CHAPTER 6

MANAGEMENT OF POSTOPERATIVE NAUSEA AND VOMITING

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Postoperative nausea and vomiting (PONV) are two of the most common and unpleasant side effects after anesthesia and surgery. The overall incidence of PONV has decreased from 60% when ether and cyclopropane were used to approximately 30% nowadays. However, in certain high-risk patients, the incidence remains as high as 70%. It is estimated that one episode of vomiting prolongs postanesthesia care unit stay by approximately 25 minutes. Furthermore, it is estimated that approximately 0.2% of ambulatory patients may experience intractable PONV, which will sometimes lead to an unanticipated hospital admission, greatly increasing medical costs and reducing patient’s satisfaction. The estimated cost of PONV to a busy ambulatory surgical unit was estimated to range from $0.25 million to $1.5 million per year in lost surgical revenue.

Several studies suggest that patients rank the absence of PONV as more important than an earlier discharge from an ambulatory surgical unit. In one survey, patients claimed that they would be willing to pay up to U.S. $100 of their own money for a completely effective antiemetic.

This Refresher Course discusses the pathophysiology and risk factors of PONV, the use of novel and multimodal approaches to prevent or treat the problem, and the cost-effectiveness of PONV management. Finally, specific recommendations for the prophylaxis and treatment of PONV are provided.

Pathophysiology of Postoperative Nausea and Vomiting

The complex act of vomiting involves coordination of the respiratory, gastrointestinal, and abdominal musculature. It is controlled by the vomiting center, which is located in the lateral reticular formation of the medulla oblongata in close proximity to the nucleus of the solitary tract in the brainstem and has access to the motor pathways that are responsible for the visceral and somatic output involved in vomiting. The vomiting reflex has two main detectors of the need to vomit: the gastrointestinal tract and the chemoreceptor trigger zone in the area postrema. The vagus is the major nerve involved in the detection of emetic stimuli from the gastrointestinal tract and has two types of afferent fibers involved in the emetic response: mechanoreceptors, located in the muscular wall of the gut that are activated by contraction and distension of the gut and chemoreceptors, located in the mucosa of the upper gut, that are sensitive to noxious chemicals. Stimulation of the vagal afferents leads to activation of the chemoreceptor trigger zone in the area postrema. The latter is located on the dorsal surface of the medulla oblongata at the...
caudal end of the fourth ventricle and is outside the blood-brain barrier and the cerebrospinal fluid barrier. Thus, the chemoreceptor trigger zone can be activated by chemical stimuli received through the blood and the cerebrospinal fluid \textsuperscript{7-9} (Fig. 1).

Multiple receptors are involved in the transmission of impulses to the vomiting center. Cholinergic receptors are found in the vomiting center and vestibular nuclei. The area postrema is rich in dopamine, opioid and serotonin (5HT\textsubscript{3}) receptors. The nucleus tractus solitarius is rich in enkephalins and in histaminic, muscarinic cholinergic and NK-1 receptors, the latter are also found in the dorsal motor nucleus of the vagus nerve \textsuperscript{10} (Fig. 2).

\textbf{Fig. 1.} Neuroanatomy associated with postoperative nausea and vomiting with a focus on gastrointestinal (GI) enterochromaffin cells, hindbrain medulla, and dorsal vagal complex. \textit{NTS} = nucleus tractus solitarius. Reprinted with permission from Gan \textit{et al.}\textsuperscript{10}
Identification of patients at increased risk for PONV enables targeting prophylaxis to those who will benefit most from it. PONV prophylaxis is not appropriate for all patients; with current agents, the practice would not be cost-effective, would be unlikely to benefit patients at low risk for PONV, and would put such patients at risk for the potential side effects of antiemetic agents. Patient-, anesthesia-, and surgery-related risk factors have been identified. Anesthesia-related risk factors include the use of volatile agents, nitrous oxide (which increases the risk for postoperative vomiting), opioids, and increased doses of neostigmine for the reversal of neuromuscular blockade. Patient-related factors include female sex, history of PONV or motion sickness, and nonsmoking status. Increased levels of anxiety and postoperative pain, especially of pelvic or visceral origin, may also be associated with a greater incidence of PONV.

