Postoperative nausea and vomiting (PONV) is a frequent source of patient distress as well as an expense for the institution. We cannot eliminate it at this time, but it is possible to lessen its incidence. Different anesthetic techniques are associated with different rates of occurrence. Various medications can raise or lower the incidence. In theory, this knowledge should lead to a rational strategy to minimize the occurrence of PONV.

At this time, there are literally dozens of studies examining various aspects of PONV prophylaxis. Taken together, they appear to establish that 1) there is a rationale for PONV prophylaxis in certain patients who receive anesthesia, that 2) it is possible to define this group with a reasonable degree of certainty, and that 3) consistent and rational PONV prophylaxis will simultaneously maximize both cost efficiency and patient satisfaction.

In reviewing this literature, please note the main results that underlie the therapeutic recommendations. The most important is that, no matter which drugs are chosen, the impact of any prophylactic drug regimen on PONV is slight. In fact, if you give prophylaxis randomly, the outcome will not be significantly different than if you had not given prophylaxis. It is only when you single out a group of patients more likely to have PONV than average that you begin to get results that are at least measurable. This should make it no surprise that, as prophylaxis, no drug is particularly effective. Finally, the serotonin antagonists have significant side effects and are far more effective at treating vomiting than preventing it. Determining their role in PONV requires a risk vs. benefit analysis.
Summary of Recommended Actions Consistent with Literature Based Evidence

1) Screen pre-op patients for PONV risk. Use these four factors in your screen: 1) Female, 2) Perioperative narcotic use, 3) Previous PONV, 4) Previous motion sickness. There are three groups of patients at risk:

   a) Those with any three factors
   b) Females who receive perioperative narcotics.
   c) Those with a history of previous PONV who receive perioperative narcotics.

2) Provide PONV prophylaxis to all patients who are at risk for PONV, consistent with indications and contraindications to the recommended drugs.

3) Use the following recommended drugs: A combination of one or more long acting agent (dexamethasone 4 mg IV, scopolamine transdermal patch) and one or more shorter acting agents (Metoclopramide 10-20 mg IV, ephedrine 35-50 mg IM).

4) Use serotonin antagonists (ondansetron [Zofran], granisetron [Kytril]) only after PONV starts and only after consideration of their side effects, because they are a much better treatment for PONV than a prophylactic. Treatment dosage for ondansetron appears to be 1-2 mg. IV. If a serotonin antagonist was given during surgery, do not give a repeat dosage in the PACU.

5) Tailor neostigmine dosages to clinical need at the time they are given.

6) Do not base a decision to use or not use nitrous oxide solely on concerns about PONV.
I. **Should you use PONV prophylaxis?**

**Issues:**
- Is PONV prophylaxis cost effective?
- Does it increase patient satisfaction?
- If it is worth giving, who should get it?
Cost-effectiveness of Prophylactic Antiemetic Therapy with Ondansetron, Droperidol, or Placebo


Background: In an era of growing economic constraints on healthcare delivery, anesthesiologists are increasingly expected to understand cost analysis and evaluate clinical practices. Postoperative nausea and vomiting (PONV) are distressing for patients and may increase costs in an ambulatory surgical unit. The authors compared the cost-effectiveness of four prophylactic intravenous regimens for PONV: 4 mg ondansetron, 0.625 mg droperidol, 1.25 mg droperidol, and placebo.

Methods: Adult surgical outpatients at high risk for PONV were studied. Study drugs were administered intravenously within 20 min of induction of nitrous oxide-isoflurane or enflurane anesthesia. A decision-tree analysis was used to group patients into 12 mutually exclusive subgroups based on treatment and outcome. Costs were calculated for the prevention and treatment of PONV. Cost-effectiveness analysis was performed for each group.

Results: Two thousand sixty-one patients were enrolled. Efficacy data for study drugs have been previously reported, and the database from that study was used for pharmacoeconomic analysis. The mean–median total cost per patient who received prophylactic treatment with 4 mg ondansetron, 0.625 mg droperidol, 1.25 mg droperidol, and placebo were $112 or $164.44, $109 or $0.63, $104 or $0.51, and $164 or $51.20, respectively ($P = 0.001, active treatment groups vs. placebo). The use of a prophylactic antiemetic agent significantly increased patient satisfaction ($P < 0.05$). Personnel costs in managing PONV and unexpected hospital admission constitute major cost components in our analysis. Exclusion of nursing labor costs from the calculation did not alter the overall conclusions regarding the relative costs of antiemetic therapy.

Conclusion: The use of prophylactic antiemetic therapy in high-risk ambulatory surgical patients was more effective in preventing PONV and achieved greater patient satisfaction at a lower cost compared with placebo. The use of 1.25 mg droperidol intravenously was associated with greater effectiveness, lower costs, and similar patient satisfaction compared with 0.625 mg droperidol intravenously and 4 mg ondansetron intravenously. (Key words: Ambulatory; anesthesia; emesis; nausea; postoperative.)

When personnel costs were excluded from the calculations, the total incremental median costs associated with the prophylactic use of 4 mg ondansetron, 0.625 mg droperidol, 1.25 mg droperidol, and placebo were $16.44, $0.51, $0.51, and $20.41, respectively.

Although the costs for drugs used by anesthesiologists account for a large share of total hospital drug expenditures, drug costs alone form a minor proportion of total patient costs. Therefore, it is important to assess the overall costs.

Nursing personnel costs constitute the major portion of the overall costs in all four groups.

Although there was no statistically significant difference in the time to home readiness among the groups, patients in the placebo group required more materials (i.e., basin, gloves, gown, linen, tissue paper) for management of PONV ($P = 0.001$) and more healthcare personnel (i.e., nursing, nurse anesthetists, anesthesiologist) time ($P = 0.001$).

The cost-effectiveness ratio of droperidol and ondansetron when used as antiemetic prophylaxis in patients at high risk of PONV is as follows: 1.25 mg droperidol > 0.625 mg droperidol > 4 mg ondansetron.

overall cost is higher in the placebo group compared with the treatment groups even when labor costs were excluded from the analysis.

The administration of a prophylactic antiemetic in day surgery patients at high risk for PONV was associated with greater effectiveness and increased patient satisfaction, which were achieved with a lower overall cost compared with placebo.
1) Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology 92:958-67, 2000. This single study establishes a rational basis for administering PONV prophylaxis, and also a compelling reason for doing so. Prophylaxis is unequivocally shown to increase patient satisfaction and decrease overall institutional costs 1) when it is given to patients more at risk than average for PONV, and 2) when giving it is compared with not giving it. Notice that not giving prophylaxis to the correct group of patients costs more than giving it to that group. Also note that patient satisfaction was equivalent for all treated groups.

The practical limitation of this study is that no method is given for identifying the group at high risk of developing PONV.
**Conclusion:** It is advantageous to the patient and to the institution to administer PONV prophylaxis. It should be used consistently in patients at risk for PONV.

II. **Can we predict which patients are at risk for PONV?**

**Issues:**
- Can we use a "risk factor" scoring system for predicting who is at risk for PONV?
- What are the limitations of such a system?
- What factors predict PONV?
- Is neostigmine a risk factor for PONV?
- Is nitrous oxide a risk factor for PONV?
What can be expected from risk scores for predicting postoperative nausea and vomiting?

