Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis
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CRD summary
This review evaluated the efficacy and safety of loperamide in the treatment of acute diarrhoea among children younger than 12 years. The authors concluded that children older than 3 years with minimal dehydration may benefit from loperamide administration. These conclusions have to be considered with some caution since they are based on relatively few studies and participants.

Authors' objectives
To assess the efficacy and safety of loperamide for the treatment of acute diarrhoea in children younger than 12 years.

Searching
MEDLINE (1966 to 2006), EMBASE (1988 to 2006) and the Cochrane CENTRAL Register (up to 24 April 2006) were searched; the search terms were reported. The bibliographies of retrieved articles and reviews were searched, while major health organisations dealing with diarrhoea prevention and treatment, experts in the field and the major manufacturer of loperamide (McNeil Consumer Healthcare) were contacted for additional studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies evaluating the use of loperamide compared with placebo were eligible for inclusion. Studies assessing the combination of loperamide with another drug were excluded. The maximum daily dose of loperamide varied from 0.1 to 0.8 mg/kg per day, where reported. Some studies did not report the maximum dose. Most of the included patients were also receiving oral or intravenous fluid rehydration therapy.

Participants included in the review
Studies of children younger than 12 years of age with acute diarrhoea were eligible for inclusion. Both in- and out-patient settings were included. The mean age ranged from 0 to 132 months. Most studies included children with mild dehydration. Some of the included studies did not enrol malnourished or systemically ill children, or children requiring antibiotics.

Outcomes assessed in the review
Studies had to report data on diarrhoea duration or severity to be eligible for inclusion. The primary outcomes were the duration of diarrhoea, the number of stools per day, the stool volume and the incidence of serious adverse events (defined as ileus, lethargy or death). The definition of diarrhoea resolution varied across studies, where reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed on the basis of allocation concealment, generation of allocation sequence, blinding and intention-to-treat analysis. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data, with any disagreements resolved by consensus. Authors were contacted for additional data when necessary. Data were extracted on the numbers of patients with diarrhoea at 24 and 48 hours, the duration of diarrhoea (mean number of days) and the mean stool count at 24 hours. Data on adverse events and serious adverse events, including sleepiness and abdominal distension,
Methods of synthesis

How were the studies combined?
Studies of binary outcomes were combined using a Mantel-Haenszel fixed-effect meta-analysis to give pooled risk ratios (RRs) with 95% confidence intervals (95% CIs). Studies of continuous outcomes were combined using the inverse variance method to give a weighted mean difference (WMD) with 95% CI. Exact Clopper-Pearson binomial methods were used to estimate the 95% CIs for the cumulative risk of an adverse effect.

How were differences between studies investigated?
Statistical heterogeneity was tested using the Mantel-Haenszel or the inverse variance methods. A priori defined subgroup analyses were planned to evaluate the influence of loperamide dose, definition of diarrhoea resolution, location of patient (in- or out-patient), methodological quality and infectious agent (virus or bacteria). Subgroup analysis was performed only if the characteristic of interest was reported in at least 3 studies. The random-effects method of DerSimonian and Laird was used to check the results.

Results of the review
Thirteen RCTs (n=1,788) were included in the review.

Six of the included studies met all four methodological quality criteria.

Compared with placebo, loperamide was associated with a lower risk of diarrhoea at 24 hours (RR 0.66, 95% CI: 0.57, 0.78; based on 4 studies) and at 48 hours (RR 0.59, 95% CI: 0.45, 0.78; based on 4 studies). There was no evidence of statistical heterogeneity for either of these outcomes.

Compared with placebo, loperamide was associated with a shorter duration of diarrhoea (WMD 0.8 days, 95% CI: 0.7, 0.9; based on 6 studies) and a 16% lower stool count in the first 24 hours (mean count ratio 0.84, 95% CI: 0.77, 0.92; based on 4 studies). For the outcomes of diarrhoea duration and stool count there was evidence of statistical heterogeneity.

Data on adverse events were available from 12 studies. Adverse events were observed in 10.1% of children treated with loperamide versus 2.1% of those on placebo (risk difference 8.6%, 95% CI: 6.4, 10.9). Serious adverse events were observed in 0.9% of children treated with loperamide and none of those on placebo (risk difference 0.8%, 95% CI: -0.1, 1.8). Serious adverse events in children receiving loperamide occurred only in children younger than 3 years.

The sensitivity analysis had no impact on the results, nor did the use of the random-effects method. Subgroup analysis could not account for all of the heterogeneity observed.

Authors’ conclusions
Oral rehydration therapy and early refeeding should remain the focus of management of diarrhoea in children younger than 12 years.

CRD commentary
This review addressed a well-defined question in terms of the participants, investigations, outcomes and study design. Several relevant databases were searched and attempts were made to identify unpublished articles, thereby reducing the potential for publication bias which was, however, not formally tested in the review. No language restrictions were applied, which reduces the possibility of language bias. The authors attempted to minimise bias and errors during the review process by carrying out the data extraction in duplicate. Since it is unclear whether the study selection and study quality assessment were also performed in duplicate, reviewer error and bias may have been introduced at these stages.

The authors stated that statistical heterogeneity was assessed, and that no statistical heterogeneity was found for the
main outcome; this supports the authors' decision to pool the results in a meta-analysis. The statistical methods used in the meta-analysis were appropriate. A priori subgroup analyses were conducted to investigate interaction between treatment assignment and specific subgroups. However, the review itself may have been limited given the nature of the available evidence, as the authors acknowledged: for example, inconsistencies in outcome measures and issues with the reporting of serious adverse events. Furthermore, the strength of the authors’ conclusions is weakened by the relatively low number of studies and patients included per outcome evaluated.

**Implications of the review for practice and research**

**Practice:** The authors stated that for children younger than 3 years who are malnourished or severely dehydrated, or who have bloody diarrhoea, adverse events outweigh benefits. In children older than 3 years with no or minimal dehydration, loperamide may be a useful adjunct to oral rehydration and early refeeding. However, the main focus of management should be early refeeding and oral rehydration.

**Research:** The authors stated that future studies should include a clear definition of minimum diarrhoea severity and should present data by age and treatment group.

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