

# Postoperative Nausea and Vomiting— Can It Be Eliminated?

Tong J. Gan, MB

**P**OSTOPERATIVE NAUSEA AND VOMITING (PONV) frequently complicates recovery from surgery. Before the 1960s, when older inhalational anesthetic agents such as ether and cyclopropane were widely used, the incidence of vomiting was as high as 60%.<sup>1</sup> Better anesthetic techniques, along with a new generation of antiemetics and shorter-acting anesthetic drugs, have reduced the overall incidence of PONV to approximately 30%.<sup>2</sup> However, PONV occurs in as many as 70% of high-risk patients,<sup>3,4</sup> and pediatric populations are not spared. Although the overall incidence may be lower in children younger than 2 years,<sup>5</sup> procedures such as tonsillectomies and strabismus surgery have a PONV incidence as high as 60%.<sup>6,7</sup> Ambulatory patients appear to have a lower incidence of PONV compared with inpatients,<sup>8</sup> but this incidence may be related to underrecognition of postdischarge nausea and vomiting. Although PONV is rarely fatal, it is an unpleasant postoperative symptom (BOX). Even mild PONV can delay hospital discharge, decrease patient satisfaction, and increase use of resources.<sup>9</sup> Avoiding PONV is important to patients, more so than avoiding postoperative pain.<sup>10</sup> In one study, patients were willing to spend up to \$100, at their own expense, for an effective antiemetic.<sup>11</sup>

## Physiology of and Pharmacology for PONV

It is important to understand the underlying physiology of emesis and the factors involved while elimination of PONV is considered. The emetic center is an ill-defined area located in the lateral reticular formation of the me-

dulla. It receives input from the chemoreceptor trigger zone, vestibular apparatus, cerebellum, solitary tract nucleus, and higher cortical center.<sup>12</sup> The receptor types implicated in nausea and vomiting include dopamine, acetylcholine (muscarine), histamine, and serotonin receptors. Opioid receptors have also been found in the chemoreceptor trigger zone.<sup>5</sup>

Pharmacologic agents acting as antagonists of these receptors have been the mainstay of PONV management. Among the dopamine antagonists, droperidol and metoclopramide are the most studied. Although metoclopramide has prokinetic effects that enhance gastric and upper intestinal motility, it is no more effective as an antiemetic than a placebo.<sup>13</sup> Droperidol (0.625-1.25 mg) is an effective antiemetic in adults, with an adverse effect profile similar to that of the serotonin antagonists.<sup>14</sup> Other dopamine antagonists, eg, promethazine and prochlorperazine, are effective but associated with sedation. Anticholinergics such as scopolamine, once widely used as an anesthetic premedication, have recently received renewed interest as antiemetics in the form of a transdermal patch. Among the commonly used antihistamines, cyclizine is effective, although it may contribute to sedation and dry mouth because of its anticholinergic properties.<sup>15</sup> Serotonin antagonists (eg, ondansetron, dolasetron, and granisetron, introduced a decade ago and brought into clinical use in 1991, 1997, and 1993, respectively) have proven effective with minimal adverse effects.<sup>16,17</sup> It is important to distinguish between symptoms of nausea and vomiting, since some drugs are more effective against nausea (eg, droperidol),

while others are more effective against vomiting (eg, serotonin antagonists).<sup>18</sup>

## Risk Factor Identification

Postoperative nausea and vomiting is a multifactorial entity, comprising patient, surgical, and anesthetic factors. Attempts have been made to identify the risk factors. A recent study concluded that female sex, a history of motion sickness or PONV, nonsmoking status, and use of postoperative opioids were most predictive. The incidence of PONV with the presence of 0, 1, 2, 3, or all 4 of these risk factors were 10%, 21%, 39%, 61%, and 79%, respectively.<sup>3</sup> Some surgical procedures are associated with a higher incidence of PONV: craniotomy; ear, nose, throat procedures; major breast procedures; strabismus surgery; laparoscopy; and laparotomy. Agents used during anesthesia, including opioids, nitrous oxide, and volatile inhalational anesthetics, are emetogenic. Pain, anxiety, and dehydration may also increase the incidence of PONV.<sup>12</sup> Suggested guidelines for antiemetic prophylaxis of PONV, based on published data of risk factors, are presented in the FIGURE.

## Combination Antiemetics

The administration of an antiemetic acting on 1 receptor type typically reduces the incidence of PONV by about 30%. Using a combination of antiemetics acting on different receptors can further re-

**Author Affiliation:** Department of Anesthesiology, Duke University Medical Center, Durham, NC.

**Financial Disclosure:** Dr Gan has received grant support and honoraria from Abbott, Aventis, GlaxoSmithKline, Novartis, and Roche.