Several risk scores have been developed to calculate the probability of postoperative nausea and vomiting (PONV). However, the power to discriminate which individual will suffer from PONV is still limited. Thus, we wondered how the number of predictors in a score affects the discriminating power and how the characteristics of a population—which is needed to measure the power of a score—may affect the results. For ethical reasons and to be independent from centre specific populations, we developed a computer model to simulate virtual populations. Four populations were created according to number, frequency, and odds ratio of predictors. Population I: parameters were derived from a previously published paper to verify whether calculated and reported values are in accordance. Population II: a gynaecological population was created to investigate the impact of the study setting. Populations III and IV: to meet ideal assumptions a model with up to seven predictors with an odds ratio of 2 and 3 was tested, respectively. The discriminating power of a risk score was measured by the area under a receiver operating characteristic curve (AUC) and an increase of more than 0.025 per predictor was considered to be clinically relevant. The AUC of population I was similar to those reported in clinical investigations (0.72). The study setting had a considerable impact on the discriminating power since the AUC decreased to 0.65 in a gynaecological setting. The AUC with the 'idealized' populations III and IV was at best in the range of 0.7–0.8. The inclusion of more than five predictors did not lead to a clinically relevant improvement. The currently available simplified risk scores (with four or five predictors) are useful both as a method to estimate individual risk of PONV and as a method for comparing groups of patients for antiemetic trials. They are also superior to single predictor models which are just using the patients' history of PONV or female gender alone. However, our analysis suggests that the power to discriminate which individual will suffer from PONV will remain imperfect, even when more predictors are considered.

Meta-analyses have shown that efficacy of prophylactic antiemetic strategies is limited and that the number-needed-to-treat (NNT) to prevent one patient from PONV is at best in the range of 5 when the basal event rate is high.

Thus, prophylactic antiemetics appear only justified in patients at increased risk for PONV.7 8

In the past, high-risk patients were intuitively classified by reference to the past medical history of PONV or the type of surgery. Recently, risk scores have provided an objective risk assessment for PONV.9–11

we created virtual populations to explore what can be expected from risk scores for predicting PONV by investigating how the number of risk factors and different study settings may affect their discriminating power.

The discriminating power of a score was measured by the area under the receiver operating characteristic (ROC) curve (AUC)

prediction with several risk factors is superior to a prediction with a single factor (e.g. female gender or the history of PONV)

it could be shown that female gender as the sole predictor already has an AUC of 0.64, but this can be improved to 0.72, when three additional predictors are considered

further inclusion of more than four or five risk factors does not lead to a clinically relevant increase in the discriminating power.

we recommend the use of one of the simplified multifactorial models70–11 for an individual risk assessment in daily practice.
2) What can be expected from risk scores for predicting postoperative nausea and vomiting? British Journal of Anaesthesia 86:822-7, 2001. Factors indicating an increased risk of PONV do exist. Using several risk factors more accurately predicts PONV than using one or two. However, the limit of accuracy is reached at four to five factors. This limitation means that using more factors does not make the prediction of PONV any more accurate. In practical terms, you can use 4-5 factors to accurately say that a person has a 60-70% chance of getting PONV; but there is no number of factors that lets you accurately say that someone has a 90-100% chance of getting PONV. This means that you can say someone is a member of a group at high risk for getting PONV, but you can never say that person will definitely get PONV.
Prediction of postoperative nausea and vomiting using a logistic regression model†


Summary
In a previous study, logistic regression analysis was used to determine the association of independent fixed patient factors with the incidence of postoperative nausea and vomiting (PONV). Female sex, previous history of PONV, use of postoperative opioids, previous history of motion sickness and an interaction between male sex and previous history of PONV were combined in an equation from which risk of PONV could be estimated. The present study was designed to test this equation in a group of patients with wide selection criteria. Data on 400 patients were collected in relation to pre-, per- and postoperative factors which may influence the incidence of PONV. The equation was used to predict PONV, and actual outcome was compared with that predicted. The overall incidence of PONV was 36%. The equation predicted an overall probability of PONV of 27.4%. If the model was used to define individual patients as predicted to have or not to have PONV, it was correct only 71% of the time. However, there was good agreement between the actual incidences of PONV and those predicted among the 16 risk groups created by the model. (Br. J. Anaesth. 1996; 76: 347–351)

Three factors were independent contributors to PONV. These were sex (odds ratio 2.9), previous emetic history (odds ratio 2.9) and opioid analgesics (odds ratio 3.7). All of these were highly statistically significant.

Summary of the Factors and the Risk

There are four risk factors:

1) Female
2) Periop Opioid Use
3) Previous PONV
4) Previous Motion Sickness

Any person with any three of these is at high risk for PONV.

Also at risk:
Any person getting periop opioids and who either:
1) is female, or
2) had previous PONV.
3) **Prediction of PONV using a logistic regression model.**

*British Journal of Anaesthesia* 76:347-51, 1996. There are four significant risk factors for getting PONV, as well as many more factors that do not predict risk. Notice the clinical confirmation of the limitations of the statistical model in the previous paper. In general, a high-risk individual is defined by having at least 3 of the following factors: female, previous PONV, administration of perioperative opioids, and a history of motion sickness. Perioperative opioids and either previous PONV or female sex also indicates a significant PONV risk.
Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review

We have estimated the effect of omitting antagonism of neuromuscular block on postoperative nausea and vomiting. A systematic search (MEDLINE, EMBASE, Biological Abstracts, Cochrane library, reference lists and hand searching; no language restriction, up to March 1998) was performed for relevant randomized controlled trials. In eight studies (1134 patients), antagonism with neostigmine or edrophonium was compared with spontaneous recovery after general anaesthesia with pancuronium, vecuronium, mivacurium or tubocurarine. On combining neostigmine data, there was no evidence of an antiemetic effect when it was omitted. However, the highest incidence of emesis with neostigmine 1.5 mg was lower than the lowest incidence of emesis with 2.5 mg. Numbers-needed-to-treat to prevent emesis by omitting neostigmine compared with using it were consistently negative with 1.5 mg, and consistently positive (3–6) with 2.5 mg. There was a lack of evidence for edrophonium. In two studies, three patients with spontaneous recovery after mivacurium or vecuronium needed rescue anticholinesterase drugs because of clinically relevant muscle weakness (number-needed-to-harm, 30). Omitting neostigmine may have a clinically relevant antiemetic effect when high doses are used. Omitting antagonism, however, introduces a non-negligible risk of residual paralysis even with short-acting neuromuscular blocking agents.


We searched systematically for relevant reports to test the evidence that antagonism of neuromuscular block at the end of surgery influences the incidence of PONV, and to evaluate the likelihood of harm when antagonism was omitted.

There was some evidence that in adults, antagonism of postoperative neuromuscular block with the highest dose of neostigmine (2.5 mg) may increase the risk of PONV. Lower doses of neostigmine either gave inconsistent results (2.0 mg) or even suggested an antiemetic effect (1.5 mg). In addition, the lowest reported incidence of PONV with the highest dose of neostigmine tested in these trials (2.5 mg) did not overlap with the highest incidence of PONV with the lowest dose of neostigmine (1.5 mg). The synthesis of these, although sparse, data may be regarded as evidence of dose-responsiveness. This could explain the confusion about antagonism of neuromuscular block and PONV.

In theory, different mechanisms could be responsible for an increased risk of PONV with the use of anticholinesterase drugs. In healthy volunteers, intrathecal neostigmine caused severe nausea and vomiting in a dose-dependent manner. A similar, dose-dependent emeogenic effect with intrathecal neostigmine was found in women undergoing Caesarean section.

The benefit of a particular intervention has to be balanced against its potential for harm. Thus the antiemetic benefit when omitting pharmacological antagonism of neuromuscular block has to be weighed against the risk of residual muscle paralysis because antagonism was omitted.