Conversely, there are many factors that are clearly unrelated to PONV. A recent systematic review confirms that the phase of the menstrual cycle has no impact on the occurrence of PONV. An increased body mass index is not a risk factor for PONV. Longer surgical procedures (each 30-minute increase in duration increases PONV risk by approximately 60% from baseline) and certain types of surgery also carry a greater risk of PONV. In adults, greater incidences of PONV are found after “open” gastrointestinal surgery, major gynecologic surgery, laparoscopic surgery, breast surgery, craniotomy, or eye and otorhinolaryngologic surgery. Pediatric surgical diagnoses and operations associated with greater risk for PONV include strabismus, adenotonsillectomy, hernia, orchidopexy, penile surgery, and middle ear procedures. However, despite these reported associations, an association between the type of surgery and the risk of PONV was not apparent in a prospective validation study. The incidence of PONV increases after the age of 3
years with a peak incidence of approximately 40% in the 11- to 14-year age group.\textsuperscript{13,27,28} Before puberty, sex differences for postoperative vomiting have not been identified.\textsuperscript{29}

A number of PONV risk scoring systems have been developed. Apfel \textit{et al.}\textsuperscript{13} developed a simplified risk score consisting of four predictors: female sex, history of motion sickness or PONV, nonsmoking status, and the use of opioids for postoperative analgesia. Figures 3 and 4 represent risk factors for adults and children, respectively.

\section*{Reduction of Baseline Risks}

There are several effective strategies that can be easily used to reduce the baseline risk for PONV. Adequate hydration is simple and inexpensive and has been shown to reduce the incidence of PONV.\textsuperscript{30} Liberal fluid regimen (median volume = 4.2 l) is associated with a lower incidence of vomiting and improved pulmonary function in patients undergoing knee arthroplasty compared with restricted fluid regimen (median volume = 1.7 l).\textsuperscript{31} Although previous studies suggest a protective effect of increased inspired concentrations of oxygen, a recent meta-analysis concluded that 80% FiO\textsubscript{2} should not be considered as an effective or reliable method to reduce overall PONV.\textsuperscript{32} Reducing the dose of opioids by adding other adjunc- tive analgesia, for example, nonsteroidal antiinflammatory drug, cyclooxygenase-2 inhibitor, acetaminophen, or gabapentin, can reduce the incidence of PONV.\textsuperscript{33} Dexmedetomidine infusion (0.2 to 0.8 \text{mcg/kg/hour}) reduces the need for rescue antiemetics in patients undergoing bariatric surgery.\textsuperscript{34} Most importantly, the

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
Risk Factors & Points \\
\hline
Female Gender & 1 \\
Non-Smoker & 1 \\
History of PONV & 1 \\
Postoperative Opioids & 1 \\
Sum & 0 ... 4 \\
\hline
\end{tabular}
\caption{Risk factors for postoperative nausea and vomiting (PONV) in adults. Reprinted with permission from Gan \textit{et al.}\textsuperscript{29}}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
Risk Factors & Points \\
\hline
Surgery $\geq$ 30 min. & 1 \\
Age $\geq$ 3 years & 1 \\
Strabismus surgery & 1 \\
History of POV or PONV in relatives & 1 \\
Sum & 0 ... 4 \\
\hline
\end{tabular}
\caption{Risk factors for postoperative nausea and vomiting (PONV) in children. POV = postoperative vomiting. Reprinted with permission from Gan \textit{et al.}\textsuperscript{29}}
\end{table}
use of propofol as the maintenance anesthetic has the greatest impact of all these drug strategies in reducing the incidence of PONV.³⁵

**Combination Antiemetic Therapy**

As discussed previously, there are at least four major receptor systems involved in PONV. Combination antiemetic therapy was first introduced in 1988 for chemotherapy-induced vomiting.³⁶ Its success prompted similar research in the field of PONV. More than 50 randomized, controlled trials have been published comparing the relative efficacy of combination *versus* single-agent antiemetic prophylaxis. Most of these studies report that two or more antiemetics acting at different receptors are more effective than monotherapy.³⁷⁻³⁹ In a meta-analysis, Habib *et al.*⁴⁰ found no statistically significant difference in the incidence of PONV when a 5-HT₃ receptor antagonist was combined with either droperidol or dexamethasone. Both combinations provided significantly better PONV prophylaxis than the 5HT₃ receptor antagonist alone.

In a large prospective study using a multifactorial design, Apfel *et al.*³⁷ evaluated three antiemetic interventions (4 mg ondansetron, 1.25 mg droperidol, 4 mg dexamethasone) and three anesthetic interventions for the prevention of PONV. Their data suggest that antiemetics with different mechanisms of action have additive rather than synergistic effects on the incidence of PONV. Each antiemetic reduced the risk of PONV by approximately 25%. When combinations of interventions were used, the benefit of each subsequent intervention was always less than that of the first intervention.

**Multimodal Approach**

In addition to using a combination of antiemetics acting at different receptor sites, the multifactorial etiology of PONV might be better addressed by the adoption of a multimodal approach. This is especially important in patients at increased risk for PONV.

