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Randomized, double-blind comparison of oral aprepitant alone compared with aprepitant and transdermal scopolamine for prevention of postoperative nausea and vomiting

M. S. Green*, P. Green, S. N. Malayaman, M. Hepler, L. J. Neubert and J. C. Horrow

Department of Anesthesiology, Drexel University College of Medicine, Hahnemann University Hospital, Philadelphia, PA, USA

* Corresponding author: Department of Anesthesiology and Perioperative Medicine, 245 North 15th Street, Mail Stop 310, Philadelphia, PA 19102, USA. E-mail: michael.green@drexelmed.edu

Editor's key points

- Postoperative nausea and vomiting (PONV) can be a challenging problem, especially in high-risk patients.
- Multimodal antiemetic therapies may provide a way to reduce PONV.
- This study examines the effects of combining oral aprepitant and transdermal scopolamine on PONV.
- There was no improvement in PONV nor increase in side-effects by combination therapy.
- Further research is needed in this area.

Background. Aprepitant blocks the emetic effects of substance P. Scopolamine antagonizes muscarinic type 1 and histamine type 1 receptors. This study compares monotherapy and multimodal therapy by looking at complete response, nausea, vomiting, and rescue medication in patients at high risk for postoperative nausea and vomiting (PONV) treated with oral aprepitant with or without scopolamine.

Methods. We enrolled 120 patients in this randomized, double-blind trial. Inclusion criteria were: >18 yr old, ASA I–III, two or more Apfel four-point risk factors, undergoing an elective surgical procedure with a high risk of PONV expected to last at least 60 min. The primary outcome variable was complete response, that is, no emesis and no rescue therapy from 0 to 24 h. The outcomes measured included the incidences of nausea, vomiting, their composite, and the need for rescue medication.

Results. The aprepitant alone and aprepitant with scopolamine did not differ in complete responses (63% *vs* 57%, $P=0.57$) or net clinical benefit (26% *vs* 19%, $P=0.38$). The number who did not experience PONV and who used rescue medication did not differ. The incidence of PONV in the post-anaesthesia care unit did not differ nor did the use of rescue medications.

Conclusions. This trial evaluating the effectiveness of aprepitant alone and in combination with scopolamine showed no difference between treatment groups. The primary objective, complete response, and secondary objectives, incidences of nausea, vomiting, their composite, and the need for rescue medication, all showed no statistical difference.

Keywords: autonomic agents, antiemetics; central nervous system agents, adjuvants anaesthesia; postoperative nausea and vomiting; receptors, neurokinin-1; tropanes, scopolamine

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Aprepitant, a selective antagonist of neurokinin-1 (NK-1) receptors, blocks the emetic effects of substance P.[1] NK-1 receptors are found on vagal afferents in the gastrointestinal tract and in the nucleus tractus solitarius in the brain. Aprepitant is equally as effective as in the prevention of postoperative nausea and rescue antiemetic use and has better control of vomiting at 24 and 48 h when compared with conventional therapies.[2]

Scopolamine antagonizes muscarinic type 1 and histamine type 1 receptors in the central nervous system, hypothalamus, and vomiting centre. The noradrenergic system is also suppressed resulting in a diminished response to vestibular stimulation.[3] A consensus panel from Society of Ambulatory Anesthesia recommended scopolamine as an effective therapeutic agent for postoperative nausea and vomiting (PONV).[4] Multimodal therapy with transdermal scopolamine (TDS) in combination with ondansetron (OND) has been show to be superior to monotherapy with OND alone with no difference in the incidence of anticholinergic-related side-effects.[5]

PONV risk in adults undergoing general anaesthesia with inhalation anaesthetic agents can be predicted by four factors: female sex, history of PONV or motion sickness, non-smoking status, and the use of postoperative opioids. The frequency of PONV is 10% with zero, 21% with one, 39% with two, 61% with three, and 79% with four risk factors.[6 7]

The primary objective of this study was to test the hypothesis that in patients with high risk for PONV, the use of

aprepitant alone is as effective at producing a complete antiemetic response (no emesis and no rescue therapy from 0 to 24 h) compared with aprepitant and TDS in combination in the first 24 h after operation. Secondary objectives included the incidences of nausea, vomiting, their composite, and the need for rescue medication.

Methods

After approval from the institutional review board, all patients provided written informed consent for this randomized, double-blind trial (clinicaltrials.gov registry # NCT00717054). Study inclusion criteria consisted of age at least 18 yr, ASA physical status I–III, elective high-risk PONV surgery expected to last at least 60 min requiring general anaesthesia, and two or more Apfel four-point risk factors for PONV. Exclusion criteria consisted of pregnant or breast-feeding patients, those treated with antiemetic medications within 24 h of their procedure, history of vomiting from identified non-surgical causes, and possession of an allergy or other contraindication to study medications. Patients having ambulatory surgical procedures and patients requiring admission were included.