The number-needed-to-harm point estimate to produce one patient with clinically relevant muscle weakness by omitting neostigmine or edrophonium compared with giving these drugs was 30.

One in 30 patients undergoing surgery with neuromuscular block but not receiving an anticholinergic drug at the end of surgery will show clinically relevant muscle weakness in the immediate postoperative period because of prolonged neuromuscular block.

Residual muscle paralysis in the postoperative period is not a minor adverse event and should be regarded as potentially very harmful.
4) Omitting antagonism of neuromuscular block: Effect on PONV and risk of residual paralysis. A systematic review. British Journal of Anaesthesia 82:379-86, 1999. Neostigmine can be a fifth PONV risk factor in dosages greater than two mg. However, not using it can pose a measurable and significant risk of clinically relevant muscle weakness for the patient.
Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials

M. TRAMÈR, A. MOORE AND H. McQUAY

Summary
We have reviewed randomized controlled trials to assess the effectiveness and safety of anaesthetics which omitted nitrous oxide (N₂O) to prevent postoperative nausea and vomiting (PONV). Early and late PONV (6 and 48 h after operation, respectively), and adverse effects were evaluated using the numbers-needed-to-treat (NNT) method. In 24 reports with information on 2478 patients, the mean incidence of early and late vomiting with N₂O (control) was 17% and 30%, respectively. Omitting N₂O significantly reduced vomiting compared with a N₂O regimen; the combined NNT to prevent both early and late vomiting with a N₂O-free regimen was about 13 (95% confidence intervals (CI) 9, 30). The magnitude of the effect depended on the incidence of vomiting in controls. In studies with a baseline risk higher than the mean of all reports, the NNT to prevent both early and late vomiting with a N₂O-free anaesthetic was 5 (95% CI 4, 10). When the baseline risk was lower than the mean, omitting N₂O did not improve outcome. Omitting N₂O had no effect on complete control of emesis or nausea. The NNT for intraoperative awareness with a N₂O-free anaesthetic was 46 compared with anaesthetics where N₂O was used. This clinically important risk of major harm reduces the usefulness of omitting N₂O to prevent postoperative emesis. (Br. J. Anaesth. 1996; 76: 186–193)

Data from N₂O and PONV interactions are based on small studies and some showed statistically significant improvement with N₂O-free regimens [30, 31, 37, 46, 47] whereas large studies involving hundreds of patients did not show any difference.

The confusion about N₂O and PONV interactions may simply reflect general difficulty in interpreting the clinical significance of this meta-analysis overcome these problems by combining results from all relevant reports.

Statistical and clinical significance of the effect of N₂O-free anaesthetics on PONV were evaluated using odds ratio and number-needed-to-treat (NNT) methods.

Risk reduction was not useful as a predictor of the emesis-reducing effect of a N₂O-free anaesthetic. For early vomiting, the combined risk reduction with a N₂O-free anaesthetic was 27% in studies with a low baseline incidence of vomiting. However, the NNT method indicated that almost 60 patients would need to be treated with a N₂O-free anaesthetic in this setting for one to profit. For late vomiting the risk reduction with a N₂O-free anaesthetic in studies with a high baseline risk of vomiting was only slightly higher (35%) but this time only six patients needed to undergo a N₂O-free anaesthetic for one to profit.

Trials with a baseline risk lower than the mean of all trials showed no improvement in the N₂O-free groups over controls trials with a baseline risk higher than the mean showed statistically significant improvement of the N₂O-free regimens over control.

Omitting N₂O in general anaesthesia had no effect on the incidence of nausea or on complete emetic control; however, omitting N₂O from general anaesthetics decreases postoperative vomiting significantly but only if the baseline risk of vomiting is high.

An interaction between baseline risk of vomiting and N₂O was present consistently.
5) Omitting nitrous oxide in general anaesthesia: Meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. British Journal Anaesthesia 76:186-93, 1996. Nitrous oxide adds to the number of patients who have postoperative vomiting only if the baseline risk of vomiting is above average. The average risk groups experience no increase in PONV when nitrous oxide is used.
Conclusion: Using a 4 factor screen, the group of patients at higher than average risk for PONV can be identified. No greater number of factors need be used, and no individual can be predicted to have PONV with certainty. Under certain circumstances, both neostigmine and nitrous oxide can increase the incidence of PONV.

III. How should ondansetron (Zofran), a serotonin antagonist, be used in the management of PONV?

Issues: How effective is ondansetron at preventing PONV?
What dosage should be given?
What adverse effects accompany ondansetron?
How effective is ondansetron at treating PONV?
How effective is ondansetron when used for both prevention and treatment in the same patient?
Efficacy, Dose–Response, and Safety of Ondansetron in Prevention of Postoperative Nausea and Vomiting

A Quantitative Systematic Review of Randomized Placebo-controlled Trials


Objective: The authors reviewed efficacy and safety data for ondansetron for preventing postoperative nausea and vomiting (PONV).

Methods: Systematically searched, randomized, controlled trials (obtained through MEDLINE, EMBASE, Biological Abstracts, manufacturer's database, manual searching of journals, and article reference lists) were analyzed. Relevant endpoints were prevention of early PONV (within 6 h after surgery) and late PONV (within 48 h) and adverse effects. Relative benefit and number-needed-to-treat were calculated. The number-needed-to-treat indicated how many patients had to be exposed to ondansetron to prevent PONV in one of them who would have vomited or been nauseated had he or she received placebo.

Results: Fifty-three trials were found that had data from 7,177 patients receiving 24 different ondansetron regimens and from 5,712 controls receiving placebo or no treatment. Average early and late PONV incidences without ondansetron were 40% and 60%, respectively. There was a dose response for oral and intravenous ondansetron. Best number-needed-to-treat to prevent PONV with the best documented regimens was between 5 and 6. This was achieved with an intravenous dose of 8 mg and an oral dose of 16 mg. Antivomiting efficacy was consistently better than antinausea efficacy. Efficacy in children was poorly documented. Ondansetron significantly increased the risk for elevated liver enzymes (number-needed-to-harm was 31) and headache (number-needed-to-harm was 36).

Conclusions: If the risk of PONV is very high, for every 100 patients receiving an adequate dose of ondansetron 20 patients will not vomit who would have vomited had they received placebo. The antinausea effect is less pronounced. Of these 100, three will have elevated liver enzymes and three will have a headache who would not have had these adverse effects without the drug. (Key words: Antiemetics: ondansetron. Postoperative complications: nausea, vomiting. Statistics and epidemiology: systematic review; metaanalysis; number-needed-to-treat.)

Of 100 patients having surgery who receive an adequate prophylactic dose of ondansetron, 20 (number-needed-to-treat, 5) will not vomit in the postoperative period who would have done so had they received a placebo. This efficacy only relates to very high control-event rates; the incidence of PONV in placebo patients in these trials was on average 40% for early outcomes and 60% for late outcomes. These results, therefore, are only applicable to a high-risk setting. The effect on nausea was less pronounced with most effective doses, optimal doses for oral and intravenous routes were 16 mg and 8 mg, respectively.

Increasing the dose from 4 mg to 8 mg led to a decrease of more than 20% in the number-needed-to-treat (i.e., an improvement) for prevention of both nausea and vomiting. When the dose was further increased to 16 mg, no clinically relevant improvement was achieved.

Fixed Doses: Early Events (within 6 h)

Only the 4-mg dose achieved consistent and clinically relevant efficacy compared with placebo.