Scuderi *et al.*⁴¹ reported a multimodal approach to the management of PONV in females undergoing outpatient laparoscopy that included total intravenous anesthesia with propofol and remifentanil, avoidance of nitrous oxide and neuromuscular blockade, generous intravenous hydration (25 ml/kg), triple prophylactic antiemetics (1 mg ondansetron, 0.625 mg droperidol and 10 mg dexamethasone), and 30 mg ketorolac. Multimodal management resulted in a 98% complete response rate (no PONV and no antiemetic rescue) in the postanesthesia care unit. More recently, a multimodal approach incorporating total intravenous anesthesia with propofol, a combination of ondansetron and droperidol, and avoidance of nitrous oxide was associated with a greater complete response rate and greater patient satisfaction in the postanesthesia care unit compared with similar antiemetic prophylaxis with isoflurane/nitrous oxide-based anesthetic.⁴⁰

**Droperidol**

After the Food and Drug Administration “black box” warning on droperidol based on concerns about prolonged QTc interval associated with use of the doses specified
in the “package insert,” droperidol use has declined dramatically. A recently published pro and con debate weighed the justification of the Food and Drug Administration’s action. Increasingly, clinicians began to use haloperidol, another drug in the butyrophenone class, resulting from its lack of “black box” warning. Haloperidol in doses of 1 mg has been shown to be effective without significant side effects. Its efficacy is enhanced when combined with dexamethasone.

**Novel Antiemetics**

**Neurokinin-1 Antagonists**

Substance P, a member of the tachykinin family of neuropeptides, is an important neurotransmitter in afferent pathways of emesis. Substance P may be released from enterochromaffin cells in the stomach and intestine (e.g., postoperative trauma) or from sensory neurons (e.g., radiation, chemotherapeutic agents). Tachykinin peptide activity is tied to at least three G-protein-coupled receptor subtypes found in the peripheral or central nervous tissue: neurokinin receptor subtype 1 (NK1), type 2 (NK2), and subtype 3 (NK3). The NK1 receptors are located in the area postrema and are thought to play a particularly important role in emesis. However, NK1 receptor antagonists (NK1 RAs) are thought to exert their mechanism of action on neurons in the “afferent relay station” situated between the medial nucleus tractus solitarius and the central pattern generator for vomiting. The potential NK1 receptor-blocking activity located deeper in the brainstem is thought to prevent both acute and delayed emesis, whereas 5HT3 RAs are largely effective only against acute emesis, leading to considerable recent interest in the use of NK1 RAs for prophylaxis of PONV.

NK1 receptor antagonists were effective for the prophylaxis and treatment of PONV. In one study in females undergoing gynecologic surgery, an NK1 receptor antagonist, CP-122,721, provided better prophylaxis against vomiting compared with ondansetron. The combination of both agents also significantly prolonged the time to administration of rescue antiemetics compared with either drug alone and was associated with a very low incidence of emesis (2%).

Aprepitant is the only NK-1 receptor antagonist currently approved by the Food and Drug Administration for the prophylactic management for PONV. It is available in an oral capsule at 40 mg to be administered between 1 and 3 hours before surgery. It has a long half-life of approximately 48 hours. It seems to have better efficacy in the prevention of PONV than ondansetron. In two randomized, double-blind, active-controlled studies, patients scheduled for mostly major gynecologic surgery under general anesthesia were randomized to 40 mg aprepitant, 125 mg aprepitant, or 4 mg ondansetron. In the combined analysis, 40 mg aprepitant was superior to ondansetron for no nausea (40% vs. 33%), no vomiting (87% vs. 72%), and no nausea, no vomiting, and no use of rescue (38% vs. 31%) (P < 0.05 for the odds ratio for each comparison). There are a number of other NK-1 antagonists currently undergoing Phases II and III human trials for PONV.

**Long-acting Serotonin Antagonist**

Palonosetron has the longest elimination half-life of all the currently available serotonin antagonists at approximately 40 hours. Its increased binding affinity for
5HT₃ receptors may also contribute to its long duration of action. Palonosetron was first introduced into the U.S. market for the management of chemotherapy-induced nausea and vomiting. Recent studies suggest 0.075 mg palonosetron intravenously was effective for the reduction of the incidence of nausea and vomiting in patients up to 72 hours postoperatively. Palonosetron also reduces nausea severity and interference in postoperative patient functioning resulting from PONV. It has recently been approved for PONV. It would be interesting to see if the longer half-life of this drug translates into prolonged clinical efficacy when compared with other serotonin antagonists. A head-to-head trial of palonosetron versus (say) ondansetron might permit us to learn whether late failure of PONV prophylaxis is the result of waning blood drug concentrations (e.g., with ondansetron) or some other factor if palonosetron and ondansetron prove equally subject to late failures.

