Efficacy of current antiemetic treatments for preventing delayed chemotherapy-induced nausea and vomiting: a meta-analysis of randomized controlled trials

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CRD summary
This review compared dexamethasone plus 5-HT3 receptor antagonists (5-HT3RA) or metoclopramide with dexamethasone alone for preventing delayed chemotherapy-induced nausea and vomiting. The authors concluded that dexamethasone plus 5-HT3RA or metoclopramide have similar efficacy to dexamethasone alone. This was a well-conducted review and the authors’ conclusions are likely to be robust.

Authors' objectives
To compare dexamethasone plus 5-HT3 receptor antagonists (5-HT3RA), dexamethasone plus metoclopramide and dexamethasone alone for controlling and preventing delayed chemotherapy-induced nausea and vomiting (CINV).

Searching
MEDLINE, EMBASE, Cancerlit and the Cochrane CENTRAL Register were searched to March 2004. Ongoing clinical trials were identified from a trials website (date accessed not provided). See Web Address at end of abstract. The reference lists of all retrieved articles were scanned iteratively and searches of abstracts from major relevant meetings (from 1997 to 2003) were conducted. The search terms were documented in the report. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The studies had to provide either raw data on intention-to-treat (ITT) analysis or sufficient information to allow the calculation of such data.

Specific interventions included in the review
Studies that compared dexamethasone plus 5-HT3RA with either dexamethasone alone or dexamethasone plus metoclopramide for preventing delayed CINV were eligible for inclusion. The studies had to use the same prophylactic regimen for preventing acute CINV before treatment allocation in each treatment arm. The included studies used dexamethasone at doses of 3 to 8 mg twice daily, and used the 5-HT3RAs ondansetron, granisetron and tropisetron. Some studies reported the use of rescue medications; other studies gave no details.

Participants included in the review
Studies of patients of any age, with any type of cancer and receiving any type of chemotherapy were eligible for inclusion. The included studies were conducted in patients receiving cisplatin- and non-cisplatin-based chemotherapy regimens (full details of the regimens were reported).

Outcomes assessed in the review
The studies had to provide a clear description of the results of treatment in relation to acute and delayed CINV. The review assessed:

acute CINV, defined as nausea and/or emesis in the first 24 hours after chemotherapy;

delayed CINV, defined as nausea, vomiting or retching more than 24 hours after chemotherapy and up to 5 to 8 days (as defined by the authors of each study);

total control of emesis, defined as no moderate-to-severe nausea and no vomiting with or without rescue medication;

complete control of emesis, defined as no vomiting with or without rescue medication; and
the use of rescue medications.

The reviewers accepted broader definitions of the time period for delayed CINV (2 to 8 days) if raw data were presented for the whole period; where combined data were not reported, the reviewers selected data for the worst day.

**How were decisions on the relevance of primary studies made?**
Two reviewers independently conducted the searches.

**Assessment of study quality**
Validity was assessed. The studies were ranked using the Jadad scale, which considers the reporting and handling of randomisation, blinding and withdrawals. Two reviewers independently assessed validity.

**Data extraction**
Two reviewers independently extracted the data. Any disagreements were resolved through discussion, with the aid of a third reviewer where required. For each study, data were extracted on the definitions of study end points, methods used to assess the outcomes, the number of patients randomised, completed and evaluated, and the number of patients with each outcome. For crossover studies, only data for the first chemotherapy cycle were extracted.

**Methods of synthesis**
How were the studies combined?
Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a fixed-effect model in the absence of significant statistical heterogeneity. The potential for publication bias was assessed using Egger's test.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using the Cochran Q statistic. The influence of emetogenicity of the chemotherapy regimen was examined. Meta-analyses were repeated after excluding one RCT using a non-cisplatin-based chemotherapy regimen.

**Results of the review**
Eight RCTs (n=2,957) were included.

Seven of the 8 RCTs were double-blind.

Dexamethasone plus 5-HT3RA versus dexamethasone alone (5 RCTs, 2,258 randomised; 1,997 included in ITT analysis).

Delayed CINV: there was no significant difference between treatments for the prevention of delayed CINV; 53.2% with 5-HT3RA versus 53.3% with dexamethasone alone (RR 1.03, 95% CI: 0.97, 1.09). No statistically significant heterogeneity was found (P=0.27). There was no evidence of publication bias (P=0.09). Excluding one study using a non-cisplatin-based regimen gave similar results.

Delayed vomiting: there was no significant difference between treatments for complete protection from delayed vomiting (RR 1.03, 95% CI: 0.99, 1.07). No statistically significant heterogeneity was found (P=0.92). There was no evidence of publication bias (P=0.54).

Delayed nausea: there was no significant difference between treatments for complete protection from delayed nausea (RR 1.03, 95% CI: 0.98, 1.09). No statistically significant heterogeneity was found (P=0.63). There was no evidence of publication bias (P=0.18).

Dexamethasone plus 5-HT3RA versus dexamethasone plus placebo (3 RCTs).

Delayed CINV: a comparison of the 95% CIs showed no significant difference between treatments for delayed CINV.
Use of rescue medications: most of the studies did not provide adequate information to assess this.

Dexamethasone plus 5-HT3RA versus dexamethasone plus metoclopramide (3 RCTs, 699 randomised; 686 in ITT analysis).

Delayed CINV: there was no significant difference between treatments for the prevention of delayed CINV; 52.2% with 5-HT3RA plus dexamethasone versus 54.2% with dexamethasone plus metoclopramide (RR 0.96, 95% CI: 0.85, 1.09). No statistically significant heterogeneity was found (P=0.36). There was no evidence of publication bias (P=0.75). Data on delayed vomiting and nausea were only available in 2 studies, neither of which found any statistically significant differences.

Use of rescue medications: only one RCT provided relevant information. It found no significant difference between treatments.

Authors' conclusions
Dexamethasone plus either 5-HT3RA or metoclopramide have similar efficacy to dexamethasone alone for the prevention of CINV.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched, attempts were made to minimise language and publication bias, and the potential for publication bias was assessed. Two reviewers independently selected the studies, assessed validity and extracted the data, thus reducing the potential for bias and errors. Validity was assessed using specified established criteria and adequate information on the included studies was given. The studies were appropriately combined in a meta-analysis, statistical heterogeneity was assessed, and the influence of type of chemotherapy regimen was explored. This was a well-conducted review and the authors' conclusions are likely to be robust.

Implications of the review for practice and research
Practice: The authors stated that there is a need to re-evaluate current approaches to anti-emetic treatments for controlling CINV.

Research: The authors stated that more head-to head comparative trials are required to confirm the review finding of similar efficacy for dexamethasone plus 5-HT3RA and dexamethasone plus metoclopramide.

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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.