There is good evidence that of 100 patients receiving prophylactic ondansetron, 3 will have transiently elevated liver enzymes, and 3 will have a headache who would not have had these adverse effects without the drug. Risk of a headache with the lowest dose tested (i.e., 1 mg given intravenously) was lower than with the higher doses used. This may indicate that ondansetron-induced headache is dose dependent. For the other adverse effects, no such dose dependence could be established.

1 mg is as efficacious to treat established PONV as an eightfold higher dose (i.e., 8 mg) is to prevent PONV. This challenges the utility of prophylactic ondansetron when risk-benefit and cost-benefit arguments are considered.

The degree of prophylactic antinausea and antivomiting efficacy puts the most effective doses of ondansetron into the same category as using a propofol maintenance anesthetic, and the antivomiting efficacy is comparable with the effect of omitting nitrous oxide from a general anesthetic.¹⁴
6) Efficacy, dose-response, and safety of ondansetron in prevention of PONV.

Anesthesiology 87:1277-89, 1997. Prophylactic ondansetron will reduce PONV, but it's effect is not impressive compared to its ability to treat established PONV. If 100 postoperative patients who are going to have PONV are given ondansetron during surgery, 20 will be kept from vomiting, 3 will have headaches who would not have, and 3 more will have elevated liver enzymes who would not have. For PONV prevention, 8 mg is the overall most effective dose, although 4 mg is almost as good. The prophylactic antiemetic effect of ondansetron is comparable to using a propofol infusion or omitting nitrous oxide. On the other hand, ondansetron is much more efficient when treating established PONV. In established PONV, 1 mg of ondansetron has as good an effect as 8 mg. This plus the adverse effect profile for ondansetron is cause to question the logic of using it as a PONV prophylactic.
The most frequently reported clinical adverse events associated with Kytril (≤5%) in postoperative patients were pain, constipation, anemia, headache, fever, abdominal pain and elevated hepatic enzymes. The use of Kytril in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

This list of side effects is representative of all the 5-HT antagonists, including Zofran (ondansetron). Notice that the incidence is equal to or greater than 5%. If you did not know we were talking about Zofran, and someone asked if this was a medication you would give freely and without a second thought, could you really answer yes?
A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting

Martin R Tramer, R Andrew Moore, D John M Reynolds, Henry J McQuay

Abstract

Objectives: To test the evidence for a dose-response with ondansetron for treatment of postoperative nausea and vomiting and to establish whether differences in efficacy between doses are of clinical relevance.

Design: Quantitative systematic review of published randomised controlled trials.

Data sources: Seven trials from 1991 to January 1996 retrieved from a systematic literature search (Medline, reference lists, hand searching of anaesthetic journals, manufacturer’s database); no restriction on language.

Main outcome measures: Estimation of efficacy (incidence of complete control of further nausea and vomiting) by using odds ratios and the “number needed to treat” method for early (within 6 hours of administration) and late (within 24 hours) periods.

Results: Four placebo controlled trials with 1043 patients studied intravenous ondansetron 1 mg, 4 mg, or 8 mg. All doses were more efficacious than placebo in preventing further episodes of nausea or vomiting. For combined data, the point estimates for the number needed to treat were between 3.1 (8 mg) and 3.8 (1 mg) for early efficacy and between 4.1 (8 mg) and 4.8 (1 mg) for late efficacy, without significant differences between doses. No difference was found between ondansetron and droperidol in two trials with 129 patients or between ondansetron and metoclopramide in one trial with 80 patients.

Conclusions: Further nausea and vomiting could be prevented with ondansetron compared with placebo in 25% of patients who had nausea or vomiting (number needed to treat, about 4). There was no evidence of a clinically relevant dose-response between 1 mg and 8 mg or a difference between ondansetron and either droperidol or metoclopramide in a limited dataset. A false impression of ondansetron’s efficacy may arise because a quarter of all relevant published reports are duplicates, and reporting of study results is uncritical.

Ondansetron used as treatment for established postoperative nausea and vomiting was effective compared with placebo. About a quarter of treated patients were prevented from further nausea and vomiting with a dose of 1 mg, 4 mg, or 8 mg.

This quantitative analysis did, however, fail to show a significant dose-response for intravenous ondansetron between the 1 mg, 4 mg, and 8 mg tested.

For all three ondansetron doses, both for early and late observation periods, the 95% confidence intervals of the estimates of efficacy (odds ratio and number needed to treat) overlapped, indicating absence of any significant difference in anti-emetic efficacy between the three doses (table 1).

Two clinical messages emerge from this analysis. The first is that the number needed to treat for intravenous ondansetron compared with placebo to treat established postoperative nausea and vomiting is about 4. This means that 1 in 4 patients with nausea or vomiting treated with ondansetron will be prevented from further nausea and vomiting, who would otherwise have continued to have nausea or to vomit with placebo.

Postoperative nausea and vomiting seem to have many causes, and it is perhaps naive to think that an anti-emetic, working at one specific receptor, should be universally effective. Given this multiple causation, from patient related factors through to the effects of anaesthesia, surgery, and opioids, preventing further postoperative nausea and vomiting in a quarter of the patients may be the best that can be achieved currently.

Key messages

• All three tested doses of ondansetron were more efficacious than placebo. There was no evidence of a clinically relevant dose-response between 1 mg and 8 mg (number needed to treat to prevent further nausea or vomiting was about 4), or a difference between ondansetron and either droperidol or metoclopramide.

• Stopping further postoperative nausea and vomiting in 25% of the patients may be the best that can be achieved currently.

The average incidence of postoperative nausea and vomiting before randomisation (before treatment was given) was 36% (22-46%).

There was no significant difference between ondansetron and droperidol when results from the two trials using droperidol were combined. Neither was there a significant difference between ondansetron and metoclopramide in the one trial that investigated this comparison.

Systematic reviewers are at risk of failing to recognise duplicates of an original report. The danger is that unreco gnised duplicates will bias the estimates of an intervention’s efficacy. Two duplicates were published in journal supplements, and the quality of supplement reports may be lower than reports in the parent journals. Both supplement articles declared that intravenous ondansetron 4 mg was the optimal dose to treat postoperative nausea and vomiting, although there was no good evidence to support this. Subsequent uncritical repetitions underline the potential influence of such unchallenged assertions.
7) A qualitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting. Tramer MR, et al. BMJ, 314:1088-92, 1997. Ondansetron is effective as a treatment for PONV once it actually occurs. Of 100 postoperative patients who vomit, about 25 will stop. This number stays essentially the same whether 1mg, 4mg, or 8 mg is used.
Efficacy of Repeat Intravenous Dosing of Ondansetron in Controlling Postoperative Nausea and Vomiting: A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial


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Study Objectives: To compare repeat intravenous (IV) dosing of ondansetron 4 mg with placebo for the treatment of postoperative nausea and vomiting (PONV) in patients for whom prophylactic, preoperative ondansetron 4 mg IV was inadequate.

Design: Randomized, double-blind, placebo-controlled study.

Setting: Ten outpatient surgical centers in the United States.

Patients: 2,199 male and female ASA physical status I, II, and III patients ≥ 12 years old scheduled to undergo outpatient surgical procedures and receive nitrous oxide-based general anesthesia.

Interventions: Ondansetron 4 mg IV was administered to all patients before induction of general anesthesia. Patients who experienced PONV or requested antiemetic therapy within 2 hours after discontinuation of inhalant anesthesia were randomized (1:1) to either a repeat IV ondansetron 4 mg dose or placebo.

