Use of 5-HT3 receptor-antagonists in patients receiving moderately or highly emetogenic chemotherapy

Systemic Treatment Disease Site Group

CRD summary
This review compared 5-HT3 receptor antagonists for the prevention of vomiting and nausea in adults receiving cancer chemotherapy. The authors concluded that ondansetron, granisetron and dolasetron are equally effective in the first 24 hours and that longer treatment may have some benefit. However, what the review shows is no evidence of a difference in effect, not that the drugs effects are equivalent.

Authors' objectives
To assess the comparative efficacy of 5-HT3 receptor antagonists for preventing vomiting and nausea in people undergoing chemotherapy for cancer, and whether giving these drugs for more than 24 hours after chemotherapy prevents delayed-onset vomiting.

Searching
The authors searched MEDLINE (1987 to January 2003), Cancerlit (1987 to October 2002), the Cochrane Library (Issue 4, 2002), PDQ, CMA Infobase, the National Guideline Clearinghouse, the proceedings of annual meetings of the American Society of Clinical Oncology (1995 to 2002), article bibliographies and personal files. The search terms were reported. Only English language studies were considered.

Study selection
Study designs of evaluations included in the review
The inclusion criteria specified double-blind randomised controlled trials (RCTs). Existing meta-analyses and practice guidelines were apparently also eligible, but this was not stated in the inclusion criteria. Some of the included trials used a crossover design.

Specific interventions included in the review
Studies were eligible for inclusion if they compared ondansetron, granisetron, dolasetron or tropisetron with each other, or a placebo or anti-emetic. Studies of treatment effect beyond 24 hours were eligible if the same anti-emetics were administered to both the treatment group and the control group during the first 24 hours after chemotherapy, or if the patients were randomised 24 hours after initial anti-emetic treatment.

The included studies of treatment effect in the first 24 hours after chemotherapy compared ondansetron with granisetron, and ondansetron or granisetron with dolasetron. The studies of treatment effect beyond 24 hours compared: ondansetron, granisetron, dolasetron or tropisetron with placebo; ondansetron plus dexamethasone with dexamethasone alone; ondansetron plus dexamethasone with granisetron plus dexamethasone; and ondansetron with dolasetron. The dose, frequency and route of administration (oral or intravenous) varied between the studies.

Participants included in the review
Studies of adults with cancer who were receiving moderately or highly emetogenic chemotherapy were eligible for inclusion. Details of the characteristics of the participants in the included studies were not reported.

Outcomes assessed in the review
The eligible outcomes were vomiting and nausea. The primary outcome used in the review was the proportion of participants without vomiting in the first 24 hours following chemotherapy. Nausea was a secondary outcome. It was defined as the proportion of participants without nausea in the first 24 hours following chemotherapy, or the mean score on a structured scale. The same parameters were used to assess delayed-onset vomiting and nausea beyond 24 hours. Other outcomes included quality of life and adverse effects.
How were decisions on the relevance of primary studies made?
It was suggested that several people were involved in selecting the studies, but how many and whether they did it independently was not reported.

Assessment of study quality
The authors did not state that they assessed validity. This review was developed using the Practice Guidelines Development Cycle, which has been reported elsewhere (see Other Publications of Related Interest).

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included: the number of participants randomised and the number evaluable; the proportion of patients free of vomiting; and the proportion of patients free of nausea, or the nausea score as a mean, median or median change from baseline.

Methods of synthesis
How were the studies combined?
Trials of treatment beyond 24 hours were combined statistically using a fixed-effect meta-analysis to estimate the pooled risk ratio (RR) of delayed-onset vomiting and its 95% confidence interval (CI). All other study results were combined in a narrative, with the rates of control of vomiting and nausea in each treatment group in each trial being tabulated.

How were differences between studies investigated?
A statistical Q-test was used to assess heterogeneity in the meta-analysis. The effect of excluding from the meta-analysis one trial, in which patients in the treatment and control groups received different 5-HT3 agonists in the first 24 hours, was investigated. Differences in chemotherapy and anti-emetic treatment regimens between trials were highlighted in the narrative synthesis.

Results of the review
The review appears to have included 24 RCTs with a total of more than 12,000 participants. The review also reported two existing meta-analyses of randomised trials and two evidence-based practice guidelines.

Treatment effect in the first 24 hours after chemotherapy.
Ondansetron was compared with granisetron in about 6,000 participants (the number of trials was unclear). There was no statistically significant difference in vomiting or nausea in the first 24 hours after chemotherapy.

Dolasetron was compared with ondansetron in three trials (n=1,703) and with granisetron in one trial (n=474). Only one study showed a difference: significantly more patients given dolasetron (2.4 mg/kg) were free from vomiting after 24 hours compared with those given ondansetron (32 mg), but no difference was shown at day 7. There was some evidence of more adverse effects with ondansetron than with the other drugs.

Treatment effect beyond 24 hours.
A meta-analysis of 10 comparisons, apparently from nine RCTs (n=3,468), showed a small but statistically significant reduction in delayed-onset vomiting with 5-HT3 receptor antagonists compared with placebo (RR 0.91, 95% CI: 0.84, 0.97, P=0.0063). This means that about 22 people would need to be treated with a 5-HT3 receptor antagonist in order to prevent delayed-onset vomiting in one additional person. Five of the trials reported more constipation associated with using 5-HT3 receptor antagonists beyond 24 hours after chemotherapy. None of the four trials that measured quality of life detected a difference in global measures of well-being compared with placebo.

Neither of two existing meta-analyses summarised in the review showed a significant difference in acute or delayed vomiting between ondansetron and granisetron (based on 14 trials), or between granisetron and ondansetron or...
tropisetron (based on 28 trials).

Due to differences between the studies, it was not possible to draw conclusions about the drug dose, schedule or route of administration.

**Authors' conclusions**
The authors concluded that intravenous ondansetron, granisetron and dolasetron in optimal doses were equally effective in preventing nausea and vomiting in adults undergoing moderately or highly emetogenic chemotherapy. Treatment for more than 24 hours after chemotherapy probably has a modest benefit.

**CRD commentary**
The questions addressed by this review were stated, but the inclusion criteria were not given in sufficient detail to convey clearly what was eligible for inclusion. Eligibility was particularly unclear regarding co-medications (e.g. dexamethasone) and the stance taken on treatment alternatives (e.g. metoclopramide) as comparator interventions. Participant eligibility for inclusion in the trials that were included in the review was also unclear. A number of relevant sources were searched, but the restriction to English language might have introduced bias. Bias in the process of selecting studies for inclusion in the review cannot be ruled out because the procedure was not described adequately. Inclusion was restricted to trials that were double-blind, but the quality of these trials does not appear to have been assessed any further, thus it is difficult to assess how reliable the results are.

The report lacked a clear statement of the total number of trials included in the review. The evidence presented cannot support a conclusion of equivalence between the three drugs, only that no evidence of a significant difference in effect was found in the trials that compared one drug with another (no single trial compared all three drugs). The conclusion regarding the effect of prolonged treatment is consistent with the data shown.

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

*Practice:* The authors stated that intravenous ondansetron, dolasetron and granisetron should be regarded as equally efficacious and well tolerated, and that 5-HT3 receptor antagonists should be administered for 24 hours following chemotherapy.

*Research:* The authors stated that there were insufficient data about the relative effects of 5-HT3 receptor antagonists when administered orally. They identified one ongoing RCT of oral granisetron versus placebo in the 48 hours after the 24 hours following chemotherapy.

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