General Anesthesia

Best evidence in anesthetic practice

Prevention: dimenhydrinate prevents postoperative nausea and vomiting

Article appraised

Kranke P, Morin AM, Roewer N, Eberhart LHJ. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand 2002; 46: 238–44.

Structured abstract

Question: In patients undergoing surgery, does prophylactic dimenhydrinate reduce the frequency of postoperative nausea and vomiting (PONV) compared to placebo?

Data sources: Studies were identified by computerized searches (MEDLINE, EMBASE, Cochrane Library) up to June 2001, citation review, and hand searches of locally available anesthesia journals. No language restrictions were applied.

Study selection: Studies were selected if they were randomized controlled trials comparing prophylactic dimenhydrinate or diphenhydramine to placebo.

Data extraction: Data was extracted in duplicate on postoperative nausea, postoperative vomiting, and PONV.

Main results: Eighteen trials with a total of 3,045 patients met the inclusion criteria. Compared to placebo, dimenhydrinate reduced the frequency of early (0–6 hr postoperatively) PONV (relative benefit [RB] 1.21; 95% confidence interval [CI] 1.07–1.21) and overall (0–48 hr postoperatively) PONV (RB 1.51; 95% CI 1.27–1.78; Table). Dimenhydrinate reduced overall PONV in subgroups of adults, children, and routes of administration (*iv/im* or *pr*).

Conclusion: Prophylactic dimenhydrinate reduces PONV up to 48 hr after surgery.

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Commentary by D.N. Buckley

Even an antiemetic drug with as long a pedigree as dimenhydrinate continues to present unanswered questions: does it in fact work, and what are its significant side

TABLE Effect of dimenhydrinate versus placebo on postoperative nausea and vomiting.

	Dimenhydrinate	*Placebo*	*Relative benefit (95% CI)*	*NNT (95% CI)*
All studies				
Early (0 – 6 hr)	523 / 813	479 / 884	1.21 (1.07 – 1.35)	8.3 (4.8 – 25.0)
Overall (0 – 48 hr)	750 / 1334	622 / 1604	1.51 (1.27 – 1.78)	5.0 (3.4 – 9.1)
Adults				
1 – 2 $mg \cdot kg^{-1}$ *iv / im*			1.20 (1.01 – 1.42)	14.3 (8.3 – 50.0)
> 1 dose given			1.55 (1.05 – 2.29)	4.8 (2.5 – 50.0)
Children				
0.5 – 2.2 $mg \cdot kg^{-1}$ *iv / im*			1.80 (1.31 – 2.47)	4.8 (2.6 – 33.3)
2 – 3 $mg \cdot kg^{-1}$ *pr*			1.71 (1.16 – 2.53)	3.6 (1.9 – 20.0)

CI = confidence interval; NNT = number-needed-treat.

effects? The systematic review by Kranke and colleagues[1] suggests that the broad answer to the first question is "yes", although the size and number of doses is still unclear. Based upon a subgroup of the studies reviewed, the dose identified for adults is approximately twice the dose that I have seen commonly administered.

I have some quarrel with the authors' decision to consider both dimenhydrinate and diphenhydramine as equivalent drugs: no evidence is presented to support the decision. In a paper with so much attention to the technique of systematic review, a crucial premise of drug equivalency is not supported in any way. Referring to both drugs under one name and submerging the fact of the decision by redefining the name "dimenhydrinate" to now include two drugs is also inappropriate. There is no information presented to permit the reader to evaluate the impact of this decision, since there is no identification of those articles that include one or the other of the two drugs.

My favourite aspect of the study of PONV, stratification of patient sample to tease apart physiological triggers of and thus identify specific therapies for PONV, is not addressed in this analysis.

The most important observation of the review is that the problem of side effects cannot be addressed from the literature reviewed. This is particularly relevant in light of the controversy surrounding droperidol, a drug with a long pedigree and demonstrable effectiveness as an anti-emetic, now withdrawn from use after reports of complications occurring in patients who had received the drug.[2]

I dispute strongly the authors' final statement that "serious side effects seem to be rare", as their own review establishes clearly that study results are not reported in a way to permit such a conclusion. This is probably the most important finding of the review. One of the underlying reasons is that combining underpowered studies will identify incorrectly rejected findings; Kranke *et al.* show that for eight of the 16 studies, the 95% CI for the relative benefit includes one,[1] suggesting that for those studies taken alone (without pooling of the studies), the relative benefit is statistically non-significant. We have no way of knowing how often side effects were incorrectly identified as insignificantly different.

Will this review change practice in perioperative PONV prophylaxis? Probably not. Is it a worthwhile review? Yes. The challenge to investigators and reviewers now is to ensure that studies report all relevant outcomes, especially side effects, in a way that will permit subsequent review.[3]

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Commentary by M.R. Tramèr

For decades, dimenhydrinate (diphenydramine) has been used by anesthesiologists for the prevention of PONV; thus, it may be useful to look at this drug a bit closer. The study by Kranke *et al.* shows nicely the strengths of a valid systematic review: it tells us what we know, and, as a consequence, what we do not know. Indeed, 18 randomized controlled trials with data from 3,045 patients provide strong evidence that dimenhydrinate is efficacious as a prophylactic antiemetic in the surgical setting. However, despite this large amount of data, there is still no reliable information on dose-responsiveness for both efficacy and harm, on optimal dose, and on the adverse effect profile. There are no data on cost-effectiveness. The efficacy of dimenhydrinate for the treatment of established postoperative sickness remains unknown. Finally, we do not know how this molecule performs when combined with other antiemetic drugs. This lack of information has not so much to do with the systematic review itself, but with the design and the quality of data reporting in the original trials. For obvious reasons, the quality of a systematic review cannot be better than the quality of the trials that are included in that systematic review. Trial quality, as estimated by the Oxford scale, was acceptable. However, there has never been a clinical trial program to define with confidence dimenhydrinate's degree of prophylactic and therapeutic efficacy and its likelihood of harm as, for instance, with some of the 5-HT_3 receptor antagonists. This may explain why such a variety of different regimens was tested in these trials. To give at least some pragmatic answers, data had to be pooled across routes of administration and across different doses. Thus, the main message of this systematic review is not so much clinical, since we still do not know very well how to use dimenhydrinate, at what dose, and in combination with what other antiemetic drugs. For instance, for 5-HT_3 receptor antagonists, D_2 antagonists (droperidol), and dexamethasone we know that it

is worthwhile to combine them in order to obtain an improved protection against postoperative nausea.[1,2] The role of dimenhydrinate for "balanced antiemesis"[3] remains to be shown. This paper provides an excellent basis for a rational research agenda.[4] Dimenhydrinate deserves further research; investigators who wish to design future studies with dimenhydrinate should read this systematic review first.

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