Measurements and Main Results: Of the 2,199 patients prophylactically treated with ondansetron 4 mg before anesthesia induction, 1,771 (80.5%) did not experience PONV or request antiemetic therapy during the 2 hours following discontinuation of anesthesia. Of the 428 patients who experienced PONV or requested antiemetic therapy during the same period, and were randomized to additional treatment (214 randomized to ondansetron, 214 randomized to placebo), the incidence of complete response (no emesis, no rescue medication, no study withdrawal) was similar for both ondansetron-randomized and placebo-randomized groups for the 2-hour (34% and 43%, respectively, p = 0.074) and 24-hour (28% and 32%, respectively, p = 0.342) postrandomization study periods. Repeat ondansetron dosing was not more effective than placebo in controlling either postoperative emesis or the severity/duration of postoperative nausea. The administration of an additional dose of ondansetron 4 mg postoperatively did not result in an increased incidence of adverse effects.

Conclusions: In patients for whom preoperative prophylaxis with ondansetron 4 mg IV is not successful, a repeat dose of ondansetron 4 mg IV in the postanesthesia care unit does not appear to offer additional control of PONV.

Ondansetron-randomized and placebo-randomized patients were similar with respect to the incidence of complete response rates both during the 2-hour PAGU observation period after randomization [34% (73/214) and 43% (92/214), respectively; p = 0.074] and the overall 24-hour study period [28% (59/214) and 32% (69/214), respectively; p = 0.342]

For those patients who experienced PONV and were randomized to treatment with ondansetron, the additional dose of ondansetron 4 mg after surgery (i.e., a total of 8 mg of ondansetron) did not lead to an increased incidence of adverse effects.

Interestingly, the 24-hour complete response rate for placebo-randomized patients was related to their history of motion sickness (40% for patients with no such history vs. 18% for patients with a positive history). In contrast, for ondansetron-randomized patients, complete response rate was not related to history of motion sickness (27% for patients with no such history vs. 28% for patients with such history).
Conclusion: Under the best of circumstances, giving prophylactic ondansetron to all high risk patients reduces their PACU vomiting rate from the untreated average base rate of 40% down to 32%. This holds for a dose of 8 mg, with the decrease being 1% or 2% less for a 4 mg dose. Also, to achieve the full 20% reduction, one must accept a 6% incidence of elevated liver enzymes and headaches as well as cautions on use related to abdominal surgery.

On the other hand, without prophylaxis, and using as little as 1 mg of ondansetron in the PACU, the 40% base rate can be decreased to 30%.

In summary, the use of high-dose/OR/prophylactic ondansetron, as opposed to low-dose/PACU/treatment ondansetron, increases the chance of adverse effect with no improvement in outcome. In addition, giving ondansetron in the OR should actually block its further use in the PACU. This is because drug exposure, and presumably side effect incidence, increases with the dual exposure with no increase in therapeutic response.

IV. Are drugs other than ondansetron useful in the management of PONV?

Issues: Which drugs have comparable effect? What is their dosage and the duration of their effect? Should they be used singly or in combination?
A Comparison of the Efficacy, Safety, and Patient Satisfaction of Ondansetron Versus Droperidol as Antiemetics for Elective Outpatient Surgical Procedures

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Two identical, randomized, double-blind, placebo-controlled studies enrolled 2061 adult surgical outpatients at high risk of postoperative nausea and vomiting (PONV) to compare IV ondansetron 4 mg with droperidol 0.625 mg and droperidol 1.25 mg for the prevention of PONV. The antiemetic drugs or placebo were administered IV 20 min before the induction of anesthesia with a barbiturate compound, followed by maintenance with N₂O/isoflurane/enflurane. Nausea, emetic episodes, adverse events, and patient satisfaction were analyzed for the 0 to 2 h and 0 to 24 h postoperative periods. In the 0 to 2 h postoperative period, there was a complete response (no emesis or rescue antiemetic) in 46% of subjects given placebo (P < 0.05 versus antiemetic groups), in 62% given ondansetron, in 63% given droperidol 0.625 mg, and in 69% given droperidol 1.25 mg (P < 0.05 versus ondansetron). In the 0 to 24 h postoperative period, there were no significant differences in complete response between the ondansetron and droperidol 0.625 mg or 1.25 mg groups; all groups remained superior to placebo. The proportion of patients without nausea during the 0 to 24 h postoperative period was greater in the antiemetic groups compared with the placebo group; however, droperidol 1.25 mg was more effective than ondansetron 4 mg or droperidol 0.625 mg (43% vs 29% or 29%, respectively). Headache incidence was higher in the ondansetron group compared with either droperidol group. Patient satisfaction scores did not differ significantly among antiemetic treatment groups, although all were superior to placebo. In conclusion, all antiemetic treatment regimens were superior to placebo for the prevention of PONV in the immediate postoperative period; however, droperidol 1.25 mg was more efficacious than ondansetron during the early recovery period (0-2 h). There were no significant differences between ondansetron and either droperidol dose for emesis prevention during the 0 to 24 h postoperative period. Implications: More than 2000 patients at high risk of postoperative nausea and vomiting were given either placebo, ondansetron 4 mg, or droperidol 0.625 mg or 1.25 mg IV before the administration of general anesthesia. After surgery, the incidence of nausea, vomiting, medication side effects, and patient satisfaction were evaluated for 24 h. Droperidol 0.625 or 1.25 mg IV compared favorably with ondansetron 4 mg IV for the prevention of postoperative nausea and vomiting after ambulatory surgery.

(Anesthesiology 1998;88:731–8)

The proportion of patients with no nausea for the 0 to 24 h period was significantly greater in the treatment groups than in the placebo group (P < 0.05)

Droperidol 1.25 mg IV was more effective in reducing the incidence of emesis in the first 2 hours postoperatively than either ondansetron 4 mg or droperidol 0.625 mg.

Droperidol 1.25 mg was also more effective than ondansetron 4 mg or droperidol 0.625 mg in reducing the incidence of nausea for the first 24 hours postoperatively.

Differences among the antiemetic treatment groups were no longer present 24 hours after surgery for all three antiemetic treatments were superior to placebo in terms of patient satisfaction with the control of PONV.

There was no increased incidence of adverse events in the droperidol groups compared with the ondansetron group.

There were no significant differences among the treatment groups with respect to the incidence of hypotension, sedation, or agitation/anxiety. Headache was the most frequent neurological complication and its incidence was significantly lower in the droperidol groups compared with the ondansetron group.

The fact that a significantly decreased number of patients in the droperidol 1.25 mg group required postoperative opioid analgesics may explain the decreased nausea experienced by these patients in the immediate postoperative period.

