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

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**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 monotherapy to prevent postoperative nausea

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 \(\mu\)g kg\(^{-1}\) provided analgesia. Neostigmine 70 \(\mu\)g kg\(^{-1}\) and glycopyrronium 10 \(\mu\)g 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 \(\mu\)g kg\(^{-1}\) and morphine boluses of 50 \(\mu\)g 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...
screening and random assignment process. Prior participation in the study excluded one randomized subject before medication administration. The use of a neuraxial anaesthesia technique after medication administration excluded three patients. One patient had surgery postponed due to an upper respiratory tract infection after medication administration. The safety analysis set included 119 patients and the efficacy analysis set included 115 patients with outcome data. The two treatment groups did not differ with regard to patient characteristic variables, including number and type of risk factors, and clinical characteristics (Table 1). The type of surgical procedures did not differ between groups.

**Efficacy**

The aprepitant alone group and the aprepitant with scopolamine group did not differ in complete response (63% vs 57%, \( P=0.57 \)) or net clinical benefit (26% vs 19%, \( P=0.38 \); Table 2). The total number of patients who did not experience PONV (51% vs 41%, \( P=0.35 \)) and the number of patients who utilized rescue medication (37% vs 40%, \( P=0.84 \)) did not differ between the monotherapy and two drug therapy groups. The incidence of PONV in the PACU did not differ between two groups (68% vs 60%, \( P=0.44 \)) nor did the use of rescue medications in the PACU (19% vs 28%, \( P=0.38 \)). The total incidence of vomiting did not differ between the two treatment groups (3.5% vs 8.6%, \( P=0.44 \)). There was no difference between the groups in the incidence of home nausea, home vomiting, or home rescue medication (Table 2). The incidence of nausea, vomiting, and the number of patients receiving rescue medication did not differ at any given time point during data collection (Table 3).

As expected, the incidence of PONV increased with increasing number of risk factors (\( P=0.0017 \)). Likewise, the complete response rate declined with the increasing number of risk factors (\( P=0.0011 \)): for two or three risk factors, a complete response occurred in 77% and 71% of the patients, respectively; four risk factors cut this response to 39% (Table 4).

The overall incidence of all adverse events did not differ between treatment groups (21% vs 26%, \( P=0.48 \)). Nor did the overall incidence of the anticholinergic side-effects dry mouth, blurry vision, dizziness, and agitation differ between treatment groups (\( P=0.54 \); Table 5). Additional side-effects included three people experiencing difficult urination, three people experiencing dyspepsia, two people affected by memory loss, two people with itching at the site of transdermal patch application, one person with constipation, and one person with throat pain.

**Discussion**

When aprepitant was ingested orally at least 1 h before induction of anaesthesia, the result was as effective as treating
with both oral aprepitant and TDS at least 1 h before induction of anaesthesia. The primary outcome variable, complete response, defined as no emesis and no rescue therapy from 0 to 24 h, showed no statistically significant difference between treatment groups. The use of rescue medication and the need for unplanned hospital admission did not differ between the monotherapy and combination therapy groups. The two patient populations did not differ with respect to patient characteristic variables, ASA classification, clinical variables, the specific type of procedures performed, or their PONV risk factor profiles.

Aprepitant, an NK-1 antagonist, works both peripherally and centrally to prevent PONV. Stimulation from peripheral and central afferents, through the lateral reticular formation, yields the sequence of events within the medulla oblongata to produce vomiting. Inputs from the vestibular system, higher cortical centres, the cerebellum, glossopharyngeal nerve stimulation, and vagal afferents can produce central vomiting activation. The NK-1 receptors are located in the area postrema, the central pattern generator for vomiting and/or afferent relay station, and nucleus tractus solitarius. These areas play important roles in emesis via these receptors.

Aprepitant has proven efficacy in the prevention of PONV. Habib and colleagues found the combination of aprepitant and dexamethasone to be more effective than the combination of OND and dexamethasone for prophylaxis against PONV in adult patients undergoing craniotomy. However, no difference occurred between the groups in the incidence or severity of nausea alone, the need for rescue antiemetics, or in complete response. In 805 patients receiving general anaesthesia for open abdominal surgery, aprepitant monotherapy was superior to OND monotherapy for the prevention of vomiting in the first 24 and 48 h, but no different for nausea control, use of rescue therapy, or complete response. Diermunsch and colleagues found aprepitant monotherapy to be non-inferior to OND for achieving complete response for 24 h after surgery in 922 patients undergoing open abdominal surgery. It was also more effective than OND for preventing vomiting 24 and 48 h after surgery and in reducing nausea severity in the first 48 h after surgery.

The efficacy of TDS in the prevention of PONV is well established.
prevention of PONV in combination with other therapies. Gan and colleagues concluded that TDS in combination with OND reduced PONV compared with OND alone after outpatient surgery and was associated with greater patient satisfaction. Sah and colleagues studied high-risk patients undergoing outpatient plastic surgery. OND + TDS provided a significant reduction in postoperative nausea between 8 and 24 h compared with OND alone. Lee and colleagues used TDS and dexamethasone for the prevention of PONV in patients with epidural patient-controlled analgesia after major orthopaedic surgery. That combination more effectively prevented PONV than dexamethasone alone or than dexamethasone plus ramosetron.

