Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials

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Authors' objectives
To assess the efficacy of ondansetron, compared with placebo or no treatment, for the prevention of post-operative nausea and vomiting (PONV); to test dose-response evidence; to identify the optimal dose for oral and intravenous routes; to compare anti-nausea with anti-vomiting efficacies; and to investigate the potential of ondansetron for toxic effects in the surgical setting.

Searching
MEDLINE, Biological Abstracts, and EMBASE were searched using different search strategies with free text combinations (the last electronic search was conducted 19th September 1996). Additional reports were identified from the reference lists of the retrieved reports, from review articles, and from handsearches of locally available anaesthetic journals. The reports identified were compared with those on a database provided by the manufacturer. The authors were contacted to clarify duplicate publications. Studies reported in any language were considered. Abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included. Quasi-randomised trials were excluded.

Specific interventions included in the review
Prophylactic ondansetron given at different doses (1 to 48 mg) and different regimens. The regimens included: fixed and variable doses; single, double or triple administrations; and different routes (oral or intravenous). The control was placebo or no treatment.

Participants included in the review
Men, women and children who had had a general anaesthetic.

Outcomes assessed in the review
The outcomes were early (within 6 hours of surgery) and late (within 48 hours of surgery) PONV including retching, any emetic event (nausea, vomiting, or nausea and vomiting), and side-effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently read each report that could meet the inclusion criteria, and met afterwards to reach a consensus.

Assessment of study quality
The trials were scored for inclusion and methodological validity using the 3-item, 5-point scale of Jadad et al. (see Other Publications of Related Interest). Two reviewers independently scored the trials and met afterwards to reach a consensus.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The relative risks and 95% confidence intervals (CIs) were calculated. A fixed-effect model was used when there was no significant heterogeneity, and a random-effects model when there was significant heterogeneity. A statistically-significant benefit of ondansetron over the control was assumed when the lower limit of the 95% CI of the relative benefit was greater than one. The number-needed-to-treat (NNT) and the 95% CI were also calculated.

How were differences between studies investigated?
A formal heterogeneity test was performed when the data from more than two trials were combined. A sensitivity analysis was performed, including and excluding those trials that fell outside of the predefined ranges of control event rates. In addition, a scatter plot (event rates with ondansetron against event rates with control) was used to explore the consistency of ondansetron's efficacy and the homogeneity of the data.

Results of the review
Eighty-five trials were considered, of which 28 were excluded after further examination. Fifty-three trials, with a total of 13,580 participants (7,321 received ondansetron) receiving 24 different ondansetron regimes, were included.

Fixed dose: early events (within 6 hours).
Only the 4-mg dose achieved consistent and clinically relevant efficacy when compared with placebo. The NNT to prevent early PONV with intravenous ondansetron (4 mg), compared with placebo, was between 5 and 6.

Fixed doses: late events (within 48 hours).
The combined analysis of data from studies of 4 mg intravenous ondansetron suggested that the anti-nausea effect with this dose was better (NNT=4.6) than with any other dose.

Dose response.
Increasing the dose from 4 to 8 mg led to a decrease of more than 20% in the NNT (i.e. an improvement) for the prevention of both nausea and vomiting. When the dose was further increased to 16 mg, no clinically relevant improvement was achieved. With 8 mg, the NNT to prevent nausea and vomiting up to 48 hours was 6.4, compared with a NNT of 5 for placebo. An increase in the oral dose from 3 to 4 mg led to an improvement of more than 20% in efficacy, as did the increase from 4 to 8 mg and the increase from 8 to 16 mg. The latter resulted in improvements of 39 and 37% in the prevention of nausea and vomiting, respectively. A further dose increase was of no benefit. The NNT to prevent nausea and vomiting with 16 mg oral ondansetron up to 48 hours was 5.9, compared with a NNT of 4.4 for placebo.

Variable doses: early (within 6 hours) and late (within 48 hours).
Most of the trials included children, and in the majority only data on preventing vomiting were available. The best-documented regimen was 100 microg/kg intravenous ondansetron; the NNT to prevent vomiting up to 6 hours was 5 (range: 3.7 to 7.6). To prevent late vomiting with this regimen, the combined NNT was 2.7 (range: 2.0 to 4.2). It was not possible to establish a dose-response.

Adverse effects.
With 1 mg ondansetron, the incidence of headache was not significantly different from placebo (number needed-to-harm 5.4). With higher doses, headache occurred significantly more with ondansetron than with placebo; the number-needed-to-harm was 30 for 4 mg, 42 for 8 mg, and 38 for combined 16 to 48 mg. With all the data combined, the number-needed-to-harm was 36. The number-needed-to-harm for elevated liver enzymes with 4 to 8 mg ondansetron in comparison with placebo (5 trials, 1,831 participants) was 31 (range: 18 to 128); this was statistically significant.

Authors' conclusions
If the risk of PONV is high, for every 100 patients receiving an adequate dose (8 mg intravenously or 16 mg orally) of ondansetron, 20 patients will not vomit who would have vomited if they had been on placebo. The anti-nausea effect is less pronounced. Of these 100 patients, there will be 3 with elevated liver enzymes and 3 with a headache who would not have had these adverse effects without the drug.

**CRD commentary**
This was a well-written review. The search strategy was not particularly comprehensive; it would be useful to assess the risk of publication bias given the decision to exclude unpublished reports and abstracts. The studies were scored for quality, but the results of the scoring do not appear to have been used in the analysis (e.g. either to include or exclude the studies or to favourably weight the results of higher quality studies). No information was provided on the decisions of relevance concerning the primary studies, or the process by which the data were extracted. Insufficient details of the individual studies were provided in the report, although tables are available from the authors. Limited information was provided on the patients included within the RCTs, specifically age, gender and morbidity. In general, the evidence reported in the review supports the authors’ conclusions.

**Implications of the review for practice and research**
The authors did not report any implications of the review.

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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.