The proportion of patients to whom opioid analgesics were administered was significantly less in the droperidol 1.25 mg group (65%, P < 0.001) compared with the ondansetron group (73%) and the placebo group (75%). The proportion of patients to whom opioid analgesics were administered was also significantly less in the droperidol 0.625 mg group (69%, P < 0.05) compared with that in the placebo group.
9) A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. Fortney, et al, Anesthesia Analgesia, 86:731-738, 1998. Three IV drug regimens were given prophylactically to reduce PONV: Droperidol 1.25 mg, droperidol 0.625 mg, and ondansetron 4 mg. Droperidol 1.25 mg was the most effective in reducing emesis in the first two hours and nausea for the first 24 hours postop. All three regimens were better than placebo. The incidence of headache was significantly higher with ondansetron than with droperidol, but otherwise the incidence of adverse events was the same for both drugs. Specifically there was no difference in the incidence of sedation, anxiety, or hypotension. Opioid analgesics were needed by a smaller percentage of the droperidol patients than the ondansetron. This may or may not be related to the lower PONV incidence seen in the droperidol 1.25 mg group.
Comparative Efficacy and Safety of Ondansetron, Droperidol, and Metoclopramide for Preventing Postoperative Nausea and Vomiting: A Meta-Analysis

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Postoperative nausea and vomiting are important causes of morbidity after anesthesia and surgery. We performed a meta-analysis of published, randomized, controlled trials to determine the relative efficacy and safety of ondansetron, droperidol, and metoclopramide for the prevention of postoperative nausea and vomiting. We performed a literature search of English references using both the MEDLINE database and a manual search. Double-blinded, randomized, controlled trials comparing the efficiency of the prophylactic administration of ondansetron, droperidol, and/or metoclopramide therapy during general anesthesia were included. A total of 58 studies were identified, of which 4 were excluded for methodological concerns. For each comparison of drugs, a pooled odds ratio (OR) with a 95% CI was calculated using a random effects model. Ondansetron (pooled OR 0.43, 95% CI 0.31, 0.61; P < 0.001) and droperidol (pooled OR 0.68, 95% CI 0.54, 0.85; P < 0.001) were more effective than metoclopramide in preventing vomiting. Ondansetron was more effective than droperidol in preventing vomiting in children (pooled OR 0.49; P = 0.004), but they were equally effective in adults (pooled OR 0.87; P = 0.45). The overall risk of adverse effects was not different among drug combinations. We conclude that ondansetron and droperidol are more effective than metoclopramide in reducing postoperative vomiting.

Implications: We performed a systematic review of published, randomized, controlled trials to determine the relative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting. Ondansetron and droperidol were more effective than metoclopramide in reducing postoperative vomiting. The overall risk of adverse effects did not differ.

(Anesth Analg 1999;88:1370–9)

Excluding the five studies using droperidol 2.5 mg from the meta-analysis resulted in no difference in central nervous system side effects between droperidol and ondansetron or metoclopramide.

Two studies included in the meta-analysis used ultra-small-dose droperidol (e.g., 0.625 mg), which is effective, yet free of side effects (35,48). These results suggest that droperidol in small doses is highly effective in adults and has minimal side effects.

Ondansetron (pooled OR 0.70) tended to be more effective than metoclopramide in reducing postoperative nausea; however, this difference was not statistically significant (P = 0.125) (Table 1). Ondansetron was 57% more effective than metoclopramide in reducing postoperative vomiting.

Ondansetron and droperidol were equally effective in preventing postoperative nausea, but not in adults. There was also no difference in efficacy in the propofol induction subgroup.

Droperidol was 34% more effective than metoclopramide in reducing postoperative nausea and 32% more effective than metoclopramide in reducing postoperative vomiting.
10) Comparative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing PONV: A meta-analysis. Anesthesia Analgesia 88:1370-9, 1999. Droperidol and ondansetron are equally effective in preventing postoperative nausea and vomiting in adults. They are significantly more effective than metoclopramide. The overall risk of adverse effects was the same for all three, except for an increased risk of headache for ondansetron as opposed to droperidol. As long as droperidol is used in doses smaller than 2.5 mg, the CNS side effects of the three drugs are similar.
Dexamethasone for the Prevention of Postoperative Nausea and Vomiting: A Quantitative Systematic Review

Iris Henzi, MD, Bernhard Walder, MD, and Martin R. Tramer, MD, DPhil

The role of dexamethasone in the prevention of postoperative nausea and vomiting (PONV) is unclear. We reviewed efficacy and safety data of dexamethasone for prevention of PONV. A systematic search (MEDLINE, EMBASE, Cochrane Library, hand searching, bibliographies, all languages, up to April 1999) was done for full reports of randomized comparisons of dexamethasone with other antiemetics or placebo in surgical patients. Relevant end points were prevention of early PONV (0 to 6 h postoperatively), late PONV (0 to 24 h), and adverse effects. Data from 1,946 patients from 17 trials were analyzed: 598 received dexamethasone; 582 received ondansetron, granioterin, droperidol, metoclopramide, or perphenazine; 423 received a placebo; and 343 received a combination of dexamethasone with ondansetron or granioterin. With placebo, the incidence of early and late PONV was 35% and 50%, respectively. Sixteen different regimens of dexamethasone were tested, most frequently, 8 or 10 mg IV in adults, and 1 or 1.5 mg/kg IV in children. With these doses, the number needed to treat to prevent early and late vomiting compared with placebo in adults and children was 7.1 (95% CI 4.5 to 18), and 3.8 (2.9 to 5), respectively. In adults, the number needed to treat to prevent late nausea was 4.3 (2.3 to 26). The combination of dexamethasone with ondansetron or granioterin further decreased the risk of PONV; the number needed to treat to prevent late nausea and vomiting with the combined regimen compared with the 5-HT3 receptor antagonists alone was 7.7 (4.8 to 19) and 7.8 (4.1 to 66), respectively. There was a lack of data from comparisons with other antiemetics for sensible conclusions. There were no reports on dexamethasone-related adverse effects. Implications: When there is a high risk of postoperative nausea and vomiting, a single prophylactic dose of dexamethasone is antiemetic compared with placebo, without evidence of any clinically relevant toxicity in otherwise healthy patients. Late efficacy seems to be most pronounced. It is very likely that the best prophylaxis of postoperative nausea and vomiting currently available is achieved by combining dexamethasone with a 5-HT3 receptor antagonist. Optimal doses of this combination need to be identified.


A single prophylactic dose of dexamethasone is antiemetic compared with placebo without evidence of any clinically relevant toxicity in otherwise healthy patients.

Approximately four patients, adults or children, need to be treated with one prophylactic dose of dexamethasone for one not to vomit within 24 hours, who would have done so had they all received a placebo.

The most frequently used regimens of dexamethasone were 8 or 10 mg IV in adults, and 1 or 1.5 mg/kg IV in children.

Incidences of PONV during the two time periods (i.e., 0–6 h and 0–24 h) were used as indicators of "early" and "late" antiemetic efficacy, respectively. Late efficacy of dexamethasone was most pronounced. Dexamethasone’s late effect on nausea was similar to its late effect on vomiting.

There was evidence of an increased antiemetic effect when dexamethasone was added to a 5-HT3 receptor antagonist. A better antiemetic efficacy with the combination of dexamethasone with a small dose of ondansetron compared with a three times higher dose of ondansetron alone may support the hypothesis of an additive (but not a synergistic) antiemetic effect when dexamethasone and ondansetron are combined.

Adverse effects were rarely reported, and they were mainly related to 5-HT3 receptor antagonists (i.e., headache, constipation).

In patients without risk factors who received dexamethasone 20 mg per day for five days for the control of chemotherapy-induced emesis, there was no evidence of immunosuppression or dysfunction of the hypothalamic-pituitary-adrenal axis.