A computer-generated process randomly assigned subjects using a sealed envelope technique to either the oral aprepitant or the combined treatment group. Each subject received a transdermal patch and an aprepitant 40 mg pill. Patients ingested the pill and a study investigator applied the transdermal patch over the mastoid area, at least 1 h before anaesthesia induction. Depending on the assigned group, the transdermal patch was either a placebo or active medication. All clinicians were blinded to the assigned group.

Premedication with i.v. midazolam, 1–2 mg, preceded transfer to the operating suite. Propofol 2–3 mg kg^{-1} induced general anaesthesia. Tracheal intubation, facilitated by rocuronium 0.6–1.2 mg kg^{-1} or placement of a laryngeal mask airway established ventilation. Volatile anaesthetics (sevoflurane, desflurane, or isoflurane) maintained general anaesthesia. Clinical judgement guided titration of volatile anaesthetic concentrations. Fentanyl boluses of 0.5–2.0 μg kg^{-1} provided analgesia. Neostigmine 70 μg kg^{-1} and glycopyrronium 10 μg kg^{-1} provided reversal from neuromuscular block if necessary. Nitrous oxide was prohibited.

In the post-anaesthesia care unit (PACU), patients received supplemental oxygen via a nasal cannula. According to the clinical judgement of the anaesthesiologist, fentanyl boluses of 0.5–2.0 μg kg^{-1} and morphine boluses of 50 μg kg^{-1} controlled postoperative pain. As rescue medication, OND 4 mg i.v. treated postoperative emesis or nausea if symptoms lasted longer than 15 min or if the patient requested treatment. Anaesthesiologists' discretion guided further necessary treatment. Oral administration of OND 4 mg and metoclopramide 10 mg provided post-discharge nausea and vomiting treatment. TDS or placebo remained in place for 24 h from PACU arrival time. Study investigators removed the patch for admitted patients during 24 h postoperative follow-up visits. Discharged patients received written instructions for the correct timing of patch removal and received a follow-up phone call by study investigators at 24 h.

The primary outcome variable was complete response, that is, no emesis and no rescue therapy from 0 to 24 h. Other outcomes measured included the incidences of nausea, vomiting, their composite, and the need for rescue medication. Trained investigators blinded to the treatment group collected nausea and vomiting information at PACU admission and every 15 min for 1 h, at 2 h, and again at 24 h after operation. The time from PACU admission until achieving a modified Aldrete score of 9, assessed every 15 min, determined the duration of PACU stay. For those patients admitted to the hospital, the investigator collected data on nausea, vomiting, rescue medication use, and side-effects in the hospital at 24 h. For discharged patients, telephone contact at 24 h assessed nausea, vomiting, or both, use of rescue medication, and other listed side-effects after discharge. The patients were asked to rate their nausea on a 0–10 point scale, with 0 being no nausea and 10 being severe nausea. Data on side-effects specifically queried visual disturbances, dry mouth, dizziness, and agitation, and then asked for additional volunteered symptoms.

Statistical analysis plan

The two pivotal trials establishing the efficacy of aprepitant for PONV prophylaxis demonstrated a 63.8% and 44.8% complete response, respectively, with mean 54%.[8] Scopolamine alone also yields a complete response of 54%.[9] Based on an expected incidence of 54% for the primary outcome variable complete response in the aprepitant-alone-treated group, with a two-sided type I error of 5% and type II error of 80%, each group needed to collect valid data on 54 patients to demonstrate a minimally detectable increase of 1.5-fold the 54% individual rates, to 81% absolute complete response, with combined therapy.[10] Assuming a dropout rate of 10%, each group needed to enrol 60 patients to obtain 54 with valid data.

We pre-specified the net clinical benefit of aprepitant compared with combined therapy as the fraction of patients free of the composite outcome of nausea, vomiting, visual disturbances, dry mouth, dizziness, or agitation. The primary outcome variable was complete response, that is, no emesis and no rescue therapy from 0 to 24 h.

Student's *t*-test was used to compare continuous patient characteristic variables of the groups, while the Fisher exact test compares frequency data and outcome variable incidences. All comparisons utilize a two-sided 5% significance level. Standard formulae provide relative risk reduction and number needed to treat for outcome variables and for the net clinical benefit.

Results

Of 120 patients randomized, 119 received study medications and 115 completed the trial. Figure 1 illustrates the patient