Efficacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: a quantitative systematic review

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Authors' objectives
To determine the efficacy of 5-HT3 receptor antagonists and the likelihood of harm in radiotherapy-induced nausea and vomiting.

Searching
MEDLINE, EMBASE, Biological Abstracts, and the Cochrane Library were searched up until 15 January 1997 using the keywords: ondansetron, granisetron, tropisetron, radiation, irradiation and radiotherapy. The bibliographies of retrieved articles and reviews were checked for additional references. Unpublished data were not sought and authors/manufacturers were not contacted. All languages were included, but abstracts and reviews were not considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Studies with post hoc subgroup analyses were not considered.

Specific interventions included in the review
5-HT3 receptor antagonists including ondansetron (8mg oral 3 times/day or 3mg/day i.v.) and granisetron (3mg/day i.v.) were included in the review. Control treatments included metoclopramide (10mg oral 3 times/day), prochlorperazine (10mg oral 3 times/day), metoclopramide (20mg/day i.v.)+ dexamethasone + lorazepam and placebo. The duration of treatment varied from 1 day to over 5 weeks.

Participants included in the review
Adults and children receiving radiotherapy. Participants reported in the review included those receiving total body, upper abdominal and abdominal radiotherapy (varying dose regimens). Patients receiving concomitant chemotherapy (arbitrarily defined as within 24hrs of radiotherapy) were excluded.

Outcomes assessed in the review
Complete control of radiation-induced emesis (vomiting including retching) and nausea. Acute radiation-induced emesis was defined as within 24hr of onset of radiotherapy, and delayed radiation-induced emesis as after 24hrs or after consecutive radiotherapy doses given during several days. Other outcomes included worst day nausea/vomiting, number or delay until first emetic episode, number of emesis-free days, treatment failure, and need for rescue medication. Scores of patient satisfaction or quality of life were excluded.

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 reviewer performed the selection.

Assessment of study quality
No formal assessment of validity was undertaken and no data relating to the validity of the included studies was presented. However, the authors make recommendations pertaining to the quality of future studies in their concluding statements.

Data extraction
Data were collected on: patients, radiation (dose per fraction, duration, total dose per treatment, site), dose and route of administration of 5-HT3 receptor antagonists and control treatments, study design, study end points and adverse events.
The authors do not state how many reviewers were involved in extracting the data.

Methods of synthesis
How were the studies combined?
Relative risks (RRs) with 95% confidence intervals (95% CI), point estimates and numbers needed to treat (NNT) with 95% CI were calculated for each study (when the relative benefit indicated a statistically significant different between two treatments). The frequency of drug-related adverse effects were estimated by calculating the number needed to harm (NNH). Treatment and control arms from different trials were combined where appropriate.

How were differences between studies investigated?
No formal assessment of heterogeneity was performed, however authors stated that studies were not combined because of the variety of treatments, controls, clinical settings and end points.

Results of the review
Five RCTs including 474 participants. Two trials compared ondansetron with placebo, one with metoclopramide and one with prochlorperazine. One trial compared granisetron with a combination of metoclopramide plus dexamethasone plus lorazepam.

Anti-emetic efficacy:
Data from the treatment and control arms were not combined across studies because of the variety of treatments, controls, clinical settings and end points. Three studies (two ondansetron, one granisetron) reported data on acute efficacy (24 hrs), two (one ondansetron and one granisetron) on delayed efficacy (after 24 hrs) and two (both ondansetron) on ‘worst day' outcome.

1. Acute efficacy (n=3) - There was no significant difference between ondansetron and placebo in the complete control of retching and vomiting (relative benefit 5.0, 95% CI: 0.7, 36, NNT 2.5) or prevention of nausea (relative benefit 4.0, 95% CI: 0.54, 30; NNT 3.3). However, ondansetron was shown to be significantly more efficacious than metoclopramide for the complete control of acute vomiting (relative benefit 1.98, 95% CI: 1.47, 2.65; NNT 2.2) and acute nausea (relative benefit 1.71, 95% CI: 1.17, 2.51; NNT 3.6) in a larger placebo-controlled trial. Granisetron was significantly better than metoclopramide in preventing vomiting and mild nausea (relative benefit 4.0, 95% CI: 1.01, 15.8; NNT 2.5).