We still do not know if a single bolus dose of dexamethasone 8 or 10 mg (the most frequently used doses in these trials) is safe in patients at risk of corticosteroid-related adverse effects, nor do we know if a single dose of dexamethasone would suppress adrenal function in otherwise healthy patients or if this was clinically relevant (for instance, if it increased the risk of wound dehiscence or infection).
11) Dexamethasone for the prevention of PONV: A quantitative systematic review. AnesthesiaAnalgesia 90:186-94, 2000. Dexamethasone given as PONV prophylaxis is as efficacious as 8 mg of ondansetron. It is different in that its time to peak efficacy is several hours and its duration of action is up to 24 hours. Significant side effects were not reported. The issues of wound infection, wound dehiscence, and adrenal suppression were not addressed. It may be significant that the amounts used in these studies, 8-10 mg, are routinely used in ENT and oral surgery without encountering these complications.
Prospective randomized, double-blind comparative study of dexamethasone, ondansetron, and ondansetron plus dexamethasone as prophylactic antiemetic therapy in patients undergoing day-case gynaecological surgery

R. Thomas* and N. Jones

Dexamethasone alone and in combination with selective 5-hydroxytryptamine receptor antagonists is of benefit in the prophylaxis of post-operative nausea and vomiting. In this study, the effectiveness of such a combination in comparison to either drug alone is investigated in day case gynaecological surgery. A total of 177 patients were randomized to three treatment groups: dexamethasone 8 mg, ondansetron 4 mg, and dexamethasone 8 mg plus ondansetron 4 mg. The only significant difference between groups was seen in the first 3 h when failure of prophylaxis was more frequent in patients who had received dexamethasone alone (P=0.0085; Fisher’s exact probability test). Confidence interval analysis indicates a modest treatment effect for the combination and the decision whether to perform a larger study depends upon whether such an effect is clinically relevant.

Br J Anaesth 2001; 87: 588–92

Our study demonstrated a significant difference between the ondansetron/dexamethasone combination and either drug alone in the 0–3 h period. Although this difference failed to maintain significance overall (0–24 h), or during the 3–12 or 12–24 h periods, the 95% confidence intervals show a trend suggesting that the combination has some benefit over the individual drugs. This is probably a result of underpowering of our study for the size of the actual difference observed.

only in the first 3 h was failure of prophylaxis seen significantly less often in patients who had received a combination of ondansetron and dexamethasone than in those who had received dexamethasone alone.

Failure of prophylaxis during the first 3 h (0–3 h) after surgery was recorded in 22, 28.3, and 8.6% of patients who had received ondansetron, dexamethasone, and ondansetron/dexamethasone, respectively. The incidences during the next 9 h (3–12) were 30.5, 35, and 24.1%, respectively. The incidences during the following 12 h (12–24) were 13.5, 15, and 15.5%, respectively. The overall incidences for the 24 h post surgery were 42.4, 48.3, and 34.5%, respectively.
12) Prospective randomized, double-blind comparative study of dexamethasone, ondansetron, and ondansetron plus dexamethasone as prophylactic antiemetic therapy in patients undergoing day-case gynaecological surgery. British Journal Anaesthesia 87:588-92, 2001. The combination of ondansetron and dexamethasone was more effective than the individual drugs in the first three hours after surgery, but not thereafter. This suggests the two drugs given together have an additive effect. It also supports the addition of a rapid onset, short acting agent to the slower onset, longer acting dexamethasone.
The Use of Dexamethasone for Preventing Postoperative Nausea and Vomiting in Females Undergoing Thyroidectomy: A Dose-Ranging Study

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We sought to determine the minimum effective dose of dexamethasone in preventing postoperative nausea and vomiting in women undergoing thyroidectomy. Two hundred twenty-five women (n = 45 in each of five groups) undergoing thyroidectomy under general anesthesia were enrolled in this randomized, double-blinded, placebo-controlled study. Immediately after the induction of anesthesia, patients received IV dexamethasone at doses of 10 mg (D10), 5 mg (D5), 2.5 mg (D2.5), 1.25 mg (D1.25), or saline (S). We found that Groups D10 and D5 were significantly different from Group S in the total incidences of nausea and vomiting, more than four vomiting episodes, the proportions of patients requiring rescue antiemetics, and the incidences of complete responses. The differences between Groups D10 and D5 were not significant. Dexamethasone 2.5 mg reduced the total incidence of nausea and vomiting. Dexamethasone 1.25 mg was not effective. Dexamethasone 5 mg IV is the minimum effective dose in preventing postoperative nausea and vomiting in women undergoing thyroidectomy.

(Anesth Analg 2000;91:1404–7)

Among the currently used antiemetics, 5-HT₃ antagonists (e.g., ondansetron, granisetron) are effective, but their cost limits their widespread clinical application (1,4,9). Other antiemetics such as antihistamines (e.g., hydroxyzine), anticholinergics (e.g., scopolamine), and dopamine receptor antagonists (e.g., droperidol, metoclopramide) have undesirable side effects of excessive sedation, tachycardia, dry mouth, dysphoria, and extrapyramidal symptoms (1,4,9,10,15). Because a single dose of dexamethasone demonstrated a significant antiemetic effect without evident side effects (6–10), it is a valuable treatment for the prophylaxis of PONV.

dexamethasone 5 mg was as effective as dexamethasone 10 mg and was more effective than saline control for preventing PONV in women undergoing thyroidectomy. Dexamethasone 2.5 mg was partially effective and dexamethasone 1.25 mg was ineffective for this purpose. Dexamethasone 5 mg IV is suggested to be the minimum effective dose.
13) The use of dexamethasone for preventing postoperative nausea and vomiting in females undergoing thyroidectomy: A dose ranging study. Anesthesia Analgesia 91:1404-7, 2000. Dexamethasone is effective for PONV in a dose-related manner. It is fully effective at doses of 5 mg and above, and less than fully effective at doses of 2.5 mg and below.
Efficacy of Ephedrine in the Prevention of Postoperative Nausea and Vomiting


Although reported in the aerospace literature and anecdotally by anesthesiologists, the putative antiemetic effect of ephedrine remains unquantitated. We therefore prospectively studied ephedrine as an antiemetic agent in the perioperative setting in 97 patients undergoing general anesthesia for outpatient gynecologic laparoscopy. Patients were assigned in a double-blind randomized fashion to receive a standardized general anesthetic followed by an intramuscular dose of either ephedrine (0.5 mg/kg), droperidol (0.04 mg/kg), or saline before the conclusion of surgery. Nausea, retching, or vomiting, as well as the degree of sedation and discharge times, were assessed in the recovery room and for 24 h postoperatively. Ephedrine was found to have a significantly antiemetic effect (P < 0.05) when compared with placebo and an antiemetic effect similar to that of droperidol. Sedation scores were also significantly less in the ephedrine group than in both placebo and droperidol groups. Finally, variations in mean arterial blood pressure among the three groups were not statistically significant. We conclude that ephedrine is an effective antiemetic agent with minimal sedative side effects in patients undergoing outpatient laparoscopy.

Key Words: VOMITING, POSTOPERATIVE—ephedrine. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—ephedrine, antiemetic effects.

0.5 mg/kg IM ephedrine is an effective prophylactic antiemetic agent in patients having general anesthesia for outpatient laparoscopy.

 Ephedrine was as effective as droperidol, and both were significantly more effective than placebo in minimizing nausea and vomiting. Both the droperidol and ephedrine groups required significantly less antiemetic therapy in the immediate postoperative period. Patients who received ephedrine had significantly lower sedation scores than patients given either droperidol or saline (P < 0.01).

All patients received 2 μg/kg IV fentanyl as part of a balanced anesthetic technique and reversal of neuromuscular blockade with 0.07 mg/kg IV neostigmine and 0.01-0.02 mg/kg IV glycopyrrolate.

The prophylactic use of ephedrine as an antiemetic agent has been described for the prevention of motion sickness. It may be particularly indicated as prophylaxis in patients prone to motion sickness or for those in whom dizziness, nausea, and/or vomiting occur upon ambulation postoperatively.

