Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies

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Authors' objectives
To assess the efficacy and safety of metoclopramide for the prevention of post-operative nausea and vomiting (PONV).

Searching
MEDLINE was searched from 1966, the Cochrane Library (Issue 1) from 1998, and EMBASE from 1982 for publications in any language, using different search strategies with the free text keywords: 'metoclopramide', 'paspertin' or 'primperan'; 'nausea', 'vomiting' or 'emesis'; 'random'; 'surgery', 'anaesthesia' or 'postoperative'. The date of the last electronic search was June 30, 1998. Additional studies were identified from reference lists of retrieved reports and review articles on PONV and metoclopramide, and by manually searching locally available anaesthesia journals. Four manufacturers of metoclopramide (Heumann Pharma GmBH, ASTA Medica AG, Synthelabo-Pharma, and Sovay Pharma) were contacted for further published and unpublished data. Abstracts, letters, review articles and animal studies were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Reports without a placebo or 'no treatment' arm were excluded.

Specific interventions included in the review
Study designs that compared prophylactic metoclopramide with placebo or 'no treatment' were eligible. The use of metoclopramide as a treatment of established PONV was excluded. Eighteen different metoclopramide regimes were tested: oral, intravenous (iv), intramuscular (im), and intranasal routes; fixed doses (5, 10, 15, 20 and 30 mg in adults) and variable doses (0.25 or 0.5 mg/kg given in adults, and 0.10, 0.12, 0.15, 0.20, 0.25 and 0.05 mg/kg in children); and single and double administrations in 24 hours.

Participants included in the review
Patients who were undergoing general anaesthesia, or combined spinal and general anaesthesia, were eligible. Both children and adults were included. Half (39/66) of the studies were conducted in women only.

Outcomes assessed in the review
Measures of anti-emetic efficacy were eligible. Points of interest had to be reported in dichotomous form for both metoclopramide and control. Anti-emetic efficacy was assessed using cumulated incidences of three different PONV events at both early (0 to 6 hours) and late (0 to 48 hours) times: nausea; vomiting, including retching; and any emetic event (nausea, vomiting, or nausea and vomiting). Events during recovery or 'post-operatively' were considered as early data. Adverse events were also assessed.

How were decisions on the relevance of primary studies made?
All authors independently read each report that could possibly meet the inclusion criteria, scored studies for inclusion and then met to reach consensus by discussion.

Assessment of study quality
Validity was assessed and scored using the three item, 5-point scale described by Jadad et al. (see Other Publications of Related Interest, no.1). All authors independently scored the identified studies and then met to reach consensus by discussion.
**Data extraction**
The following data were extracted: patients; surgery; dose and route of administration of metoclopramide; study end points; and adverse effects. The authors do not state how data were extracted for the review, or how many of the reviewers performed the data extraction.

**Methods of synthesis**

**How were the studies combined?**
Data from studies that represented clinically homogeneous subgroups (same PONV event), same observation period, same dose, same route of administration, and only in adults or only in children, were combined using a fixed-effect model to calculate relative risk (RR) and 95% confidence intervals (CIs). Clinical relevance was assessed by calculating the number-needed-to-treat (NNT) using the weighted means of the experimental and control event rates. A pre hoc decision was made that a NNT of 5 or less to prevent PONV, compared with placebo, would represent clinically-relevant efficacy. Strong evidence of dose responsiveness between two doses of metoclopramide, did not overlap. The additional risks of drug-related adverse effects were estimated by calculating RR and numbers-needed-to-harm with 95% CI.

**How were differences between studies investigated?**
The consistency of event rates with metoclopramide against those with control and homogeneity was explored graphically, by plotting the incidence of PONV with metoclopramide against event rates with control (see Other Publications of Related Interest no.2). Relative benefit and NNT were calculated for the best-documented regimes within two predefined ranges of control event rate, i.e. early outcomes within 20 to 60% of control event rates and late outcomes within 40 to 80% of control event rates. Data outside these ranges were excluded from the sensitivity analyses.

**Results of the review**
Sixty-six RCTs were included (9,656 patients randomised; data analysed from 9,242 patients).

Median number of patients per study was 104 (range: 38 - 1,044). Median validity score was 3 (range: 1 - 5).

Average incidence of early nausea with metoclopramide and placebo was 13 and 18%, respectively; early vomiting rates, 21 and 31% respectively; late nausea rates, 30 and 38% respectively; and late vomiting rates 34 and 44% respectively.

Adults (47 studies were adults only).

Early events (within 6 hours).

The best-documented dose was 10 mg iv. At this dose, there was no statistically-significant difference in nausea between metoclopramide and placebo.

Metoclopramide, 10 mg iv.

Nausea (10 RCTs): RR, 1.07 (95% CI: 0.99, 1.17); NNT, 16 (95% CI: 7.5, -210). Vomiting (9 RCTs): RR, 1.16 (95% CI: 1.05, 1.28); NNT, 9.1 (95% CI: 5.5, 27).

Other doses studied in more than 2 studies.

Metoclopramide, 20 mg iv (3 RCTs): no significant difference between treatment groups. Nausea and/or vomiting: RR, 1.08 (95% CI: 0.99, 1.18); NNT, 16 (95% CI: 7.4, -115).