**Corresponding Author and Reprints:** Tong J. Gan, MB, Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710 (e-mail: gan00001@mc.duke.edu).

**Contempo Updates Section Editor:** Janet M. Torpy, MD, Fishbein Fellow.

duce this incidence. Many antiemetic combinations have been investigated, most often a serotonin antagonist with a dopamine antagonist or a corticosteroid (dexamethasone).<sup>19</sup> Combination

antiemetic therapy in general exhibits greater effectiveness than a single agent.<sup>20</sup> Specifically, ondansetron and droperidol combined can achieve at least a 90% response rate (no nausea, vomiting, or

rescue antiemetics).<sup>21,22</sup> Evidence suggests similar effectiveness when a serotonin antagonist is combined with droperidol or dexamethasone.<sup>23</sup>

Although a single dose of dexamethasone (<8 mg) appears to be safe, larger doses and prolonged use may cause adverse effects. Avascular necrosis of the femoral head is a recognized complication of prolonged glucocorticoid therapy and can develop following relatively brief courses (7 days) of orally administered corticosteroids.<sup>24</sup> In a recent warning by the Food and Drug Administration (FDA), droperidol, when used in antiemetic doses, was associated with prolongation of QTc interval and fatal arrhythmias in a number of anecdotal reports.<sup>25</sup> The FDA recommended that droperidol not be used as a first-line therapy, and electrocardiographic monitoring should be performed before treatment and continued for 2 to 3 hours afterward to monitor for arrhythmias. The Medicines Control Agency, part of the Department of Health in the United Kingdom, did not mandate electrocardiographic monitoring with the use of droperidol perioperatively.<sup>26</sup> In the 31 years of droperidol use, there has not been a single case report in a peer-reviewed journal in which droperidol used for the management of PONV has been associated with QTc prolongation, arrhythmias, or cardiac arrest.

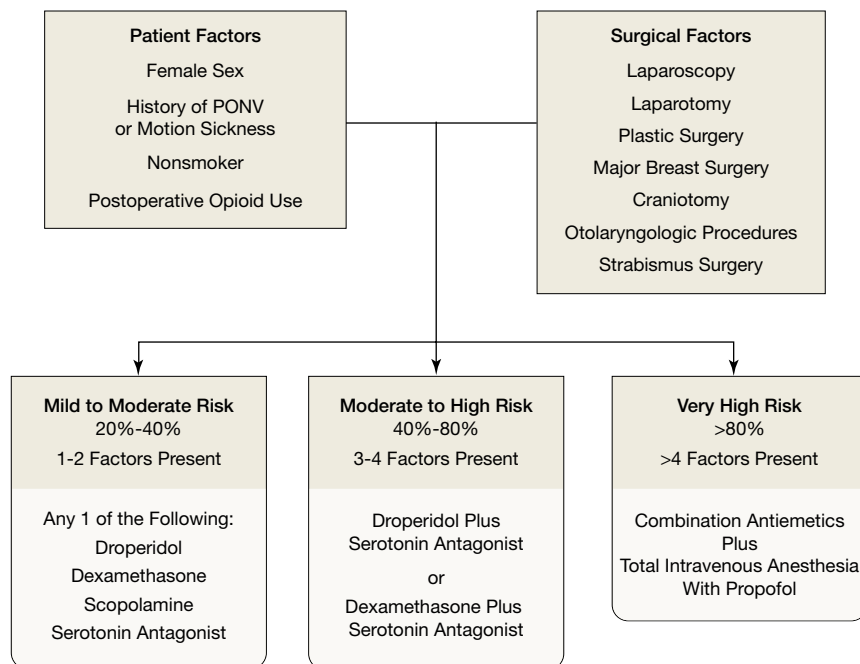
Although it may be logical to extrapolate that use of multiple (>2) drug combinations will further enhance effectiveness, published evidence is scarce. Scuderi et al<sup>26</sup> showed that multimodal management incorporating combination antiemetics and propofol resulted in a 98% complete response rate. A high concentration of oxygen as an antiemetic is a use that few appreciate.<sup>27,28</sup> Greif et al<sup>27</sup> used intraoperative oxygen and continued oxygen administration 2 hours after surgery, while Goll et al<sup>28</sup> used it only intraoperatively. The use of 80% oxygen intraoperatively as a component of general anesthesia significantly reduced the incidence of PONV compared with 30% oxygen. However, it is unclear whether the antiemetic effect

