Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review

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CRD summary
This review found that neurokinin-1 receptor antagonists improved the control of chemotherapy-induced nausea and vomiting, but that they may increase infection rates. This was a well-conducted review with a large number of trials and patients; the results and authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the efficacy and safety of neurokinin-1 receptor antagonists in preventing chemotherapy-induced nausea and vomiting.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS were searched, generally up to September 2010, with no language restrictions; search terms were reported. Relevant conference proceedings were searched from 1998 to 2010, as were reference lists of all identified trials and reviews.

Study selection
Randomised controlled trials that involved the addition of a neurokinin-1 receptor antagonist to standard antiemetic therapy (dexamethasone with a 5-hydroxytryptamine-3 antagonist) for the prevention of chemotherapy-induced nausea and vomiting were eligible for inclusion. Trials had to use adequate dual-therapy antiemetic therapy in the control group and report outcomes that could be pooled in a meta-analysis.

The primary outcome was the proportion of patients who achieved a complete response during the overall period of assessment (defined as absence of vomiting or retching and absence of need for rescue antiemetic drugs). Secondary outcomes included complete patient response during the acute phase (0 to 24 hours after chemotherapy) and delayed phase (24 to 120 hours), and adverse events.

In the included trials, the neurokinin-1 receptor antagonists used were aprepitant, casopitant and ezlopitant. Other drugs used were dexamethasone, granisetron and ondansetron. Most trials used chemotherapy with high emetogenic potential; three trials had moderate emetogenic potential. Included trials were published from 1999 to 2010.

Two reviewers independently performed the study selection, with disagreements resolved by consensus.

Assessment of study quality
Trial quality was assessed for randomisation, allocation concealment, blinding, description of drop-outs, sample size calculation, use of intention-to-treat analysis and funding source.

Two reviewers independently performed the quality assessment, with disagreements resolved by consensus.

Data extraction
Numbers of patients with a complete response and numbers of adverse events in both treatment and control groups were extracted to calculate odds ratios with 95% confidence intervals. Two reviewers independently performed the data extraction.

Methods of synthesis
Pooled odds ratios were estimated in a random-effects Mantel-Haenszel meta-analysis. Heterogeneity was assessed using the $X^2$ test and $I^2$. Heterogeneity was considered substantial if $I^2$ was over 50%.

Various subgroup analyses were performed to investigate the effect of chemotherapy emetogenic potential, treatment duration, route of administration, and the drugs used in both treatment and control groups. Sensitivity analyses based on trial quality were performed.
Publication bias was assessed using a funnel plot and Egger's test.

**Results of the review**
Seventeen trials were included in the review with 8,740 patients (sample size range 46 to 1,933). Randomisation, blinding, description of drop-outs and sample size calculation were deemed adequate in nearly all trials. Only three trials used an intention-to-treat analysis, but drop-out rates were generally low.

Overall, neurokinin-1 receptor antagonists increased the rate of patients' complete response (OR 0.51, 95% CI 0.46 to 0.57; 13 trials; $I^2=12\%$) with a significant decrease in the frequency of vomiting, nausea and use of rescue medication. Neurokinin-1 receptor antagonists increased the rate of complete response in the acute phase (OR 0.56, 95% CI 0.48 to 0.65; 15 trials; $I^2=22\%$) and in the delayed phase (OR 0.48, 95% CI 0.42 to 0.56; 15 trials; $I^2=47\%$).

A benefit of neurokinin-1 receptor antagonists was seen for both highly emetogenic chemotherapy (OR 0.46, 95% CI 0.40 to 0.53) and moderately emetogenic chemotherapy (OR 0.59, 95% CI 0.51 to 0.67). The benefit was slightly greater if ondansetron was not used in the control group (OR 0.47, 95% CI 0.41 to 0.53) than if it was (OR 0.64, 95% CI 0.54 to 0.76). There was no evidence of differences for any other subgroups.

There was some evidence that neurokinin-1 receptor antagonists significantly increased the incidence of severe infections, hiccups, and asthenia or fatigue, but reduced the incidence of constipation. There were no statistically significant differences between groups for other adverse events.

There was no evidence of publication bias.

**Authors' conclusions**
Neurokinin-1 receptor antagonists improved the control of chemotherapy-induced nausea and vomiting in the acute, delayed and overall phases. They were effective for both moderately and highly emetogenic chemotherapy regimens. Their use may be associated with increased infection rates.

**CRD commentary**
The review had a clear research question and appropriate inclusion criteria. A suitable search was performed with no language restrictions that also sought trials only reported in conference proceedings. Action was taken to reduce reviewer error and bias throughout the review process.

Trial quality was assessed; the included trials were generally of good quality. Details on the nature of the populations in the included trials was not presented, which made it difficult to evaluate the generalisability of the results. Trials were pooled in a number of meta-analyses. The review included a substantial number of trials and patients.

This was a well conducted review with a large number of trials and patients; the results and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors suggested that neurokinin-1 receptor antagonists should be considered for use in patients receiving moderately emetogenic chemotherapy as well as highly emetogenic chemotherapy.

**Research:** The authors suggested that a comprehensive evaluation of the safety of neurokinin-1 receptor antagonists was needed.

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Record Status
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