Comparative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting: a meta-analysis

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Authors' objectives
To determine the relative efficacy and safety of the following drugs used prophylactically for the prevention of post-operative nausea and vomiting: ondansetron; droperidol; and metoclopramide.

Searching
A search was conducted of MEDLINE from January 1966 to May 1998 using the following terms: 'prevention', 'postoperative complications', 'nausea and vomiting', separately for 'ondansetron', 'droperidol' and 'metoclopramide'. A manual search was conducted of the table of contents in English anaesthesiology journals and reference list from all articles, review articles, correspondence, and abstracts relating to PONV. Only studies published in the English language were included. Abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) that compared at least two drugs from ondansetron, droperidol, and metoclopramide were included if validity score exceeded a specified level (see below). Reasons were given for exclusion of identified studies.

Specific interventions included in the review
Antiemetic therapy had to be given prophylactically and not just in the treatment of severe post-operative nausea and vomiting (PONV) and studies had to compare at least two drugs. The following pairs of antiemetic drugs were compared: ondansetron and metoclopramide; ondansetron and droperidol; and droperidol and metoclopramide. Ondansetron was given both orally and intravenously. Different doses of the drugs within the therapeutic range were given and administration was at variable times including pre-operative, after induction of general anaesthesia, or immediately before emergence.

Participants included in the review
Female, male and paediatric patients undergoing general anaesthesia for the following types of surgery were included: gynaecological; head and neck; orthopaedic; abdominal surgery; and others. The following types of general anaesthesia were used: narcotics; propofol; nitrous oxide; and volatile anaesthetics.

Outcomes assessed in the review
Studies had to assess vomiting, nausea or the use of rescue antiemetic therapy. The primary outcome assessed was vomiting. Other outcomes included nausea, the use of rescue medications for severe PONV and adverse reactions (sedation, anxiety, restlessness, abnormal muscle movements and headache). In most studies, outcomes were determined for 24 hours after surgery.

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

Assessment of study quality
Validity was assessed using the following criteria adapted from Chalmers et al. (See Other Publications of Related Interest no.1): design and conduct of trial (inclusions and exclusion criteria, experimental and control regimes, outcome measurements, randomisation and assessment procedures, and sample size estimation given possible total of 50 points), the data analysis (withdrawals, statistical analysis, and presentation of data and statistical significance given possible total of 30 points), and the presentation (all sections of the manuscript given possible total of 20 points). Two authors
blindly evaluated the design, conduct and analysis of the studies according to validity criteria and scored each trial out of a possible 100 points. Studies with scores < 65 were excluded.

**Data extraction**
The authors do not state how or what data was extracted. From the data extraction tables it appears that the following data was extracted: author; type of patients and type of surgery; dose of antiemetic agent; end points reported; and odds ratios and 95% confidence intervals of outcomes. In some studies counts were calculated from percentages in tables.

**Methods of synthesis**

How were the studies combined?
Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for PONV and adverse reactions for different drug combinations using a random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Wolf’s test for homogeneity. OR and 95% CI from individual studies were plotted and presented graphically. Analysis of the following subgroups was undertaken: women; adults children; with propofol; without propofol; ear, nose and throat; and eye surgery. A meta-analysis of adverse effects was repeated after excluding studies using 2.5 mg of droperidol.

**Results of the review**

Ondansetron vs metoclopramide: 19 RCTs (2502 patients).

Ondansetron vs droperidol: 23 RCTs (3863 patients).

Droperidol vs metoclopramide: 22 RCTs (1584 patients).

Heterogeneity was statistically significant for all drug comparison (P < 0.05). OR are reported for ratio of odds for first drug to the odds of the second drug.

Ondansetron vs metoclopramide: There was a non-significant trend for ondansetron to be better than metoclopramide in reducing post-operative nausea. OR for nausea (10 RCTs, 1697 patients) = 0.70 (95% CI: 0.45, 1.10; P = 0.125).