**Box. Recommended Strategies for Minimizing the Incidence of Postoperative Nausea and Vomiting**

1. Identify high-risk patients (Figure)
2. Avoid emetogenic stimuli
  - Etomidate
  - Inhalational anesthetic agents
  - Opioids\*
3. Multimodal therapy
  - Antiemetics (consider combination therapy)
  - Total intravenous anesthesia with propofol
  - Adequate hydration
  - Effective analgesia incorporating local anesthetics and inhibitors of cyclooxygenase 2
  - Anxiolytics (benzodiazepines)
  - Intraoperative supplemental oxygen (FiO<sub>2</sub> ≥0.8)
  - Nonpharmacologic techniques

\*Although opioids are emetogenic, optimal analgesia should be the goal and can be achieved by incorporating preoperative education, local anesthetics, and inhibitors of cyclooxygenase 2. Optimal analgesia may include an opioid.

**Figure.** Risk Factors for PONV and Guidelines for Prophylactic Antiemetic Therapy



Based on references 3 and 38. PONV indicates postoperative nausea and vomiting. Percentages denote risk of developing PONV. Consideration should be given to avoid risk factors associated with PONV and other strategies (Box) to further reduce the incidence. Serotonin antagonists may be preferred antiemetics in operative settings where nursing labor costs are directly related to the length of postanesthesia care unit stay.

was due to the increase in oxygen concentration or the decrease in nitrous oxide concentration.

There is mounting evidence to suggest that total intravenous anesthesia with propofol reduces the incidence of PONV.<sup>29</sup> A dose-response relationship of propofol for improvement of nausea has been established.<sup>30</sup> A recent study on anesthesia use (comparing propofol with isoflurane) demonstrated a reduction of absolute risk of PONV by 18% among outpatients (from 46% to 28%) up to 72 hours after surgery, as well as a shorter postanesthesia care unit stay. However, the propofol anesthetic was more expensive.<sup>8</sup> Used as an induction agent only, propofol is not as protective against PONV, probably because of its short duration of action.<sup>4,29</sup> The mechanism for propofol's action as an antiemetic has not been conclusively elucidated; however, recent evidence suggests that propofol may act by reducing serotonin levels in the area postrema.<sup>31</sup>

### Complementary Techniques

Compared with placebo, acupuncture in various forms (acupressure, laser acupuncture, manual acupuncture, and transcutaneous acupoint stimulation) effectively reduced PONV.<sup>32</sup> These studies used the acupuncture point Pericardium 6 (Neiguan), the sixth point on the pericardial meridian, located about 5 cm proximal to the palmar aspect of the wrist between flexor carpi radialis and palmaris longus tendons. Other acupuncture points may also possess antiemetic properties.<sup>33</sup> Perioperative hypnosis has been demonstrated to reduce emesis following breast surgery.<sup>34</sup> The perioperative use of ginger, however, has not been found to be effective for PONV prevention.<sup>35</sup>

### Postdischarge Nausea and Vomiting

More than 60% of all US surgery is performed in the ambulatory setting, and this trend is increasing.<sup>36</sup> Postoperative nausea and vomiting may continue after discharge from the ambulatory surgery unit, with a reported incidence of

30% to 50%.<sup>37,38</sup> Many of these patients did not have symptoms while in the surgical center. It is important to prevent nausea and vomiting beyond discharge for 2 reasons: patients' resumption of normal activities and readiness to return to work may be delayed if PONV is prolonged,<sup>37</sup> and ambulatory patients are not under direct medical supervision after their discharge. Hence, the presence of PONV may be distressing because patients cannot easily request an antiemetic. Most antiemetics have short half-lives and may not be effective after discharge. There is a lack of effective over-the-counter antiemetics. The prophylactic use of the ondansetron orally disintegrating tablet beyond discharge appears to reduce emetic symptoms.<sup>38</sup> Other options include transcutaneous acupoint electrical stimulation on Pericardium 6<sup>39</sup> (Relief Band, Woodside Biomedical Inc, Carlsbad, Calif) or a transdermal scopolamine patch (Transderm Scop, Novartis Consumer Health Inc, Summit, NJ).<sup>40</sup>

