Gastrointestinal promotility drugs in the critical care setting: a systematic review of the evidence

Booth C M, Heyland D K, Paterson W G

Authors' objectives
To systematically review and critically appraise the studies of promotility agents in the critical care setting.

Searching
MEDLINE and EMBASE were searched from 1980 to 2001 using the following key terms: 'randomized controlled trial' and 'intensive care', 'intensive care units' or 'critical care' combined with 'gastrointestinal motility', 'gastrointestinal intubation', 'cisapride', 'erythromycin', 'metoclopramide', 'domperidone' or 'octreotide'. The authors' own files were searched and the primary authors were contacted for additional citations. The reference lists in all review articles and primary studies were also checked. Published abstracts of the American Gastrointestinal Association and the Society of Critical Care Medicine were manually searched from 1995 to 2000.

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

Specific interventions included in the review
Treatments with gastrointestinal motility agents were eligible. The following interventions were compared with placebo or each other: metoclopramide (10 to 20 mg intravenously) and erythromycin (200 to 500 mg intravenously), both alone and in combination; and cisapride (10 to 20 mg by nasogastric tube and 30 to 60 mg rectally).

Participants included in the review
Adult patients (older than 18 years) in intensive care units were eligible. The participants included surgical, medical, trauma and mixed intensive care unit patients.

Outcomes assessed in the review
Studies that reported measures of gastrointestinal motility were eligible. The actual outcomes were: success of feeding tube placement (duodenal and small bowel placement); gastrointestinal transit and feeding tolerance; gastric microbial overgrowth; and clinical outcomes (pneumonia and mortality). The gastrointestinal transit and feeding tolerance outcomes included tolerance to feeds, acetaminophen absorption, gastric emptying (as measured by bedside scintigraphy), gastric residuals, and antral contractions (as measured by manometry).

How were decisions on the relevance of primary studies made?
Two reviewers independently reviewed all the identified primary studies according to the inclusion criteria. There was 100% agreement on study selection.

Assessment of study quality
Validity was assessed and scored using the following criteria: concealed randomisation; blinding; intention to treat analysis; consecutive patient enrolment; baseline comparability of the treatment groups; extent of follow-up; description of protocol; equal use of cointerventions; and assessment of clinically important outcomes. At least two reviewers assessed validity and compared the results. There was 100% agreement on the validity scores.

Data extraction
Two authors independently extracted the data and any disagreements were resolved by consensus. The primary authors were contacted where the data were unclear or missing. The information tabulated in the review included details of the...
author, population, sample size, intervention and outcome.

Methods of synthesis
How were the studies combined?
The studies were grouped according to outcome (tube placement, feeding tolerance and clinical outcomes) and a narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the studies (including methodological quality) were discussed in the text of the review.

Results of the review
Eighteen RCTs (908 patients) were included.

The quality scores ranged from 5 to 12 out of a maximum possible score of 14 points. The methodological flaws included: a lack of intention to treat analysis; studies that were not double-blind; consecutive patients were not enrolled; a lack of baseline measurement of illness; the use of other drugs that may affect gastric motility was unequal or not reported; and only one study assessed clinical outcomes.

Tube placement (6 RCTs, 351 patients).
Metoclopramide versus placebo (3 RCTs, 175 patients): the results differed across the studies. Two of the 3 RCTs (quality scores 5 and 7) found no significant difference between the treatments in the success rate of duodenal feeding tube placement. The third RCT (10 patients, quality score 5) found that metoclopramide significantly increased the success rate compared with placebo: 4 out of 5 versus 0 out of 5 (P=0.048). Erythromycin versus placebo (2 RCTs, 93 patients): both RCTs (quality scores 8 and 9) found that erythromycin significantly increased the success rates of small bowel intubation in comparison with placebo. The success rates were 61 and 96% with erythromycin and 35 and 77% with placebo (p<0.05).
Metoclopramide versus erythromycin versus placebo (1 RCT, 83 patients, quality score 10): there was no significant difference between the treatments in terms of the tube placement success rates.

Gastrointestinal transit and feeding tolerance (11 RCTs, 252 patients).
Cisapride versus placebo (4 RCTs, 147 patients): the results differed across the studies. Two of the 4 RCTs (27 patients in each study) found no significant difference in tolerance to feeds and acetaminophen absorption, respectively. Two RCTs (21 and 72 patients) found that cisapride, compared with placebo, significantly increased gastric emptying and lower gastric residuals (p<0.01 to p<0.02). Erythromycin versus placebo (3 RCTs, 55 patients): the studies reported different outcomes. One RCT (10 patients) found that erythromycin significantly increased acetaminophen absorption and antral contractions (P<0.01), while another (20 patients) found it significantly increased successful feeds and gastric emptying (P=0.05 and P=0.03). A further RCT (25 patients) found no significant difference between the treatments in terms of gastric and pulmonary colonisation. Metoclopramide (4 RCTs, 50 patients): the studies used different comparators and reported different outcomes.

Clinical outcomes. Metoclopramide versus placebo (1 RCT, 305 patients): there was no significant difference between the treatments in the rates of pneumonia or mortality.

Authors' conclusions
As a class of drugs, promotility agents appear to have a beneficial effect on gastrointestinal motility in critically ill patients. A single dose of erythromycin may facilitate small-bowel feeding tube insertion. Administration of metoclopramide appears to increase physiologic indexes of gastrointestinal transit and feeding tolerance. Concerns about the safety and lack of effect on clinically important outcomes preclude strong treatment recommendations.
CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the study design, intervention and participants. The search was adequate and the methods used to select the studies were described. Validity was formally assessed and scored, the results were reported, and the methodological limitations of the primary studies were discussed in the text of the review. Relevant data were extracted, and details of the methods used to extract the data were provided. Information on the primary studies was clearly presented in tabular format. A narrative synthesis was appropriate given the small number of studies comparing similar interventions.

Conclusions drawn, based on the findings of this review, were hampered by the different results reported by a small number of studies, most of which had very few patients. As the authors correctly state, the evidence is predominantly based on physiological rather than clinical outcomes. The clinical importance of the results are unclear. Hence, any conclusions are tentative rather than definitive.

Implications of the review for practice and research
Practice: The authors state that with cisapride no longer available and the concerns regarding the use of erythromycin, they recommend metoclopramide. They also state that a single dose of erythromycin may facilitate small-bowel feeding tube insertion. The authors report that cisapride was withdrawn from the market due to its association with lethal cardiac dysrhythmias (see Other Publications of Related Interest).

Research: The authors state that future studies need to evaluate metoclopramide and erythromycin in a rigorous manner and measure the clinical outcomes.

Bibliographic details

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Other publications of related interest

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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.