Ondansetron was significantly better than metoclopramide in reducing post operative vomiting. All studies but two, showed greater efficacy of ondansetron over metoclopramide. OR for vomiting (17 RCTs, 2272 patients) = 0.43 (95% CI: 0.31, 0.61; P < 0.001).

Ondansetron vs droperidol: these were equally effective in preventing postoperative nausea. Overall OR for nausea (13 RCTs, 2743 patients) = 0.99 (95% CI: 0.66, 1.47; P > 0.9). Ondansetron was significantly more effective than droperidol in preventing postoperative vomiting. Overall OR vomiting (22 RCTs, 3750 patients) = 0.70 (95% CI: 0.52, 0.94; P= 0.018).

There was substantial variability among studies in the relative efficacy of droperidol and ondansetron.

Subgroup analysis showed that ondansetron was significantly better than droperidol in preventing vomiting in children (6 RCTs): OR = 0.49 (95% CI: 0.30, 0.80; P < 0.01), but not in adults (11 RCTs): OR = 0.87 (95% CI: 0.61, 1.25).

There was no difference in the propofol induction group.

Droperidol vs metoclopramide: Droperidol was significantly better than metoclopramide in preventing both postoperative nausea and post operative vomiting. OR nausea (15 RCTs, 1021 patients) = 0.66 (95% CI: 0.48, 0.90; P = 0.008). OR vomiting (20 RCTs, 1374 patients) = 0.68 (95% CI: 0.54, 0.85; P < 0.001). Subgroup analysis showed that droperidol was significantly better than metoclopramide in preventing vomiting in women and all adults but there was no difference in children. Children (7 RCTs): OR = 0.63 (95% CI: 0.36, 1.10). Adults (13 RCTs): OR = 0.70 (95% CI: 0.57, 0.86; P < 0.001). Women (13 RCTs): OR = 0.70 (95% CI: 0.57, 0.86; P < 0.001).
Adverse effects: Ondansetron vs metoclopramide (4 RCTs, 1285 patients). Ondansetron vs droperidol (7 RCTs, 2403 patients).

Droperidol vs metoclopramide (13 RCTs, 936 patients). None of the drugs differed significantly for any adverse effects.

Authors' conclusions
Ondansetron and droperidol were more effective than metoclopramide in reducing postoperative vomiting. The overall risk of adverse effects did not differ among drugs studied.

CRD commentary
This was a reasonable review. The aims and inclusion criteria were stated. Attempts were made to exclude duplicate data. Validity was assessed, methods used to score validity described and only articles scoring above a specified value were included. Statistical heterogeneity was assessed and results from individual studies presented graphically. In view of the significant heterogeneity, a random-effects model was used, but studies should not be pooled if heterogeneity is significant. Instead some investigation of the heterogeneity should have been undertaken either by meta-regression or presenting a narrative summary of the results. Sensitivity analysis was undertaken by repeating the meta-analysis using subgroups. Adverse effects were compared and investigation of the influence of droperidol dose on the results undertaken. The discussion includes consideration of the following factors which may have limited the results from the review: individual trials were small and lacked adequate power; potential publication bias; exclusion of articles written in languages other than English; and pooling across heterogeneous studies with the combination of data with different dosages and routes of administration, patients of different ages and genders, different surgical procedures, different general anaesthetics, and different protocols of prophylactic drug administration.

By limiting the literature search to one database, other relevant studies may have been omitted. Methods used to select primary studies and extract data were not described.

As the authors state, in view of the differences among studies, caution is advised in the interpretation of these results with respect to care of individual patients.

Implications of the review for practice and research
Practice: The authors consider that the usual clinical doses of either ondansetron or droperidol rather than metoclopramide be administered for greater antiemetic efficacy. However, they recommend caution in applying these results to the clinical care of an individual patient.

Research: The authors consider that formal cost-effectiveness analysis is necessary before developing guidelines for drug use.

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