### Cost-effectiveness of Antiemetics

The cost-effectiveness of antiemetics is increasingly scrutinized in this era of limited resources. With PONV prophylaxis, some patients will receive antiemetic therapy prophylactically without actually needing it, while others will have PONV despite receiving prophylaxis. Confining attention to drug acquisition costs without considering direct and indirect costs may lead to an inefficient use of resources.<sup>41</sup> In a cost-incremental analysis (cost per additional patient who benefits from a change in clinical practice), prophylaxis with ondansetron in all patients is less cost-effective than treatment with the same drug.<sup>16</sup> In this context, ondansetron (1 mg intravenous) appears to be effective when patients with established PONV are treated.<sup>42</sup> However, the use of prophylactic antiemetic therapy in selected high-risk surgical patients (history of PONV and having emetogenic procedures) is cost-effective and associated with greater patient satisfaction.<sup>9</sup> In that study, droperidol (1.25 mg) was associated with

greater effectiveness and less cost compared with droperidol (0.625 mg) and ondansetron (4 mg). Most of the costs (70%-80%) were from nursing labor costs from prolonged postanesthesia care unit stay as a result of persistent nausea and vomiting or adverse effects of antiemetics. Hence, the cost-effectiveness of prophylactic antiemetic therapy will depend on where the procedure is performed. For example, nursing labor costs are more likely to be directly related to the duration of postanesthesia care unit stay in an office-based setting and, to a lesser extent, an ambulatory surgery unit, whereas prolonged postanesthesia care unit stay may not have a significant impact in nursing labor costs in an inpatient hospital setting, unless nursing staff can be reduced. In light of the recent FDA advisory on droperidol, further investigation of the cost-effectiveness of other therapies is required.

### Future Development

The natural ligand of the neurokinin 1 (NK-1) receptor, substance P, is found in the nucleus tractus solitarius and the area postrema, as well as in the peripheral nervous system.<sup>43</sup> A recent study suggests that NK-1 receptor antagonists may effectively prevent PONV.<sup>44</sup> Combining this new class of antiemetics with a serotonin antagonist may eliminate PONV. Use of the combination of an NK-1 receptor antagonist and ondansetron significantly prolonged the time to administration of rescue antiemetic compared with the use of either drug alone and almost completely abolished emesis.<sup>45</sup> The discovery and development of nonopioid analgesics will help reduce opioid-induced nausea and vomiting. Selective inhibitors of cyclooxygenase 2 (eg, parecoxib, celecoxib, and rofecoxib) can reduce opioid requirement or may be used as an opioid substitute.

### Conclusion

Although PONV management has advanced significantly, PONV still occurs too frequently in high-risk patients. Inquiring about each patient's history and educating patients regard-

ing their risk for developing PONV should be a preoperative routine. Because there are many factors involved in PONV, a multimodal approach to its

prevention should be adopted: preoperative risk factors should be identified, avoidable risk factors should be reduced, and the use of combination

antiemetics should be considered (Box). Adopting these practices should serve as the best strategy to minimize and even eliminate PONV.