2. Delayed efficacy after 24hrs (n=2) - There was no evidence of any significant differences with ondansetron or granisetron compared with placebo or other anti-emetics in terms of delayed outcomes.

3) Worst day (n=2) - Ondansetron was found to be significantly better in terms of its anti-vomiting effect (‘worst day’) compared with placebo (relative benefit 1.51, 95% CI: 1.06, 2.13; NNT 4.4), but not in terms of its anti-nausea effect (relative benefit 1.94, 95% CI: 0.69, 5.41; NNT 11.9). Ondansetron was also significantly better than prochlorperazine in preventing vomiting (relative benefit 1.74, 95% CI: 1.19, 2.53; NNT 3.8), but again not in terms of its anti-nausea effect (relative benefit 1.53, 95% CI: 0.86, 2.7; NNT 8.8).

Adverse effects (n=4 studies):
Only one study reported dichotomous data on constipation with patients receiving ondansetron reporting constipation significantly more often than patients taking prochlorperazine (NNH 6.4, 95% CI: 4.1, 13.9). Headache data was combined across the studies assuming that there was no difference in the incidence of adverse effects between different 5-HT3 receptor antagonists and different controls. During or after radiotherapy headache occurred significantly more often in patients receiving ondansetron or granisetron compared with the controls (combined NNH 17.1, 95% CI: 9.6, 80, n=3 studies).

Authors' conclusions
Only 14% of published data enabled valid estimation of the anti-emetic efficacy of 5-HT3 antagonists in radiotherapy.
There was some evidence that these drugs prevent acute vomiting: 40% of treated patients will benefit (NNT approximately 2.5). The evidence for nausea was less clear. There was no evidence that these drugs are of any benefit beyond 24 hours. There was some evidence that they produce specific adverse effects.

**CRD commentary**

This is a clearly presented review with well-defined inclusion criteria. A reasonable search for published literature was carried out which was not limited by the language of publication. No specific attempts were made to locate unpublished data however and abstracts were excluded. There is therefore a possibility of publication bias. In addition no details were reported about methods used to select studies and extract data. The number of individuals involved in these processes was also not stated. No data was presented on the validity of the included studies and it would appear that no formal assessment was performed. Despite this the authors do make recommendations about study quality in their concluding remarks. However RCTs were included in the review and so the data are probably reasonably robust.

The authors present the effectiveness findings without combining the data from different studies due to differences between the studies. However, the authors do make assumptions about the similarity of different 5-HT3 antagonists and different controls when they combine adverse effects data on headaches across studies (i.e. combining control and treatment arms across studies to estimate an overall effect). This also has the effect of breaking the randomisation within the studies and is not an appropriate method for pooling, so these findings should be treated with great caution. In addition the data are presented as NNTs and NNHs in the abstract, although RRs are also presented in the results. RRs are the more reliable estimate of effect size across different studies. If the studies being pooled vary in their baseline risk and outcome frequency, to report NNTs and NNHs could be misleading. This should be borne in mind when interpreting the findings in terms of NNTs and NNHs. Overall, given the problems outlined above the overall findings and conclusions of the review should be treated with great caution.

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

**Practice:** The authors state that 'ondansetron is efficacious in preventing acute vomiting after total body or upper abdominal irradiation' however 'these drugs were of no benefit after 24 hours compared with placebo or other anti-emetics'. In addition 'there was a significant anti-vomiting effect of ondansetron compared with placebo or prochlorperazine, but no effect on nausea', however 'ondansetron and granisetron are associated with an increased incidence of headache and constipation'.

**Research:** The authors state that 'valid comparisons are needed between 5-HT3 receptor antagonists and other anti-emetic drugs in the radiotherapy setting'. 'Validity criteria should include proper randomisation of a reasonable number of patients, clinically useful endpoints (incidence of nausea and vomiting and acute and delayed outcomes separated, for instance) and a placebo group to ensure internal sensitivity of the trial'. In addition 'clinically relevant questions which remain to be addressed are dose-responsiveness, efficacy in low risk settings and relative efficacy of prevention compared with treatment of radiotherapy-induced sickness including cost-effectiveness of these strategies'.

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