### Recommended Strategy for Postoperative Nausea and Vomiting Prophylaxis

Tables 1 and 2 show drug options and dosing regimens for adult and pediatric populations, respectively. Figure 5 provides a suggested algorithm for PONV prophylaxis. The risk of PONV should be estimated for each patient. No prophylaxis is recommended for patients at low risk for PONV unless they are at risk for adverse medical consequences from vomiting, for example, patients with wired jaws. For patients at moderate or greater risk for PONV, regional anesthesia should be considered. If this is not possible or contraindicated and a general anesthetic is used, strategies to minimize the baseline risk of PONV should be adopted. The use of combination antiemetic therapy and, more appropriately, a multimodal approach in

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Evidence</th>
<th>Timing</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>4-5 mg IV</td>
<td>SR</td>
<td>At induction</td>
<td>RCT</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>1 mg/kg IV</td>
<td>SR, RCT</td>
<td>End of surgery; timing may not affect efficacy</td>
<td>RCT</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>12.5 mg IV</td>
<td>RCT</td>
<td>End of surgery</td>
<td>RCT</td>
</tr>
<tr>
<td>Droperidol*</td>
<td>0.625-1.25 mg IV</td>
<td>RCT</td>
<td>End of surgery</td>
<td>SR</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0.5 mg/kg IM</td>
<td>RCT</td>
<td>End of surgery</td>
<td>RCT</td>
</tr>
<tr>
<td>Granisetron</td>
<td>0.35-1.5 mg IV</td>
<td>RCT</td>
<td>End of surgery</td>
<td>RCT</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5-2 mg IM/IV</td>
<td>SR</td>
<td>End of surgery</td>
<td>RCT</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>5-10 mg IM/IV</td>
<td>RCT</td>
<td>End of surgery</td>
<td>RCT</td>
</tr>
<tr>
<td>Promethazine</td>
<td>6.25-25 mg IV</td>
<td>RCT</td>
<td>At induction</td>
<td>RCT</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4 mg IV</td>
<td>RCT</td>
<td>End of surgery</td>
<td>SR</td>
</tr>
<tr>
<td>Scopolamine Transdermal patch</td>
<td>Previous evening or 4 hours before surgery</td>
<td>SR</td>
<td>Previous evening or 4 hours before surgery</td>
<td>RCT</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>2 mg IV</td>
<td>RCT</td>
<td>End of surgery</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

These recommendations are evidence-based and not all the drugs have a Food and Drug Administration (FDA) indication for postoperative nausea and vomiting.

*See FDA black box warning.

IM = intramuscular; IV = intravenous; RCT = randomized controlled trial; SR = systematic review.
Recommendations for the Treatment of Established Postoperative Nausea and Vomiting

There is a paucity of data on the use of antiemetics for the treatment of PONV in patients who failed prophylaxis or did not receive prophylaxis. This is the result of the difficulty in performing such studies because a large number of patients would need to be recruited to obtain the required target of patients who eventually experience PONV.

The 5HT₃ receptor antagonists were the most commonly tested drugs in rescue clinical trials. Similar to their use in PONV prophylaxis, the antivomiting efficacy of the 5HT₃ receptor antagonists is more pronounced than their antinausea efficacy. There is no evidence of dose-responsiveness for these agents when used for rescue. Therefore, small doses of these agents have been recommended for treatment: 1 mg ondansetron, 12.5 mg dolasetron, 0.1 mg granisetron, and 0.5 mg tropisetron.

In patients who fail ondansetron prophylaxis, there is evidence that the use of ondansetron for rescue is no more effective than placebo. A drug acting at a different receptor might be more effective in this case. Droperidol was not different from ondansetron when used for the treatment of established PONV. In contrast, 4 mg ondansetron was more effective than 10 mg metoclopramide in this setting. When evaluating PONV after surgery, the role of medication and mechanical factors should be considered first. Such contributing factors might include opiates, blood draining down the throat, or bowel obstruction. When any contributing
factors have been addressed, rescue therapy can be initiated. If PONV occurs within 6 hours postoperatively, patients should not receive a repeat dose of the prophylactic antiemetic; a drug from a different class should be used for rescue. Beyond 6 hours, PONV can be treated with any of the agents used for prophylaxis except dexamethasone and scopolamine, which are longer-acting.

In summary, PONV is still common after surgery. The thorough understanding of the mechanism of nausea and vomiting and a careful assessment of risk factors provide a rationale for appropriate management of PONV. Strategies that include reductions of the baseline risk and a multimodal approach will most likely ensure success in preventing and treating PONV.

Fig. 5. Algorithm for the management of postoperative nausea and vomiting (PONV) and portfolio of antiemetics recommended by the Society for Ambulatory Anesthesia PONV Consensus Group. $5\text{-HT}_3 = 5$-hydroxy tryptamine 3; PACU = postanesthesia care unit; POV = postoperative vomiting. Reprinted with permission from Habib and Gan.55
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