted. Linear regression was used to calculate the standard error of the mean time to last unformed stool for studies where this was not reported, using the standard error from the studies where this was reported.
Methods of synthesis
Studies were combined using Mantel-Haenszel fixed-effect models. Or, if there was statistical heterogeneity present, using DerSimonian and Laird random-effects models. Pooled odds ratios were calculated for dichotomous outcomes. Heterogeneity between studies was assessed using Forest plots and $X^2$ tests.

Non-parametric subgroup analyses and meta-regression were used to explore possible reasons for heterogeneity between studies.

Results of the review
Nine studies (1,435 participants) were included in the review. The mean quality score was 59 per cent (range 33 to 76).

Clinical cure: Loperamide plus antibiotic was associated with an increased probability of cure at 24 hours (odds ratio was 2.58, 95% CI: 1.84 to 3.61; six RCTs). Although there was no statistical evidence of heterogeneity (p=0.20), the Forest plot indicated that the study in Thailand (with a high prevalence of Campylobacter) showed no benefit of adjunct loperamide when all the other studies did. The benefit of adjunct loperamide was also evident at 48 hours (odds ratio was 2.15, 95% CI: 1.50 to 3.09; six RCTs), but was not statistically significant at 72 hours (odds ratio was 1.40, 95% CI: 0.91 to 2.14; five RCTs).

Time to last unformed stool: Loperamide plus antibiotic was associated with a significantly reduced time to last unformed stool in all five studies that reported this outcome. The time to last unformed stool ranged from two to 23 hours less in the intervention group. There was significant (p<0.001) statistical heterogeneity between groups.

There were no significant differences in treatment failures between the loperamide plus antibiotic and antibiotic only groups, and no adverse events associated with loperamide.

Subgroup analyses: showed no effect of age, sex, study quality, regimen, antibiotic type, country of study, traveler characteristics or pre-treatment duration of symptoms.

Authors' conclusions
Adding loperamide to antibiotic therapy for the treatment of traveller's diarrhoea reduced illness duration and increased the probability of early clinical cure.

CRD commentary
The review question was clear and inclusion criteria were clearly defined. The search strategy covered many sources, but as the search terms used were not given in the review the comprehensiveness of the search could not be assessed. As only studies published in English were included, there was a potential for language bias. The authors did not assess publication bias because of the small number of included trials. Appropriate attempts were made to reduce error and bias in the selection of studies, validity assessment and data extraction. The quality of the included trials was generally low, but the authors did not give sufficient data from the included studies for the reader to know what aspect of the trial methodology was poor. It appeared that three included studies did not meet the inclusion criteria, although these were not included in the main meta-analysis. One study included in the meta-analysis did not report all required outcomes. Due to the small range of countries in which the studies were set, it was questionable whether the results were generalisable to all cases of traveller's diarrhoea. The limitations mean that the reliability of the authors' conclusions is uncertain.

Implications of the review for practice and research
Practice: The authors stated that the results should be considered for informing practice guidelines.

Research: The authors stated that further well-controlled studies were required for the use of adjunctive loperamide in the treatment of more invasive forms of traveller's diarrhoea. The effectiveness of recommendations to self-treat mild diarrhoea with loperamide prior to starting antibiotic therapy should be investigated.
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