Treatment of established postoperative nausea and vomiting: a quantitative systematic review

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Authors' objectives
To systematically review the literature for valid data on any treatment of established post-operative nausea and vomiting (PONV) symptoms, to critically appraise the data, to test for dose-responsiveness for each drug, and to estimate the relative efficacy and likelihood for harm of the various treatments.

Searching
MEDLINE (via PubMed) and EMBASE were searched from 1966 and from 1974, respectively, using different search strategies. The Cochrane Controlled Trials Register in the Cochrane Library (Issue 4, 2000) was also searched. The searches were conducted using the free text terms ('postoperative' or 'postoperative' or 'postsurg*'), ('nausea' or 'vomiting' or 'emesis' or 'retching'), ('randomised' or 'randomized'), ('treatment'), not ('chemotherapy' or 'radiotherapy'), not ('prevention' OR 'prophylaxis'), and combinations of these terms. The last electronic search was conducted on the 21st August, 2000.

The reference lists of retrieved reports and relevant review articles, and the authors' comprehensive in-house bibliography were also examined. Authors of the original trials were contacted when there was ambiguity about the data, but there was no attempt to contact the manufacturers.

Study selection
Study designs of evaluations included in the review
Full reports of randomised controlled trials (RCTs), where the control was a placebo, no treatment or another anti-emetic, were eligible for inclusion. Studies with inadequate randomisation were excluded.

Specific interventions included in the review
Comparisons of any treatment for established PONV with a placebo, another anti-emetic or with no treatment, were eligible for inclusion. Studies that investigated both pre-operative prophylaxis and post-operative treatment were excluded.

The specific drugs studied included the following: dolasetron (12.5 to 100 mg, intravenous, i.v.), granisetron (0.1 to 3 mg, i.v.), tropisetron (0.5 to 5 mg, i.v.), ondansetron (1 to 8 mg, i.v.), propofol (6 to 27 mg or 0.2 mg/kg, i.v.), GR205171 (25 mg, i.v.), isopropyl alcohol (unspecified dose, nasal vapour), metoclopramide (10 mg, i.v.), domperidone (10 mg, i.v.) and midazolam (1 mg and 1 mg/hour, i.v.).

Participants included in the review
Only studies of patients with PONV were eligible for inclusion.

Outcomes assessed in the review
The principal outcome reviewed was 'success'. This was defined as 'no further nausea or vomiting in a nauseated or vomiting patient'.

Successes were categorised as either 'early' (i.e. within or close to 6 hours post-operatively) or 'late' (i.e. within or close to 24 hours post-operatively). Adverse event details were an additional outcome of interest. Data on the patients' satisfaction, duration of hospital stay, number of vomiting episodes, degree of nausea, or number of rescue treatments were not analysed, as these data were inconsistently reported.

How were decisions on the relevance of primary studies made?
The retrieved reports were screened by one author. Those reports which did not clearly meet the inclusion criteria were excluded at this stage.
Assessment of study quality
The quality of the included studies was assessed using the 5-point validity assessment tool devised by Jadad et al. (see Other Publications of Related Interest no.1). This takes into account randomisation, double-blinding and description of withdrawals. All potentially relevant reports were read by all authors independently, who scored them for methodological validity. The authors met to agree consensus on validity scores, and any discrepancies were resolved by discussion.

Data extraction
The data were extracted by one author and checked by the two others independently. The authors met to agree consensus on extracted data, and any discrepancies were resolved by discussion.

Dichotomous data on anti-vomiting and anti-nausea efficacy were extracted separately. When no distinction was made between nausea and vomiting, the data were not analysed further. The data on adverse drug reactions were analysed when they were reported in dichotomous form.

Data were extracted on the validity score, drug name, dose and route of administration, number of patients, type of surgery, sponsorship, definition of time scales and success rate, for both the early and late time scales.

Methods of synthesis
How were the studies combined?
For both the efficacy and harm data, the relative risk (as both the risk ratio and risk difference) and 95% confidence intervals were calculated. The risk difference was used to calculate the number-needed-to-treat; the 95% confidence intervals of this value were also calculated.

The data from the independent trials were only combined when the data represented clinically homogeneous subgroups, i.e. comparisons of data for the same dose and route of administration of the same experimental intervention, with the same control intervention (e.g. placebo), and reporting on the same emesis end point (e.g. vomiting) during the same observation period (e.g. late success). A fixed-effect model was used to combine these clinically homogeneous data.

The dose-responsiveness was assessed using the methods described in previous analyses (see Other Publications of Related Interest nos.2-3).

How were differences between studies investigated?
Differences in the characteristics of the included studies were assessed during the narrative synthesis of the review.

Results of the review
Twenty-five studies were included. The total number of patients was 5,076.

The studies were grouped into those with active controls (7 trials, n=1,267) and those with placebo controls (18 trials, n=3,809). The placebo-controlled trials were further grouped into those which investigated 5-HT3 antagonists (11 trials, n=3,427) and those investigating any other anti-emetics (7 trials, n =382).

In the 7 non placebo-controlled trials, 11 different anti-emetics were tested. These data were not analysed further since they constituted a very homogeneous group of studies.

Data from the placebo-controlled trials with inactive control therapy were briefly described but were not analysed further.

In studies of 5-HT3 antagonists, dolasetron, granisetron, tropisetron and ondansetron each prevented further vomiting. There was little evidence of dose-responsiveness. The absolute risk reductions in comparison with placebo were 20 to 30%. The anti-nausea effect was less pronounced. The incidence of headaches was found to be dose-dependent. The median validity scores for these studies was 3 (range: 2 to 5). Most of the data were derived from multicentre dose-
finding studies, which had been sponsored by the manufacturers of the anti-emetic.

The results on propofol were contradictory. GR205171, isopropyl alcohol vapour, metoclopramide, domperidone and midazolam were tested in one trial each, all with a limited number of patients.

**Authors' conclusions**
Of 100 vomiting surgical patients receiving a 5-HT3 receptor antagonist, 20 to 30 will stop vomiting who would not have done so had they received a placebo; less will profit from the anti-nausea effect. There was a lack of evidence for a clinically relevant dose-response; minimal effective doses may be used. There was also a discrepancy between the plethora of trials on the prevention of PONV and the paucity of trials on the treatment of established symptoms. Valid data on the therapeutic efficacy of classic anti-emetics, which have been used for decades, are needed.

**CRD commentary**
The review was based on a well-framed research question and was fairly well conducted. The search strategy was appropriate. The included studies were quality-assessed using a validated scale and appropriate details of the studies were provided. However there were some limitations in the review process: only two databases were searched; no attempt to locate unpublished studies was reported; the authors did not contact the manufacturers of the relevant drugs; only one reviewer applied the inclusion and exclusion criteria to potential studies; and combination regimes were excluded, so the review is unable to provide information on the relative merits of individual drugs and these combinations. In addition, an overview of the non placebo-controlled trials may have been beneficial.

The conclusions follow from the results presented. The implications for both practitioners and researchers appear to be appropriate.

**Implications of the review for practice and research**
- **Practice:** The authors state that evidence-based treatment strategies that take into account all possible anti-emetic interventions have not yet been established.
- **Research:** The authors state that there is a lack of valid data for the classic anti-emetics.

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