Metoclopramide, 10 mg im (3 RCTs): metoclopramide was significantly better than placebo. Nausea and/or vomiting: RR, 1.21 (95% CI: 1.07, 1.36); NNT, 7 (95% CI: 4.4, 18).

Late events (within 48 hours).
The best-documented dose was 10 mg iv. At this dose, there was no statistically-significant difference in nausea between metoclopramide and placebo.

Metoclopramide, 10 mg iv.

Nausea (5 RCTs): RR, 1.19 (95% CI: 1.00, 1.42); NNT, 12 (95% CI: 6, -1587). Vomiting (8 RCTs): RR, 1.24 (95% CI: 1.10, 1.40); NNT, 10 (95% CI: 6, 41).

Other doses studied in more than 2 studies.

Metoclopramide, 10 mg orally (4 RCTs): no significant difference between treatment groups except for nausea and/or vomiting. Nausea and/or vomiting: RR, 1.24 (95% CI: 1.05, 1.47); NNT, 8.5 (95% CI: 4.7, 44).

Metoclopramide, 20 mg iv (4 RCTs): metoclopramide was not significantly better than placebo for nausea and/or vomiting; RR, 1.11 (95% CI: 0.99, 1.26); NNT, 14 (95% CI: 6.3, -77). There was no significant difference for nausea or vomiting when the outcomes were considered separately.

Most regimes were tested in one study only. There was no evidence of dose-responsiveness with any route of administration for early or late outcomes in children or adults.

Children (18 studies were children only).

Most studies analysed prevention of vomiting only.

Early events (within 6 hours).

The best-documented dose was 0.25 mg/kg iv (7 RCTs): metoclopramide was significantly better than placebo in preventing vomiting; RR, 1.44 (95% CI: 1.11, 1.87); NNT, 5.8 (95% CI: 3.9, 11).

Other doses studied in more than 2 studies.

Metoclopramide, 0.15 mg/kg (3 RCTs): metoclopramide was significantly better than placebo in preventing vomiting; RR, 1.71 (95% CI: 1.33, 2.19); NNT, 4 (95% CI: 2.7, 7.6).

Late events (within 48 hours).

Only a minority of studies reported late events.

The best-documented dose was 0.15 mg/kg iv (2 RCTs): metoclopramide was significantly better than placebo in preventing vomiting; RR, 2.28 (95% CI: 1.37, 3.78); NNT, 4.2 (95% CI: 2.7, 9.5).

Sensitivity analysis.

After exclusion of studies reporting early incidence of nausea or vomiting with placebo of less than 20% or greater than 60%, the antinausea effect for metoclopramide was no different from placebo in adults; NNT was 13 for nausea and 11 for vomiting.

In children, 0.25 mg/kg iv metoclopramide was significantly better than placebo; NNT was 7.9 for vomiting (95% CI: 4.6, 28).

Adverse events.

There were no significant differences between metoclopramide and placebo for any of the adverse reactions (extrapyramidal symptoms, sedation and drowsiness, dizziness and vertigo, and headaches). No dose-responsiveness was established.
Authors' conclusions
Metoclopramide has no clinically-relevant anti-emetic effect, and does not show an increased risk of adverse reactions in doses currently used in anaesthesia. It is very likely that the doses used in daily clinical practice are too low. The continued use of metoclopramide in the doses tested in these studies is inadequate. Randomised dose-finding studies, which evaluate higher doses of metoclopramide, are clearly needed to establish the optimal dose of metoclopramide for the prevention of PONV.

CRD commentary
The aims were stated, and inclusion criteria were defined in terms of study design, participants, intervention, and outcome. Several relevant sources were searched, no language restrictions were applied, attempts were made to locate unpublished material, and methods used to select studies were described. Validity was assessed and scored using defined criteria, the methods for which were described. Some relevant details of the primary studies were presented in tabular format. Data were not analysed on an intention to treat basis. Statistical heterogeneity was reported as being assessed graphically, but no mention was made of the results of this assessment and so it was not possible to confirm that meta-analysis was appropriate. No comment was made on the influence of study validity on the results.

The strength of evidence presented would be increased by providing results of an assessment of the statistical homogeneity of pooled studies, and by taking into account the validity of studies when considering results. There was some suggestion that metoclopramide may be of more benefit than placebo in children, and of more benefit than placebo in preventing vomiting (but not nausea) in adults, but this was not addressed in the conclusion.

Implications of the review for practice and research
Practice: The authors state that it is very likely that the doses used in daily clinical practice are too low, and that the continued use of metoclopramide in the doses tested in these studies is inadequate.

Research: The authors state that randomised dose-finding studies, which evaluate higher doses of metoclopramide, are clearly needed to establish the optimal dose of metoclopramide for the prevention of PONV.

Funding
Swiss National Research Foundation, grant number 3233-051939.97.

Bibliographic details

PubMedID
10690140

Original Paper URL
http://bja.oxfordjournals.org/cgi/reprint/83/5/761

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
AccessionNumber
1200000068

Date bibliographic record published
31/10/2001

Date abstract record published
31/10/2001

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