Efficacy of perphenazine to prevent postoperative nausea and vomiting: a quantitative systematic review
Schnabel A, Eberhart LH, Muellenbach R, Morin AM, Roewer N, Kranke P

CRD summary
The review concluded that perphenazine was effective for postoperative nausea and vomiting in adults and children; it may be comparable to established newer drugs and was well tolerated. Given the small amount of data available for each comparison, suboptimal trial quality and lack of consistent evidence about the equivalence of perphenazine with active comparators, these conclusions may require cautious interpretation.

Authors' objectives
To evaluate the effectiveness and safety of perphenazine for the prevention of postoperative nausea and vomiting in adults and children.

Searching
The Cochrane Central Register of Controlled Trials (CENTRAL, March 2008), MEDLINE, EMBASE and CINAHL were searched from inception for studies in any language. Search terms were reported. Reference lists of retrieved studies were checked.

Study selection
Randomised controlled trials (RCTs) that compared perphenazine with placebo or any other drug for preventing postoperative nausea and vomiting after a general anaesthetic were eligible for inclusion. The primary outcome was nausea, vomiting and/or retching. Secondary outcomes were need for rescue medication and adverse effects.

Adults in the included trials were undergoing cholecystectomy or gynaecological surgery; most were women. Trials of children included similar numbers of boys and girls (where reported), all of whom were undergoing tonsillectomy. Perphenazine was given intramuscularly, orally or intravenously at a dose of 2.5 to 5mg or a variable dose of 0.11mg/kg⁻¹. In all trials, children received a dose of 0.07mg/kg⁻¹. The timing of intervention administration varied. Control groups received either placebo, or one or more of a variety of other active drugs. Included trials were published between 1965 and 1999.

Two reviewers independently selected the studies.

Assessment of study quality
Trials were awarded up to 5 points for quality, using the Jadad scale/Oxford score. This assessed the adequacy of reported randomisation, double-blinding, and withdrawals or drop-outs.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Relative risks (RRs) were calculated, with 95% confidence intervals (CIs). Data for adults and children were analysed separately at three postoperative time intervals: early period (under six hours); late period (at six hours or over); and overall period (zero to 48 hours postoperatively).

Two reviewers independently extracted the data, with disagreements resolved by a third reviewer or by discussion.

Methods of synthesis
The trials were grouped by type of comparator and were combined, where possible, to calculate pooled relative risks and 95% confidence intervals. Heterogeneity was assessed using I². A fixed-effect model was ultimately used, as I² was
under 25%, but it was planned to use a random-effects model.

Subgroup analyses were planned to explore clinical differences between the trials, but few were conducted as there were insufficient data.

Publication bias was assessed by compiling a funnel plot for the most frequently reported outcome.

Results of the review

Eleven RCTs were included in the review, six of adults (n=1,191) and five of children (n=890). Trial quality scores ranged from 2 to 5 points. One RCT clearly described randomisation. Nine RCTs clearly described blinding. Five RCTs described drop-outs.

Adults: Perphenazine at a dose of 5mg or a variable dose of 0.11 mg/kg\textsuperscript{-1} was significantly more effective than placebo for adults for preventing postoperative nausea and/or vomiting in the early postoperative period (RR 0.50, 95% CI 0.37 to 0.67; three RCTs) and the overall postoperative period (RR 0.73, 95% CI 0.55 to 0.96; one RCT), but no significant benefit was found for a 2.5 mg dose (one RCT). Adults receiving perphenazine (0.11mg/kg\textsuperscript{-1}) were significantly less likely to need rescue medication than the placebo group (RR 0.51, 95% CI 0.31 to 0.83, one RCT).

Children: Perphenazine was more effective than placebo in children for preventing vomiting in the early postoperative period (RR 0.31, 95% CI 0.18 to 0.54; one RCT) and late postoperative period (RR 0.66, 95% CI 0.44 to 0.97; one RCT). It was also more effective than placebo for preventing nausea and vomiting in the overall postoperative period (RR 0.71, 95% CI 0.56 to 0.91, one RCT). There was no significant difference between the groups in need for rescue medication (one RCT).

Active comparators: All 11 RCTs compared perphenazine with an active comparator, but due to clinical heterogeneity only a small number were suitable for combining. Perphenazine was significantly less effective for preventing early postoperative vomiting in children than ondansetron or granisetron serotonin antagonists (RR 1.97, 95% CI 1.27 to 3.06; three RCTs). Comparisons of perphenazine versus ondansetron and droperidol for preventing early postoperative nausea and vomiting in adults (one RCT), and perphenazine versus dexamethasone for preventing early postoperative vomiting in children (one RCT) found no significant difference between the groups. The results of other active comparisons were not reported in the review.

Adverse events were poorly reported. Sedation was no more frequent in the intervention group than in the placebo group in adult trials (three RCTs).

The funnel plot for comparisons of early postoperative nausea and vomiting in adults showed asymmetry, but as there were only three RCTs, this did not necessarily indicate publication bias.

Authors’ conclusions

Perphenazine was effective for preventing postoperative nausea and vomiting in adults and children; it may be comparable to established newer drugs and was well tolerated. Further research is needed to identify the optimal treatment.

CRD commentary

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies with no language restriction. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies and extract the data, but it was unclear how many reviewers assessed validity.

There were some discrepancies in reporting (for example, quality scores of included trials). Few details were reported about trial quality (for example, the number of drop-outs). Methods used to combine the trials and assess for statistical heterogeneity were appropriate. As the authors noted, there was considerable variation across trials, which limited the potential to pool data. The authors questioned the reliability of data reported by two of the included RCTs and appeared to discount their findings in the review conclusions. These factors made it difficult to determine the reliability of the review findings. The results of five out of six RCTs that compared perphenazine with an active comparator were not
reported in the review. As the authors noted, data were sparse; they recommended caution in interpreting comparisons of perphenazine with active drugs.

In view of the small amount of data available for each comparison, suboptimal trial quality and lack of consistent evidence about the equivalence of perphenazine with active comparators, the authors' conclusions may require cautious interpretation.

**Implications of the review for practice and research**

**Practice:** The authors stated that clear recommendations cannot be given for the most suitable timing for administering perphenazine.

**Research:** The authors stated that further research is needed to establish the best timing, route and dose of perphenazine for prevention of postoperative nausea and vomiting in adults and children. They suggested that further studies should compare perphenazine with other antiemetics and recommended large observational studies to investigate adverse events associated with perphenazine.

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