Concerns about the prophylactic use of ephedrine in patients with hypertension or organic heart disease are valid; therefore, we avoided its use in such patients so as to minimize the risk of potential myocardial or cerebrovascular damage. In otherwise healthy patients the risks of prophylactic ephedrine appear to be minimal.
14) Efficacy of ephedrine in the prevention of PONV. Anesthesia Analgesia 72:58-61, 1991. Intramuscular ephedrine has prophylactic efficacy against PONV. The effect is significantly greater than placebo and similar to IM droperidol. Sedation scores were significantly lower with ephedrine than with either droperidol or placebo.
Intramuscular ephedrine reduces emesis during the first three hours after abdominal hysterectomy

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Background: We tested the hypothesis that intramuscularly administered ephedrine prevents postoperative nausea and vomiting. Ephedrine is cheap, and for this indication poorly documented.

Methods: One hundred and nine patients undergoing elective abdominal hysterectomy under general anaesthesia were studied in a randomized, double-blind placebo-controlled study. Ten minutes before the end of the procedure patients received either ephedrine 0.5 mg/kg i.m. or placebo. The patients were closely observed for 24 h for postoperative nausea or vomiting (PONV) and received a standardized two-step antiemetic treatment of i.v. metoclopramide 10 mg, supplemented with ondansetron 4 mg i.v. if needed.

Results: The ephedrine treated patients had significantly less nausea, retching and vomiting, and need of antiemetic rescue during the first 3 h postoperatively compared with the placebo patients. No difference between the groups was evident in the 3–24 h postoperative observation period. All the patients with PONV during 0–3 h experienced PONV in the 3–24 h period. Treatment or prophylaxis with one drug was less efficient than two or more drugs combined. No significant differences in hypotension, tachycardia or other side-effects between the groups were noted.

Conclusion: Ephedrine 0.5 mg/kg i.m. administered at the end of abdominal hysterectomy has a significant antiemetic effect during the first 3 h after administration with no evident side-effects.

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Key words: Ephedrine; vomiting, postoperative; nausea, postoperative; hysterectomy; antiemetic treatment, multimodality.


There were no significant differences between the groups in postoperative blood pressure, pain or pain medication. There was a nonsignificant tendency (P=0.1) for the ephedrine patients to be more awake during the first three postoperative hours. Because patients who are drowsy and sleep are less prone to report PONV than those who are more alert, the tendency of less drowsiness combined with less PONV may further support the antiemetic action of ephedrine.

It has been speculated whether the antiemetic action of ephedrine is purely an effect of minimizing hypotension postoperatively (8). In our study, however, we were not able to demonstrate any difference in postoperative blood pressure between the two groups, results seem to support the impression that ephedrine has a specific antiemetic effect on PONV, not just only by reducing the incidence of hypotension or the emesis provoked by patient movements.

The antiemetic effect of ephedrine on motion sickness has also been claimed to be the main effect in the postoperative period (1). This may be relevant as the patients are often wheeled through different parts of the hospital or mobilized to sitting or standing positions after minor day-surgery.
15) Intramuscular ephedrine reduces emesis during the first three hours after abdominal hysterectomy. ActaAnesthesiolScand 44:107-111, 2000. Intramuscular ephedrine was effective during the first three hours after surgery, but not later. There was no difference in pulse or blood pressure between IM ephedrine and placebo. The ephedrine patients were more awake during the first three hours.
The Efficacy and Safety of Transdermal Scopolamine for the Prevention of Postoperative Nausea and Vomiting: A Quantitative Systematic Review

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The role of scopolamine administered via transdermal therapeutic systems in the prevention of postoperative vomiting, nausea, and nausea and vomiting is unclear. We performed a systematic search for full reports of randomized comparisons of transdermal scopolamine with inactive control. Dichotomous data were extracted. In the meta-analysis, relative risks and numbers-needed-to-treat/harm were calculated with 95% confidence intervals (CI). In 23 trials, 979 patients received transdermal scopolamine, and 984 patients received placebo. Sensitivity analyses were performed using restricted data for truncated control event rates (40%–80%) and for large trials. With these data, the relative risks for postoperative vomiting (five reports), nausea (five reports), nausea and vomiting (eight reports), and rescue treatment (three reports) were 0.69 (95% CI, 0.58–0.82), 0.69 (95% CI, 0.54–0.87), 0.76 (95% CI, 0.66–0.88), and 0.68 (95% CI, 0.54–0.85), respectively. This means that of 100 patients who receive transdermal scopolamine, approximately 17 will not experience postoperative vomiting who would have done so had they all received a placebo. However, 18 of 100 patients will have visual disturbances, eight will report dry mouth, two will report dizziness, one will be classified as being agitated, and 1–13 patients who are prescribed transdermal scopolamine will not use it correctly. The timing of application does not alter efficacy.

(Anest Analg 2002;95:133–43)

Transdermal scopolamine significantly reduces the risk of suffering from emetic symptoms in the postoperative period (0–24 h).

of 100 patients having anesthesia for a surgical procedure who receive standardized transdermal scopolamine, 17 (NNT = 5.9) will not vomit in the postoperative period who would have done so had they all received a placebo.

With a NNT of five to seven for the prevention of emetic symptoms in a moderate to high-risk setting, these results do not seem reassuring. However, it should not be left unmentioned that efficacy data for ondansetron are in the same range.

Transdermal scopolamine significantly reduced the incidence of early emetic symptoms. (0–6 h)

Scopolamine’s antiemetic effect is associated with side effects, such as visual disturbances or dry mouth, which should be considered when scopolamine patches are prescribed.

of 100 patients who receive standardized transdermal scopolamine, 18 (NNH = 5.6) will have visual disturbances, eight patients will report a dry mouth (NNH = 12.5), two patients will report dizziness (NNH = 50.0), and one patient would be classified as being agitated (NNH = 100.1) who would not have reported these side effects had they all received a placebo.

of 100 patients receiving transdermal scopolamine, in approximately 1 to 13 patients it will not work properly because of problems associated with the correct use of the patch, assuming a best and worst case scenario.

it is our impression that, in trials on antiemetics, the fact that a sponsor is involved does more good than harm with respect to the reporting of side effects;

our approach does seem to provide a hint that trial size and baseline incidences are important in the efficacy evaluation, thus confirming previous results on this issue related to meta-analyses.
16) The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: A quantitative review. Anesthesia Analgesia 95:133-43, 2002. Transdermal scopolamine is as effective as ondansetron (Zofran) in preventing PONV. This is true throughout the 24-hour postoperative period. Neither the type of anesthesia (balanced, inhaled, or neuraxial) nor the timing of the application (night before, immediate pre-op, or intra-op) affected the efficacy. Incidence of side effects was about 15-20%.
**Conclusion**: Dexamethasone, droperidol, metoclopramide, IM ephedrine, and transdermal scopolamine are comparable to ondansetron for PONV prophylaxis. Dexamethasone and transdermal scopolamine have a relatively long duration of action and a longer time to onset than the other drugs. There is no contraindication currently known to multidrug prophylaxis, and there are indications that it is preferable to single drug therapy.

Droperidol may be unavailable due to FDA action.
Recommended actions for PONV prophylaxis:

Screen all patients for PONV risk.

If a patient is in the group at increased risk, provide two or more prophylactic drugs to which the patient has no contraindications. One of these should be dexamethasone 4 mg and/or a transdermal scopolamine patch. In addition, ephedrine 35-50 mg IM, and metoclopramide 10-20 mg IV should be considered.

Use a serotonin antagonist only to treat PONV as it occurs. If using ondansetron, give 1-2 mg IV.

Tailor neostigmine dosage to the clinical need at the time given.

Do not give too much weight to PONV risk when deciding whether or not to use nitrous oxide.

4.2
March 27, 2003