Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review

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Authors' objectives
To determine the relative efficacy and harm of interventions that are used prophylactically to reduce the incidence of opioid patient controlled analgesia (PCA) related nausea and vomiting.

Searching
Searches were conducted of MEDLINE (1966 to April 1998), EMBASE (1980 to April 1998) and the Cochrane Library (Issue 1, 1998) using the free text keywords 'nausea', 'vomiting', 'emesis', 'patient controlled analgesia' and their combination. Only full publications in peer-reviewed journals were considered. Reference lists of retrieved reports, relevant review articles and meta-analysis were checked. Locally available anaesthesia journals were handsearched. No language restrictions were applied. Authors were contacted by letter when there was uncertainty about data and additional information on unpublished data was requested.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that investigated the prophylactic efficacy of antiemetic interventions compared with placebo or no treatment were included. Only studies in which data on efficacy could be extracted in dichotomous form were included. Abstracts, letters and review articles were excluded.

Specific interventions included in the review
The following prophylactic antiemetic interventions given concomitantly with the PCA containing an opioid were included: droperidol; hyoscine TTS; ondansetron; tropisetron; propofol; metoclopramide; clonidine; and promethazine. Interventions to treat established post-operative nausea and vomiting were not analysed. In most trials the observation period exceeded 24 hours (range 18 hours to 3 days).

Participants included in the review
Adult patients who were receiving opioid patient-controlled analgesia (PCA) to treat acute post-operative pain after either general or spinal anaesthesia were included. Settings included orthopaedic and major abdominal surgery including gynaecological surgery. Opioids included morphine (in all but one trial) and tramadol. Morphine boluses were 1-2 mg with lockouts ranging from 3 to 12 minutes. In trials with reporting of morphine dose the average dose in the period of observation ranged approximately from 40 to 90 mg.

Outcomes assessed in the review
The main outcome was prevention of emetic events classified as nausea, vomiting (including retching), and any emetic event (nausea, vomiting or nausea and vomiting). Drug related adverse event rates were also assessed with adverse events that did not lead to study withdrawal being classified as minor harm and adverse events leading to study withdrawal being classified as major harm. Other end-points such as patient satisfaction, cost, or length of hospital stay were inconsistently reported and therefore were not analysed.

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 and scored using the Jadad criteria which consider the adequacy of randomisation and blinding and the description of withdrawals (see Other Publications of Related Interest no.1). Scores possible ranged from a minimum of 1 to a maximum of 5. Both authors read each report independently and scored validity using the Jadad
criteria. Allocated scores were compared and differences resolved by discussion.

Data extraction
The following data were extracted: patients; surgical setting; dose and regime of antiemetics; PCA programme; opioid doses; study end points; and drug-related adverse events.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RR) and 95% confidence interval (CI) and pooled number-needed-to-treat (NNT) and 95% CI were calculated for each drug. A fixed-effect model was used to combine data when data from no more than two trials was combined or when there was no significant heterogeneity (P > 0.1). Otherwise the DerSimonian and Laird random-effects model was used.

How were differences between studies investigated?
Evidence of dose-responsiveness was tested to evaluate the propriety of pooling data on droperidol using the NNT as the effect size. The following doses of droperidol dose were plotted against NNT: dose per any observation period; dose per 24 hours; dose per mg morphine; and dose per PCA-bolus.

Pooled RR and NNT were calculated for the outcome nausea with and without one trial reporting low rates of nausea in control patients.

Results of the review
Fourteen RCTs were included (1,117 patients).

Without antiemetic drug (opioid PCA plus placebo/no treatment) the incidence of nausea was on average 43% (range 22% to 80%), of vomiting was 55% (range 45% to 71%), and of any emetic event was 67% (range 54% to 87%). Hyoscine TTS, ondansetron, tropisetron, propofol; metoclopramide, and promethazine were documented in one or two trials with only limited numbers of patients.

The most documented antiemetic was droperidol (6 placebo-controlled RCTs): Jadad scores ranged from 1 to 4. A wide range of different droperidol regimes was used with doses ranging from approximately 1 mg to 10 mg. There was no graphical evidence of any-dose responsiveness (graphs presented). Thus efficacy data were combined.

Nausea (3 trials, 202 patients): RR = 1.33 (95% CI: 0.88, 2.00); NNT = 5.1 (95% CI: 3.1, 15). After exclusion of one trial with an outlier for (2 trials, 118 patients): RR = 1.59 (95% CI: 1.14, 2.22); NNT = 2.7 (95% CI: 1.8, 5.2).

Vomiting (5 RCTs with 313 patients): RR = 1.72 (95% CI: 1.38, 2.15; heterogeneity P = 0.89); NNT = 3.1 (95% CI: 2.3, 4.8). Nausea and/or vomiting (3 trials, 301 patients): RR = 2.13 (95% CI: 1.63, 2.78; heterogeneity P = 0.23); NNT = 2.8 (95% CI: 2.1, 3.9).

Minor adverse reactions to droperidol (4 placebo controlled RCTs plus 6 RCTs without a placebo or no-treatment group): a plot of the absolute risk of minor adverse event against droperidol dose and against placebo and showed that the absolute risk increased with increasing dose of droperidol above 4 mg (graph presented). No obvious differences were noted between rates with droperidol in doses of 4 mg or less compared with placebo.

Major adverse reactions to droperidol (2 RCTs, 78 patients): 2 patients withdrew. One due to feeling excessively drowsy (average dose 8.8 mg/24 hours), the other due to lethargy (average dose 2.8 mg/d). No extra pyramidal symptoms were reported.

Authors’ conclusions
Droperidol was statistically significantly more effective than placebo without any evidence of dose-responsiveness. The number needed to treat to prevent nausea compared to placebo was 2.7 (95% CI: 1.8, 5.2) and that to prevent vomiting was 3.1 (95% CI: 2.3, 4.8). Compared with placebo the incidence of minor adverse effects with droperidol compared to
placebo was increased with doses > 4 mg/dl. There is a lack of evidence for other antiemetics.

**CRD commentary**
The aims and inclusion criteria were clearly stated. No language restrictions were applied to primary studies. Relevant details of the included studies were presented. Methods used to assess validity were described and results from this assessment were reported. Results were clearly presented as point estimates and 95% CI. Statistical heterogeneity was assessed and results reported for droperidol. Sensitivity analysis was conducted by investigating the potential dose-responsiveness of droperidol. Methods used to select primary studies and to assess statistical heterogeneity were not described.

Validity scores for the pooled studies on droperidol varied from 1 to 4 but no investigation was conducted of the influence of the quality of the study on results. Significant statistical heterogeneity was found and therefor pooling of data (even with the use of a random-effects model) was not appropriate.

The authors' conclusions were supported by the evidence presented.

**Implications of the review for practice and research**
Practice: The authors do not report any clinical implications of the review.

Research: The authors consider that large, randomised placebo-controlled trials comparing different doses of droperidol are required to establish the optimum dose for morphine PCA related nausea and vomiting.

**Funding**
Swiss National Science Foundation, grant number 3233-051939.97.

**Bibliographic details**

**PubMedID**
10357345

**Original Paper URL**
http://www.anesthesia-analgesia.org

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Analgesia, Patient-Controlled; Analgesics, Opioid /administration & dosage /therapeutic use; Antiemetics /adverse effects /therapeutic use; Droperidol /adverse effects /therapeutic use; Humans; Morphine /administration & dosage /therapeutic use; Postoperative Nausea and Vomiting /prevention & control; Randomized Controlled Trials as Topic; Risk Assessment

**AccessionNumber**
11999001173
Record Status

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