Antiemetics

14

Wendy A. Haft and Richard McAffee

Postoperative nausea and vomiting (PONV) remains one of the most common complications of anesthesia and is estimated to occur in approximately 20–30 % of patients receiving general anesthesia. PONV is associated with multiple risk factors including certain patient characteristics, specific surgical and anesthetic techniques, and commonly used medications in the perioperative period. This anesthetic complication contributes to preoperative anxiety in patients with a history of PONV, decreased patient satisfaction, and even serious postoperative complications such as wound dehiscence and aspiration.

Risk Factors for PONV

An understanding of the risk factors for PONV can help anesthesia providers identify at-risk patients and work toward prevention with prophylactic antiemetics. Some common risk factors include female gender, history of PONV, history of motion sickness, use of volatile anesthetics, use of opioids, laparoscopic procedures, gynecologic procedures, and nonsmoking status. Risk scores have been developed to assist in identifying such patients. For example, the Apfel score used in adult patients utilizes four factors: female gender, history of PONV or history of motion sickness, postoperative use of opioids, and nonsmoking status. Zero factors correspond to 10 % risk, one factor to 20 % risk, two factors to 40 % risk, three factors to 60 % risk, and four factors to 80 % risk of PONV.

W.A. Haft, M.D. • R. McAffee, M.D. (✉)
Department of Anesthesiology, University of Pittsburgh Medical Center, 200 Lothrop Street, C-Wing, Suite C-200, Pittsburgh, PA 15213, USA
e-mail: mcaffeer@upmc.edu

Physiology of Nausea and Vomiting

Nausea and vomiting are physiologic processes that require coordination of multiple organ systems, extending from the brain to the gastrointestinal tract. There are many causes of nausea including medications, motion sickness, and certain diseases (i.e., malignancy and pregnancy). The chemoreceptor trigger zone (CTZ) in the area postrema at the end of the fourth ventricle contains receptors for numerous neurotransmitters involved in vomiting, including dopamine, opioid, serotonin $5HT_3$, and NK_1 receptors. The CTZ receives input from the binding of these neurotransmitters and relays signals to the nucleus tractus solitarius (NTS) in the brainstem and the vomiting center in the lateral medullary reticular formation to initiate the coordination of vomiting. Similarly, the vestibular system, which contains numerous H_1 histamine and M_1 muscarinic receptors, and the gastrointestinal tract, which is rich in $5HT_3$ receptors, also send afferent signals to the vomiting center in the medulla as a result of emetic stimuli. Stimulation of these brainstem centers results in activation of pharyngeal, thoracic, and abdominal muscles to help expel gastric contents.

Pharmacology of Antiemetics

Given the numerous factors involved in the experience of nausea and the coordination of vomiting, there exist many categories of antiemetic drugs that act at different receptors along these pathways. Some antiemetic drugs act as antagonists at histamine, dopamine, serotonin, muscarinic, or NK_1 receptors (Table 14.1). Other commonly used antiemetics act through alternate mechanisms, as discussed below. The multifactorial nature of PONV highlights the importance of multimodal antiemetic therapy. Studies have shown that the effects of antiemetics are generally additive. In addition, if a patient fails treatment with one class of antiemetics, another class should then be instituted, rather than giving multiple doses of either the same drug or other drugs within that class.

P.K. Sikka et al. (eds.), *Basic Clinical Anesthesia*,
DOI 10.1007/978-1-4939-1737-2_14,

Table 14.1 Overview of antiemetics

Drug category	Mechanism of action	Specific drugs	Typical dose
Serotonin ($5HT_3$) antagonists	Antagonism of serotonin $5HT_3$ receptors in the CTZ, the medullary vomiting center, and in the periphery	Ondansetron	4–16 mg IV
		Granisetron	1 mg IV
		Dolasetron	100 mg IV
		Palonosetron	0.25 mg IV
Dopamine antagonists	Inhibition of dopaminergic receptors in the CTZ	Droperidol	0.625–1.25 mg IV
		Haloperidol	1–2 mg IV
		Perphenazine	4–8 mg by mouth
		Prochlorperazine	5–10 mg IV
		Metoclopramide	10–20 mg IV
Corticosteroids	Unknown mechanism – possibly due to anti-inflammatory effect	Dexamethasone	4–10 mg IV
Anticholinergics	Inhibition of muscarinic receptors in the vestibular system and the vomiting center in the medulla	Scopolamine	1.5 mg transdermal patch
Histamine (H_1) blockers	Antagonism of histamine receptors in the vestibular system	Diphenhydramine	4–10 mg IV
Neurokinin (NK_1) antagonists	Inhibition of substance P in the area postrema and throughout the GI tract and blockade of signals from the CTZ to the NTS in the brainstem	Aprepitant	40 mg by mouth

CTZ chemoreceptor trigger zone, *NTS* nucleus tractus solitarius

Serotonin $5HT_3$ Receptor Antagonists

Serotonin $5HT_3$ receptors are present in the CTZ, the medullary vomiting center, and peripherally in vagal and spinal afferent nerves. $5HT_3$ receptor antagonists are common antiemetics used for both the prevention and treatment of PONV. The most commonly used $5HT_3$ receptors available in the United States are ondansetron, dolasetron, granisetron, and palonosetron. Ondansetron, dolasetron, and granisetron are available in oral and intravenous (IV) preparations, whereas palonosetron is available for administration by IV route only.

