CRD summary
The review evaluated the safety and effectiveness of proton pump inhibitors in the treatment of gastro-oesophageal reflux disease in infants and found limited evidence that omeprazole significantly reduced reflux. The review was generally well conducted. The authors’ conclusion that there was insufficient evidence for the use of proton pump inhibitors for treatment of gastro-oesophageal reflux disease in infants seems reliable.

Authors' objectives
To evaluate the safety and effectiveness of proton pump inhibitors in the treatment of gastro-oesophageal reflux disease (GORD) in infants.

Searching
MEDLINE (1966-2007), EMBASE (1980-2007), Cochrane Central Register of Controlled Trials (Issue 4, 2007), CINAHL (up to October 2007), and proceedings of the European and North American paediatric gastroenterology conferences (2000 to October 2007) were searched for publications in any language. Retrieved articles, key review articles and books were cross-checked. Search terms were reported.

Study selection
Published randomised controlled trials (RCTs) that evaluated proton pump inhibitors with any dosage regime in the treatment of infants (age two years or less) diagnosed with gastro-oesophageal reflux (however defined) were eligible for inclusion if the control group received a placebo or no treatment. The included studies were of preterm infants (34 to 40 weeks postmenstrual age) and infants aged three to 12 months with a reflux index (RI) of more than 5% (reflux index is percentage of time during which the oesophageal acid pH is less than 4) or with oesophagitis measured by biopsy.

Intervention groups for the included studies used either 0.7mg/kg omeprazole in 2mL/kg antacid solution given by a nasogastric tube for seven days or 10mg omeprazole (once or twice daily depending on weight) for two weeks. Control groups used either a placebo or sterile water. The primary eligible outcomes were: symptoms or change in symptoms of gastro-oesophageal reflux (such as regurgitation, crying, irritability, vomiting, gagging) assessed subjectively by the parent/guardian and/or the treating physician; adverse events; occurrence of any clinical complications of gastro-oesophageal reflux (such as respiratory symptoms); and weight gain. Secondary eligible outcomes that related to reflux index reported in the included studies included: number of episodes of pH less than 4; number of episodes of pH less than 4 lasting more than five minutes; and duration of longest episode of pH less than 4. Eligible studies had to report at least one primary outcome.

Two researchers independently screened potentially relevant articles.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using the following criteria: method of randomisation; concealment of allocation; blinding of investigators; use of outcome assessors; and loss to follow up. Disagreements were resolved by discussion between all authors.

Data extraction
Two researchers independently extracted data using a standardised extraction data form. Inconsistencies were resolved by discussion with all authors.

Methods of synthesis
Mean differences or weighted mean differences between treatment groups and controls were extracted and standard
deviations calculated. Relative risk and 95% confidence intervals (CI) were calculated. Meta-analysis was conducted and where appropriate the weights given to each study were based on inverse variance using a fixed-effect model. The $X^2$ test (Q statistic) with a cut-off point of 0.1 was used to assess heterogeneity among pooled estimates.

**Results of the review**

Two relevant double-blind cross-over RCTs were identified (n=40) and considered to be of reasonable quality. Both trials compared omeprazole with placebo. Only one study reported the method of randomisation.

One trial found that there was no significant reduction in cry/fuss time or in irritability using a visual analogue score measured by parent/guardian in infants who took omeprazole compared to controls. There was a significant overall reduction in both cry/fuss time and irritability in both groups of infants from baseline at the end of a two-week period of treatment. The other study found no difference in vomiting or in behavioural changes (which covered irritability/fussing, back arching grimacing and gagging) in preterm infants taking omeprazole compared to controls. Both RCTs reported no adverse events.

A meta-analysis of the two trials found a significant reduction in reflux index (weighted mean difference -4.8%, 95%CI: -7.3 to -2.3) in infants treated with omeprazole.

**Cost information**

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**Authors’ conclusions**

There was insufficient evidence to determine the role of proton pump inhibitors for treatment of gastro-oesophageal reflux disease in infants. Further trials were needed to address the safety and efficacy of proton pump inhibitors in infants.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. It was unfortunate that only two relevant RCTs were identified and that one of them was of preterm infants (which may be more vulnerable than infants born at term). Relevant databases were searched in any language and reference lists were reviewed, but unpublished studies were not considered and publication bias was not assessed. Study quality was assessed using suitable criteria. Study selection was performed, study quality assessed and data extraction carried out independently in duplicate with disagreements resolved by consensus, which reduced the chances of reviewer error and bias. Relevant study details were reported, although details of the sex of the infants were not provided. The statistical analysis method used for the meta-analysis of the RCTs seemed appropriate. The review was generally well-conducted and the author’s conclusions seem reliable.

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

**Practice:** The authors advised that until reliable information on the efficacy and safety of proton pump inhibitors was available, when prescribing the questionable benefit should be weighed against the possible risk of these drugs.

**Research:** The authors identified a need for further RCTs on the use of proton pump inhibitors in the management of gastro-oesophageal reflux disease in infants, particularly to identify the children who were most likely to benefit from treatment while minimising the risk of infections.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.