A systematic review of the antiemetic efficacy of prophylactic ondansetron compared with droperidol and with metoclopramide in children

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Authors' objectives
To compare prophylactic ondansetron with metoclopramide and with droperidol in the prevention of post-operative vomiting (POV) in children.

Searching
Details of the search strategy were presented in a companion paper (see Other Publications of Related Interest no.1). Searches were conducted of MEDLINE from 1966, EMBASE from 1987, and Globe (a non-commercial database) from 1987, using the following index terms: 'ondansetron', 'metoclopramide', 'droperidol' and 'post-operative'. Studies published in any language were considered. Additional material was located by examining references from identified articles, review articles of the drugs studied, and conference abstracts. The search was not extended to unpublished trials.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Comparisons of ondansetron (alone) with metoclopramide (alone) or droperidol (alone) were eligible. Most studies compared ondansetron (0.1 or 0.15 mg/kg) with droperidol (0.075 mg) or metoclopramide (0.25 mg/kg). All but one study administered the drugs as a single intravenous dose.

Participants included in the review
Post-operative children were eligible. The participating male and female children were aged from 4 months to 24 years, with the majority aged between 2 and 14 years. Most of the participants had undergone strabismus surgery. Other types of surgery were major orthopaedic, ear-nose and throat, orchidopexy, hernia and dental restoration.

Outcomes assessed in the review
Studies assessing POV or post-operative nausea and/or vomiting (PONV) were eligible. The outcomes assessed were: POV over a 24-hour period using the time period closest to 24 hours; and PONV, defined to include all studies that did not contribute to the 24-hour POV outcome.

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
Details of the validity criteria were presented in a companion paper (see Other Publications of Related Interest no.1). Validity was assessed using the following criteria: whether there was adequate concealment; whether there was adequate sequence generation; whether any exclusions had taken place, either reported or implied; whether the study was double-blind; and the source of the data, i.e. full-length peer-reviewed journal publication or conference abstract. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Details of the methods used were presented in a companion paper (see Other Publications of Related Interest no.1).
Two authors independently extracted the following data from each study, and any disagreements were resolved through discussion between three authors. Data were extracted for: year of publication; country in which the study was conducted; age of participants; the number of operations performed; time of measurement of POV or PONV; analgesics or anaesthetics used; drug dosage and formulation; the number of participants treated; and the number of participants experiencing POV or PONV. The relative risks (RRs) of outcome were calculated for each study.

Methods of synthesis
How were the studies combined?
A pooled RR for ondansetron versus metoclopramide, and for ondansetron versus droperidol, was estimated using fixed-effect and random-effects models. Potential sources of heterogeneity of rates of PONV were explored. Where sufficient data were available, an intention to treat analysis was conducted to calculate the risk of emesis for each study. Publication bias was assessed using funnel plots and Rosenthal's fail-safe N (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Statistical heterogeneity was assessed. Subgroup analyses were conducted to explore the influence of the following factors on the results: outcome type (POV versus PONV); duration of observation (0 to 6 hours versus 0 to 24 hours); ondansetron dose (0.1 versus 0.15 mg/kg); operation type (strabismus versus other); and validity criteria.

Results of the review
Nineteen RCTs (1,548 children) were included.

Most studies were underpowered. Four studies had adequate concealment of randomisation, 7 studies used adequate sequence generation, and 15 studies reported or gave the impression that no exclusions had taken place.

Ondansetron was associated with a significantly lower risk of POV than droperidol or metoclopramide.

There was no evidence of statistical heterogeneity for ondansetron, compared with either metoclopramide (p=0.25) or droperidol (p=0.14 for POV and p=0.10 for PONV).

The drug dose, study quality and type of outcome (POV or PONV) were not associated with effect. It was unlikely that the results were influenced by publication bias.

Ondansetron versus droperidol (8 RCTs with 563 children): the pooled RR of POV using a random-effects model was 0.67 (95% confidence interval, CI: 0.49, 0.90, p=0.0092). The pooled RR of PONV was 0.70 (95% CI: 0.53, 0.92, p=0.010). The fail-safe N was 17. The number-needed-to-treat with ondansetron was estimated as 11, assuming the risk of emesis with droperidol was 30%.

Ondansetron versus metoclopramide (13 RCTs with 985 children): the pooled RR of POV using a random-effects model was 0.56 (95% CI: 0.44, 0.71, p<0.001). The fail-safe N was 19. The number-needed-to-treat with ondansetron was estimated as 8, assuming the risk of emesis with metoclopramide was 20%.

Authors' conclusions
Prophylactic ondansetron is effective and superior to both droperidol and metoclopramide in the prevention of emesis in children. The relative cost-effectiveness of the drugs in routine practice needs to be explored.

CRD commentary
The aims were stated and inclusion criteria were defined in terms of study design, participants, intervention and outcome. Details of the methods used to conduct the review were not included in the article, although this information was provided in a referenced, companion publication. Searches were conducted of several relevant sources and no language restrictions were applied. The exclusion of unpublished studies raised the possibility of publication bias, though no indication of this was provided by funnel plots and the fail-safe N. Validity was assessed using defined
criteria, but the methods used to assess validity and select the studies were not described. Details were given of methods used to extract data and relevant information on the primary studies was presented in tabular format, including results of the validity assessment. Statistical heterogeneity was assessed and subgroup analyses were conducted to examine the influence of various factors on results.

The evidence presented supports the authors' conclusions. Financial support came from a pharmaceutical company.

**Implications of the review for practice and research**
Practice: The authors state that prophylactic ondansetron is effective and superior to both droperidol and metoclopramide in the prevention of emesis in children.

Research: The authors state that the relative cost-effectiveness of drugs in routine clinical practice needs to be explored.

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**Other publications of related interest**

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