## REFERENCES

- Bonica J, Crepps W, Monk B, Bennett B. Post-anesthetic nausea, retching and vomiting. *Anesthesiology*. 1958;19:532-540.
- Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg*. 1994;78:7-16.
- Apfel CC, Laara E, Koivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91:693-700.
- Gan TJ, Ginsberg B, Grant AP, Glass PS. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. *Anesthesiology*. 1996;85:1036-1042.
- Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. *Br J Anaesth*. 1999;83:104-117.
- Ved SA, Walden TL, Montana J, et al. Vomiting and recovery after outpatient tonsillectomy and adenoidectomy in children. *Anesthesiology*. 1996;85:4-10.
- Shende D, Bharti N, Kathirvel S, Madan R. Combination of droperidol and ondansetron reduces PONV after pediatric strabismus surgery more than single drug therapy. *Acta Anaesthesiol Scand*. 2001;45:756-760.
- Visser K, Hassink EA, Bonsel GJ, et al. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide. *Anesthesiology*. 2001;95:616-626.
- Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology*. 2000;92:958-967.
- Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? *Anesth Analg*. 1999;89:652-658.
- Gan T, Sloan F, Dear G, et al. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg*. 2001;92:393-400.
- Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention [review]. *Anesthesiology*. 1992;77:162-184.
- Henzi I, Walder B, Tramer MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. *Br J Anaesth*. 1999;83:761-771.
- Fortney JT, Gan TJ, Graczyk S, et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. *Anesth Analg*. 1998;86:731-738.
- Ahmed AB, Hobbs GJ, Curran JP. Randomized, placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery. *Br J Anaesth*. 2000;85:678-682.
- Tramer MR, Phillips C, Reynolds DJ, et al. Cost-effectiveness of ondansetron for postoperative nausea and vomiting. *Anaesthesia*. 1999;54:226-234.
- Zarate E, Watcha MF, White PF, et al. A comparison of the costs and efficacy of ondansetron versus dolasetron for antiemetic prophylaxis. *Anesth Analg*. 2000;90:1352-1358.
- Tramer MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. *Acta Anaesthesiol Scand*. 2001;45:4-13.
- Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting. *Anesth Analg*. 2000;90:186-194.
- Habib AS, Gan TJ. Combination therapy for postoperative nausea and vomiting—a more effective prophylaxis? *Ambulatory Surgery*. 2001;9:59-71.
- McKenzie R, Uy NTL, Riley TJ, Hamilton DL. Droperidol/ondansetron combination controls nausea and vomiting after tubal banding. *Anesth Analg*. 1996;83:1218-1222.
- Pueyo FJ, Carrascosa F, Lopez L, et al. Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. *Anesth Analg*. 1996;83:117-122.
- Habib AS, El-Moalem HE, Gan TJ. Should 5-HT<sub>3</sub> receptor antagonists be combined with droperidol or dexamethasone for PONV prophylaxis? *Anesthesiology*. 2001;95:A41.
- Virlik K, Karapetis C, Droufakou S, Harper P. Avascular necrosis of bone: the hidden risk of glucocorticoids used as antiemetics in cancer chemotherapy. *Int J Clin Pract*. 2001;55:344-345.
- Food and Drug Administration. FDA strengthens warnings for droperidol. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01123.html>. Accessibility verified January 24, 2002.
- Scuderi PE, James RL, Harris L, Mims GR III. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. *Anesth Analg*. 2000;91:1408-1414.
- Greif R, Laciný S, Rapf B, et al. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. *Anesthesiology*. 1999;91:1246-1252.
- Goll V, Akca O, Greif R, et al. Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. *Anesth Analg*. 2001;92:112-117.
- Tramer M, Moore A, McQuay H. Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth*. 1997;78:247-255.
- Gan TJ, Glass PS, Howell ST, et al. Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. *Anesthesiology*. 1997;87:779-784.
- Cechetto DF, Diab T, Gibson CJ, Gelb AW. The effects of propofol in the area postrema of rats. *Anesth Analg*. 2001;92:934-942.
- Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting. *Anesth Analg*. 1999;88:1362-1369.
- Kotani N, Hashimoto H, Sato Y, et al. Preoperative intradermal acupuncture reduces postoperative pain, nausea and vomiting, analgesic requirement, and sympathoadrenal responses. *Anesthesiology*. 2001;95:349-356.
- Enqvist B, Bjorklund C, Engman M, Jakobsson J. Preoperative hypnosis reduces postoperative vomiting after surgery of the breasts: a prospective randomized and blinded study. *Acta Anaesthesiol Scand*. 1997;41:1028-1032.
- Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting. *Br J Anaesth*. 2000;84:367-371.
- Centers for Disease Control and Prevention. *Vital and Health Statistics, Ambulatory and Inpatient Procedures in the United States*. Washington, DC: US Dept of Health and Human Services; 1996.
- Carroll NV, Miederhoff P, Cox FM, Hirsch JD. Postoperative nausea and vomiting after discharge from outpatient surgery centers. *Anesth Analg*. 1995;80:903-909.
- Gan TJ, Franak R, Reeves J. Comparison of ondansetron orally disintegrating tablet (ODT) versus placebo for the prevention of postdischarge nausea and vomiting following ambulatory surgery. *Anesth Analg*. In press.
- Zarate E, Mings M, White PF, et al. The use of transcutaneous acupoint electrical stimulation for preventing nausea and vomiting after laparoscopic surgery. *Anesth Analg*. 2001;92:629-635.
- Bailey PL, Streisand JB, Pace NL, et al. Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. *Anesthesiology*. 1990;72:977-980.
- Watcha MF. The cost-effective management of postoperative nausea and vomiting [editorial]. *Anesthesiology*. 2000;92:931-933.
- Scuderi PE, James RL, Harris L, Mims GR III. Antiemetic prophylaxis does not improve outcomes after outpatient surgery when compared to symptomatic treatment. *Anesthesiology*. 1999;90:360-371.
- Gillis R, Helke C, Hamilton B, et al. Evidence that substance-P is a neurotransmitter of baro- and chemoreceptor afferents in nucleus tractus solitarius. *J Brain Res*. 1980;181:476-481.
- McLean S, Ganong A, Seymour PA, et al. Characterization of CP-122,721, a nonpeptide antagonist of the neurokinin NK1 receptor. *J Pharmacol Exp Ther*. 1996;277:900-908.
- Geszteszi Z, Scuderi PE, White PF, et al. Substance P (neurokinin-1) antagonist prevents postoperative vomiting after abdominal hysterectomy procedures. *Anesthesiology*. 2000;93:931-937.