The TDS delivery system allows constant uptake of medication through the skin for 72 h. This slow release provides a more constant medication level, thus minimizing medication-related anticholinergic side-effects. This current study supports this premise because no significant statistical difference in anticholinergic side-effects between the two groups was found. This is in contrast to a meta-analysis done by Kranke and colleagues. In their review of 23 randomized, controlled trials published between 1984 and 1996, they found for every 100 patients who receive TDS, ~17 will not experience postoperative vomiting. However, 18 of 100 patients will have visual disturbances, 8 dry mouth, 2 dizziness, and 1 agitation. In another meta-analysis completed by Apfel and colleagues including 25 randomized controlled trials and 3298 patients, TDS proved to be valuable in the prevention of both early and late PONV during the first 24 h after the start of anaesthesia. In this meta-analysis, TDS was associated with a higher incidence of visual disturbances at 24–48 h but no other adverse events, compared with placebo. Gan and colleagues studied 618 patients in two groups. The incidence of anticholinergic side-effects between the group that received TDS and those who did not were not different. Our current study found similar results with regard to anticholinergic side-effects.

Multimodal therapy for the prevention of PONV is a widely accepted treatment approach. In 2004, Apfel and colleagues published a large multicentre study of more than 5000 patients showing each intervention to act independently while decreasing the incidence of PONV by 25–30% in an additive manner but not synergistic. Other studies have drawn similar conclusions. Singla and colleagues studied multimodal therapy using the NK-1 receptor antagonist casopitant in over 700 patients with a history of PONV or motion sickness undergoing a laparoscopic or laparotomic gynaecological surgical procedure or laparoscopic cholecystectomy with general anaesthesia. Compared with OND monotherapy, casopitant and OND provided superior

### Table 3: Incidence of nausea, vomiting, and antiemetic treatment at different time points.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprepitant alone, N = 57</th>
<th>Per cent</th>
<th>Aprepitant and scopolamine, N = 58</th>
<th>Per cent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, t=0</td>
<td>10</td>
<td>18</td>
<td>12</td>
<td>21</td>
<td>0.81</td>
</tr>
<tr>
<td>Vomiting, t=0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3.5</td>
<td>0.50</td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>2</td>
<td>3.5</td>
<td>5</td>
<td>8.6</td>
<td>0.44</td>
</tr>
<tr>
<td>Nausea, t=15 min</td>
<td>12</td>
<td>21</td>
<td>14</td>
<td>24</td>
<td>0.82</td>
</tr>
<tr>
<td>Vomiting, t=15 min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>1</td>
<td>1.8</td>
<td>3</td>
<td>5.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Nausea, t=30 min</td>
<td>11</td>
<td>19</td>
<td>13</td>
<td>22</td>
<td>0.82</td>
</tr>
<tr>
<td>Vomiting, t=30 min</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>5</td>
<td>8.6</td>
<td>2</td>
<td>3.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Nausea, t=45 min</td>
<td>11</td>
<td>19</td>
<td>12</td>
<td>21</td>
<td>1.00</td>
</tr>
<tr>
<td>Vomiting, t=45 min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>2</td>
<td>3.5</td>
<td>3</td>
<td>5.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Nausea, t=60 min</td>
<td>12</td>
<td>21</td>
<td>14</td>
<td>24</td>
<td>0.82</td>
</tr>
<tr>
<td>Vomiting, t=60 min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>3</td>
<td>5.3</td>
<td>7</td>
<td>12.1</td>
<td>0.60</td>
</tr>
<tr>
<td>Nausea, t=2 h</td>
<td>2</td>
<td>3.5</td>
<td>4</td>
<td>6.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Vomiting, t=2 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rescue antiemetic</td>
<td>2</td>
<td>3.5</td>
<td>2</td>
<td>3.4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### Table 4: Number of risk factors and the incidence of postoperative nausea and vomiting and complete response.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Number</th>
<th>Postoperative nausea and vomiting (%)</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>26</td>
<td>8 (31)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>27 (53)</td>
<td>36 (71)</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>27 (71)</td>
<td>15 (39)</td>
</tr>
</tbody>
</table>
emesis prevention during the first 24 h after operation, thus supporting multimodal therapy while using NK-1 receptor antagonists.20 Our study found that two drug therapy did not prove more efficacious in the prevention of PONV. Several factors might explain the different outcomes: inherent differences between the two NK-1 receptor antagonists, different second therapies, OND and TDS, different data collection, surgical procedures, or opioid administration. Different study designs may have contributed. The time of administration, both medications take prolonged periods of time to reach maximal effect, may have contributed to lack of difference. A trend towards a relative risk reduction in PONV did exist when comparing the two groups. The current study may have been underpowered to show a significant difference. The combination of two long-acting medications, TDS and aprepitant, may be a poor choice of combination therapy. A quicker onset shorter acting medication might complement aprepitant better.

In summary, this randomized, double-blind trial evaluating the effectiveness of aprepitant alone and in combination with TDS for the prevention of PONV 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. The results of this study question the combination of aprepitant and TDS for prophylaxis of PONV.

**Funding**

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**Declaration of interest**

The concept of the project was originated by M.S.G., DO, who served as the Principal Investigator. Merck & Co. reviewed the protocol before issuing any funding. Funds received paid for medications administered, research personnel, pharmacy administrative fees, Western IRB fees, and statistical analysis. Merck & Co. had no involvement in the analysis of the data or the preparation of the manuscript. The manuscript was reviewed and approved by Merck & Co. before submission with no changes made. M.S.G. has received a small project grant from Merck & Co. for the completion of this research project. P.G.’s husband has received a small project grant from Merck & Co. for the completion of this research project.

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