Erythromycin as a prokinetic agent in preterm neonates: a systematic review

Patole S, Rao S, Doherty D

CRD summary
This review assessed the efficacy and safety of erythromycin as a prokinetic agent in pre-term neonates. The authors concluded that differences between the studies made it difficult to draw any clear conclusions. The authors’ conclusions correctly reflect the many well-described differences between the studies and are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of erythromycin as a prokinetic agent in pre-term neonates.

Searching
The Cochrane CENTRAL Register (Issue 4, 2002), MEDLINE, EMBASE, CINAHL, and proceedings of the Pediatric Academic Societies and the European Society for Pediatric Research were searched in June 2004. Proceedings of the first and second World Congress of Pediatric Gastroenterology, Hepatology and Nutrition, reference lists and personal files were also searched. No language restrictions were applied. The keywords were reported.

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 of any dose (low or antimicrobial), route (oral or intravenous) or mode of administration (prophylactic or rescue) of erythromycin as a prokinetic agent were eligible for inclusion. All of the included studies compared erythromycin with placebo, but the studies used erythromycin in varying doses, including low dose (3 to 12 mg/kg per day) and antimicrobial (12 to 15 mg/kg every 6 to 8 hours), and for varying time period (until full enteral feeds or one week after, or for 7 to 14 days). The studies used different feeding protocols.

Participants included in the review
Studies of pre-term neonates with gestation of 37 weeks or less were eligible for inclusion. The mean gestational age in the included studies ranged from 27.1 to 30 weeks. The studies used different definitions for feed intolerance.

Outcomes assessed in the review
The primary review outcome was the time to reach a full enteral feed of 150 mL/kg per day. The secondary outcomes were erythromycin-related adverse effects, duration of total parenteral nutrition, duration of hospital stay, weight at discharge from hospital, and necrotising enterocolitis of stage 2 or worse.

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
Validity was assessed on the basis of the guidelines of the Cochrane Neonatal Group. The criteria used were blinding of randomisation, allocation concealment, blinding of the outcome assessment, and completeness of follow-up. The authors also assessed whether sample size calculations were performed. The authors did not state who performed the validity assessment.

Data extraction
The data were extracted by two independent reviewers and cross-checked by all three reviewers. Any discrepancies
were resolved through discussion. The authors of the primary studies were contacted for additional information and to clarify the data. Where possible, for each study, the reviewers extracted the median (and range) of values for the outcomes. The reviewers classified the results of each study as showing erythromycin to be 'useful' or 'not useful' according to the authors' conclusion.

**Methods of synthesis**

How were the studies combined?
There were insufficient data to perform a meta-analysis. The studies were combined in a brief narrative.

How were differences between studies investigated?
The studies were grouped by mode of administration (prophylactic or rescue). Differences were described in the text and were apparent from an examination of the data extraction tables.

**Results of the review**

Seven RCTs (n=359) were included.

In terms of study quality, all studies used blinding of randomisation, 5 studies used adequate allocation concealment, 5 studies used blinding of the outcome assessment, 5 studies had complete follow-up and 5 studies had sample size calculations. Prophylactic studies (3 RCTs, n=192).

Two RCTs used antimicrobial doses (n=149); one classified erythromycin as useful, the other as not useful. The third RCT used low-dose erythromycin (n=43); erythromycin was classified as not useful.

Rescue studies (4 RCTs, n=167).

Three RCTs used low-dose erythromycin (n=111); all classified erythromycin as not useful. The fourth RCT used an antimicrobial dose (n=56); erythromycin was classified as useful.

**Authors' conclusions**

Differences between the studies made it difficult to draw any clear conclusions. Conflicting results may be due to differences in dose, route, mode of administration, feeding condition, and gestational and postnatal age.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The search was comprehensive and attempts were made to minimise publication and language bias. The methods used to select studies and assess validity were not described, so it is not known whether any efforts were made to reduce errors and bias. Methods were used to minimise bias in the data extraction process. Validity was assessed using specified established criteria and the results were reported.

Adequate details of each included study were given. Differences between the studies were described in the text, with additional information presented in accompanying tables. The narrative synthesis was appropriate given these many differences. However, the criteria used to classify study outcomes as 'useful' or 'not useful' were not described. The authors' conclusions correctly reflect the differences between the studies and are likely to be reliable.

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

Practice: The authors stated that erythromycin should only be used for a limited duration in a very small subset of high-risk pre-term neonates with persistent or severe feed intolerance.

Research: The authors stated that infants treated with erythromycin should be followed up long term.
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