Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence

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Authors' objectives
To synthesise the available randomised evidence on the efficacy of dexamethasone when used for protection against acute and delayed nausea and vomiting in patients receiving highly or moderately emetogenic cancer chemotherapy.

Searching
MEDLINE (from 1966 to April 1999), EMBASE, Cancerlit, Derwent Drug File and the Cochrane Controlled Trials Register (Issue 1, 1999) were searched. In addition, the bibliography of retrieved RCTs, meta-analyses and narrative review articles were reviewed.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies in which dexamethasone was compared with placebo, no treatment, or another active agent, or in combination with another active agent versus that active agent alone, were eligible for inclusion.

In the included studies, dexamethasone (intravenous and oral, mean dose 56 mg) was compared with placebo, no treatment, metoclopramide (with a background of no other therapy or tropisetron), and ondansetron.

Participants included in the review
Patients with chemotherapy-induced nausea and/or vomiting. Trials in which the patients had received regimens of high or moderate emetogenicity were eligible for inclusion.

Outcomes assessed in the review
The complete protection from emesis, nausea and both events combined was assessed. Control of emesis (complete protection from emesis) was defined as no vomiting or retches in the defined emesis phase (acute or delayed). Acute emesis was defined as vomiting or retching within the first 24 hours after chemotherapy. Delayed emesis was defined as vomiting or retching more than 24 hours after chemotherapy and up to 5 to 8 days. The authors agreed a priori to select the rates of the worst day for inclusion in the data pooling.

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 reviewers performed the selection.

Assessment of study quality
The authors do not report a formal method for assessing validity, but study quality is assessed within the text of the review.

Data extraction
The data were extracted in duplicate and independently by two reviewers. Any discrepancies were handled through consensus.

Data were extracted on the following: the method of random allocation and adequacy of concealment; adequacy of blinding of the investigators and patients to the investigational drug; definition of the condition of interest and of the
outcome of interest; type and dosage of chemotherapy (highly emetogenic versus moderately emetogenic); the cycle of chemotherapy in which dexamethasone was being tested (first cycle versus later cycles); previous chemotherapy and history of chemotherapy-induced emesis; possible pre-selection of patients on the basis of prior anti-emetic response; patient demographics; comparator treatment; concurrent background anti-emetics given to all patients; and data on the main outcomes.

Methods of synthesis
How were the studies combined?
The outcome data were combined using both fixed-effect and random-effects models (see Other Publications of Related Interest no.1). The authors included calculations for the odds ratio (OR), risk ratio (RR), risk difference and the number-needed-to-treat.

Cumulative meta-analyses, with studies ordered by dexamethasone dosage, were used to identify possible relationships between the magnitude of the treatment effect and the dexamethasone dosage.

Inverted funnel plots were used to evaluate whether the magnitude of the treatment benefit was related to the sample size of the included trials, which might be suggestive of publication bias (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Heterogeneity was tested by the Q statistic and was considered significant if P was less than 0.10. The authors performed various types of sensitivity analyses. The effect of the methodologic quality of the studies was assessed by subgroups comparing unblind studies with single- and double-blind designs. The adequacy of randomisation was similarly assessed.

Subgroup and meta-regression analyses were performed to explore possible relationships between covariates and treatment effects (see Other Publications of Related Interest no.3).

Results of the review
Thirty-two studies (n=5,613) were eligible for inclusion. Twenty-eight of the included studies were RCTs; seven studies used crossover designs with extractable first-period data. The remaining four studies used a parallel open-label design.

Complete protection from emesis in the acute phase (less than 24 hours).
For studies which provided data on complete protection from emesis (29 studies, n=4,176), the random-effects OR and RR were 2.14 (95% confidence interval, CI: 1.78, 2.59) and 1.24 (95% CI: 1.18, 1.31), respectively. Twenty-five studies (n=3,714) in which dexamethasone was compared with placebo or no treatment gave a random-effects OR of 2.22 (95% CI: 1.89, 2.60) and a random-effects RR of 1.26 (95% CI: 1.21, 1.32). There was no significant heterogeneity for any of the treatment effect metrics (p>0.10 for all).

In the summary estimates, dexamethasone increased the chance of no vomiting by about 25 to 30%, and offered an additional 15 out of 100 patients a vomit-free first 24 hours after receiving chemotherapy.

Complete protection from emesis in the delayed phase (greater than 24 hours).
For studies which provided data on the specific end point of complete protection from emesis (20 studies, n=2,772), the random-effects OR and RR were 2.06 (95% CI: 1.65, 2.56) and 1.27 (95% CI: 1.18, 1.37). In sixteen studies (n=2,278) in which dexamethasone was compared with placebo or no treatment, the random-effects OR and RR were 2.04 (95% CI: 1.63, 2.56) and 1.29 (95% CI: 1.18, 1.40), respectively. There was no evidence of statistical heterogeneity.

In the summary estimates, dexamethasone increased the chance of no vomiting during the delayed phase by approximately 25 to 30%, and offered an additional 15 out of 100 patients a vomit-free delayed period.
In cumulative meta-analyses of studies ordered by increasing dexamethasone dosages, no obvious trend was seen; this indicated the lack of a strong dose-response relationship. The control rate meta-regressions showed no statistically-significant relationship between the treatment effects and the control rates of acute- or delayed-phase emesis.

Publication bias.

Inverse funnel plots of the acute and delayed data did not suggest strong evidence for publication bias, although in the case of acute-phase protection, the largest study showed a more conservative effect.

Authors' conclusions
Dexamethasone was clearly effective for protection against emesis both in the acute and delayed phases, with emesis avoided in one patient out of six treated. Future trials should determine whether the delayed-phase effect is independent of the acute-phase benefit.

CRD commentary
The authors reported clear inclusion criteria for the review. The literature search was comprehensive and included non-English language publications. In addition, the authors assessed publication bias. Details of the studies were well presented and the pooling included an assessment of heterogeneity. The authors discussed the study designs of the included studies within the text, but there was no formal assessment of study validity. The authors stated a priori that methodological quality would be explored in sensitivity analyses, but no details of this were reported in the paper.

On the whole, the authors' conclusions are supported by the data from the included studies, but should be considered with caution due the lack of weighting by study quality.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that future trials should determine whether the delayed-phase effect is independent of the acute-phase benefit.

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