The influence of a dominating centre on a quantitative systematic review of granisetron for preventing postoperative nausea and vomiting

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Authors' objectives
To perform a meta-analysis of studies investigating the efficacy of granisetron in the prevention of post-operative nausea and vomiting (PONV). A second objective was to investigate if the results from one centre, which published reports of numerous comparisons, were giving a bias to the evidence on the effectiveness of the drug.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched for studies published in any language, using the following keywords: 'granisetron', 'nausea', 'vomiting', 'retching', 'anaesthesia', 'anaesthesia'. The date of the last search was 10th July, 2000. In addition, the reference lists of the retrieved publications were examined. No attempt to locate unpublished information or information held by the drug manufacturers was reported.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled clinical trials (RCTs) were included.

Specific interventions included in the review
Granisetron, an anti-emetic compound from the 5-hydroxytryptamine antagonist group of drugs. This was administered as either a fixed dose of 3 mg (independent of body weight) or a variable dose of between 1.5 and 20 microg/kg body weight.

Participants included in the review
Patients who had undergone general anaesthesia and who had received granisetron as a prophylactic against PONV were included. The patients had undergone operations for a range of conditions including breast, gynaecological, abdominal and oto-rhinolaryngeal conditions.

Outcomes assessed in the review
The main end point of the review, which was defined a priori, was the number of patients in each study who had experienced PONV within 24 hours of 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
The validity of the included studies was assessed using the scale of Jadad et al. (see Other Publications of Related Interest). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The data were extracted independently by two of the reviewers. The extracted data were cross-checked for validity, and in cases of disagreement, consensus was reached with a third reviewer.

The data extracted included the following: the study authors; the quality score; the number of patients; the control event rate (an indicator of the baseline risk in the placebo group); whether nausea and/or vomiting was observed; the dose of granisetron administered to the patients in the active arm; whether a fixed or variable dose of granisetron was...
administered; the route of administration; whether the drug was administered before, during or after the anaesthetic; if the study was conducted at one or more institutions; the age range of the patients in the study; the gender ratio of the patients in the study; the country in which the study was conducted; the type of surgery conducted; and whether epidural anaesthesia or analgesia was used in addition to a standard balanced anaesthetic.

Methods of synthesis
How were the studies combined?
The relative risk (RR) was calculated from the data using the RevMan software (version 4.1). No details were provided on how the data were entered into the computer program, or by how many of the reviewers. The 95% confidence intervals (CIs) were calculated for point estimates using the computer program ‘Confidence Interval Analysis’ (version 1.0).

A random-effects model was used to pool the data across the studies since significant heterogeneity was observed.

The reviewers compared the efficacy of high-dose granisetron with low-dose granisetron. For the meta-analysis of trials using a fixed dose of 3 mg, it was assumed that the average body weight was 75 kg; this resulted in an extracted value of 40 microg/kg being used.

The reviewers also combined data from all the studies at one centre, which published the majority of the drug assessments, and compared the results with all other studies.

The authors do not report if any attempt was made to assess publication bias.

How were differences between studies investigated?
Evidence for heterogeneity was assessed using the chi-squared test.

Results of the review
Twenty-seven randomised controlled trials (RCTs), involving a total of 2,938 patients, were included. A number of studies involved multiple arms and consequently a total of 51 comparisons were included in the review.

The chi-squared test was positive for heterogeneity (chi-squared 255.35, d.f.=50, p<0.00001).

When comparing patients who received granisetron with those who received a placebo, the pooled RR of developing PONV was 0.46 (95% CI: 0.39, 0.54).

High-dose granisetron appeared to be more effective at preventing PONV than low-dose therapy: the RRs were 0.34 (95% CI: 0.28, 0.41) and 0.7 (95%: CI 0.6, 0.81), respectively.

The number of patients who would need to be treated in order for one patient to benefit was 3.55 (95% CI: 3.13, 4.08). The numbers- needed-to-treat (NNT) for high- and low-dose therapy were 2.71 (95% CI: 2.43, 3.08) and 5.15 (95% CI: 3.89, 7.63), respectively.

One institution published all but 6 of the studies. This centre therefore contributed 37 of the 51 comparisons and 1,867 of the 2,938 patients (63.5%). A sensitivity analysis was conducted to compare the data from the studies at this centre with those conducted at other institutions. A marked difference in the RR of developing PONV was observed between patients who were investigated at the largest centre (RR 0.41, 95% CI: 0.34, 0.49) and those studied elsewhere (RR 0.60, 95% CI: 0.49, 0.73). As the CIs do not overlap, this implies a probability of error (p-value) of 0.0025. Additionally, the NNT at the largest centre (NNT 3.01, 95% CI: 2.66, 3.47) was lower than that at the other centres (NNT 3.74, 95% CI: 3.09, 4.78). The probability of error for this comparison was less than 0.05. This suggests that granisetron therapy is more successful at the institution that has published the most research on the drug in this setting.

Authors’ conclusions
Overall, granisetron appears to be an effective intervention for the prevention of PONV in patients who have undergone
a range of surgical procedures.

The authors explicitly conclude that the inclusion of data from a single institution, which conducted a large number of trials with a large number of patients, had significantly altered the results of the review.

**CRD commentary**

The review question was well stated and the inclusion criteria were appropriate. The participants to be included, the intervention and the comparators to be evaluated and the outcome of interest, were explicitly stated.

The search strategy appeared appropriate. The report, however, could have been strengthened by additional details of the review process. In particular, where one research group is predominant, it would have been useful to have known whether the reviewer was blinded to the identity of the primary researchers when applying the inclusion criteria.

A recognised system was used to assess the validity of the studies, but it would have been beneficial to have known how these ratings were applied.

The data were analysed in an appropriate manner. The heterogeneity of the publications was identified and an appropriate statistical approach was subsequently used in the data analysis. However, the data-outputs from the software package (figures 1 to 3 in the paper) included a reference to a weighting. The authors of the review did not state the derivation of this weighting, or clarify how the weighting was used.

A comparison was conducted of the results obtained in the use of granisetron in PONV prophylaxis between the centre which reported 37 of the 51 trials and the remaining 14 trials. This was appropriate given the proportion of the total number of patients treated at this institution (63.5%) included in the meta-analysis. Reasons why granisetron appeared to be more effective in trials conducted at this institution were not fully discussed in this publication.

The authors’ conclusions appear to follow from the results presented. The implications for future secondary research appear appropriate.

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

Practice: The authors did not state any implications for practice.

Research: The authors state that in situations where results from one institution can significantly alter the overall results, or when their results do not appear to be valid for other lower volume providers, it may be advisable to either exclude data from the dominating institution or to provide a subgroup sensitivity analysis excluding that institution.

**Bibliographic details**


**PubMedID**

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**Other publications of related interest**


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Subject indexing assigned by NLM

**MeSH**
Antiemetics /administration & dosage /therapeutic use; Databases, Bibliographic; Granisetron /administration & dosage /therapeutic use; Humans; MEDLINE; Multicenter Studies as Topic /statistics & numerical data; Postoperative Nausea and Vomiting /prevention & control; Randomized Controlled Trials as Topic; Research Design

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.