$5HT_3$ receptor antagonists have fewer side effects compared to other available antiemetics; however, they have been known to cause constipation, headache, dizziness, QTc prolongation, and cardiac arrhythmias. Palonosetron has greater $5HT_3$ receptor affinity, which results in its longer half-life of 40 h (compared to a half-life of 4–9 h for the other drugs in this class), and it is not associated with QTc prolongation. Administering a $5HT_3$ receptor antagonist with a corticosteroid at the induction of general anesthesia may provide better PONV prophylaxis than either drug class alone.

Ondansetron, the most commonly used $5HT_3$ receptor antagonist, is generally administered in doses ranging from 4 to 16 mg IV prophylactically at the induction of anesthesia or for the treatment of PONV postoperatively. Other research has demonstrated increased efficacy when ondansetron is given at the end of surgery but prior to leaving the operating room. Some studies have shown that 4 mg of ondansetron IV is effective for the prevention and treatment of PONV, whereas other studies have demonstrated 8 mg IV to be the minimum effective dose in adults.

Dopamine Antagonists

There are three classes of dopamine receptor antagonists commonly used as antiemetics: phenothiazines, butyrophenones, and benzamides. The antiemetic properties of these drugs are due to inhibition of dopaminergic receptors in the CTZ. The use of this class of medications is limited by side effects, especially sedation and extrapyramidal symptoms, and should be avoided in patients with Parkinson's disease.

The most commonly used phenothiazines are perphenazine, promethazine, and prochlorperazine. Perphenazine is available only in an oral form and it is recommended that it be given preoperatively. The typical dose is 4–8 mg, which has been shown to result in effective control of PONV while producing limited side effects. Studies have demonstrated that perphenazine given preoperatively enhances the antiemetic effects of ondansetron and dolasetron. Promethazine is used for both prophylaxis and treatment of PONV. It also has anticholinergic and antihistaminic properties, which can result in substantial sedation, thus limiting its use.

The most commonly used butyrophenone as an antiemetic is droperidol. Droperidol acts through the same mechanism as the phenothiazines and is also typically used as prophylaxis against PONV. Studies have demonstrated that droperidol is equally effective in preventing PONV as the combination of ondansetron and dexamethasone. However,

droperidol is still most effective when used in combination with other antiemetics. The recommended dose of droperidol is 0.625–1.25 mg IV. A "black box" warning on droperidol does exist for higher doses (>/=2.5 mg IV) due to cases of QTc prolongation and torsades de pointes, so discretion should be exercised when using droperidol in patients taking other medications that may prolong the QTc interval. Haloperidol, another butyrophenone, has also been shown to have antiemetic properties in low doses (1–2 mg IV), but it has a shorter duration of action than droperidol.

Metoclopramide, a benzamide used as an antiemetic, works by inhibiting dopaminergic receptors in the CTZ and by increasing gastric motility through peripheral activity as a cholinomimetic. Prophylactic and treatment doses of metoclopramide usually range 10–20 mg by mouth or IV every 6 h. Many recent studies comparing metoclopramide and other antiemetics, such as ondansetron and droperidol, have shown that metoclopramide is less effective in the prevention of PONV.

Corticosteroids

Dexamethasone and methylprednisolone are two corticosteroids used as antiemetics. As described above, dexamethasone has been shown to have enhanced antiemetic properties when combined with ondansetron. Corticosteroids are well known for their anti-inflammatory properties, but the basis behind their use as antiemetics is not well understood. Dexamethasone is generally administered in doses of 4–10 mg IV at the induction of anesthesia. It is recommended that dexamethasone not be routinely given as PONV prophylaxis in patients with diabetes mellitus. No convincing data has shown that adrenal suppression or inhibition of wound healing occurs with a single dose preoperatively.

Histamine (H_1) Blockers

H_1 receptor antagonists act through inhibition of histamine receptors in the vestibular system. Nearly all drugs in this category are also weak anticholinergics through inhibition of muscarinic M_1 receptors present in the vestibular system. The mechanism of action of this class of drugs makes them most useful in patients with a history of motion sickness, and they are generally weak antiemetics when used alone. In practice, antihistamines are used in combination with other more potent antiemetics. H_1 receptor antagonists can also decrease the risk of extrapyramidal side effects when given with dopamine antagonists used for the prevention and treatment of PONV. Commonly used H_1 blockers are diphenhydramine, dimenhydrinate, hydroxyzine, and meclizine. These medications can cause significant sedation and dry mouth secondary to their anticholinergic properties and thus should be used with caution in some patients.

Anticholinergics

The most commonly used anticholinergic in the prevention of PONV is scopolamine. Scopolamine is traditionally given as a 1.5 mg patch placed behind the ear that acts transdermally over 72 h. It is recommended that scopolamine be administered preoperatively and is most effective when initiated the day prior to surgery. However, it has also been shown to be effective if given 2–4 h before the end of surgery or even in the postoperative period. Scopolamine acts by inhibiting muscarinic receptors in the vestibular system as well as the vomiting center in the medulla. Thus, it is particularly effective in patients with a history of motion sickness. The fact that scopolamine is long acting, when given transdermally, and does not require repeated dosing is one benefit for its use in same-day surgery patients. However, the use of scopolamine in such patients can be limited by its sedating effects, and care should be exercised in elderly patients, who are most sensitive to these effects. Transdermal scopolamine has been showed to cause less sedation than oral or IV preparations.

Neurokinin 1 Receptor Antagonists

Neurokinin 1 (NK_1) receptor antagonists have been shown to decrease the incidence of PONV in high-risk patients, particularly when used with other antiemetics. NK_1 receptor antagonists function by inhibiting signals received from the chemoreceptor trigger zone (CTZ) by the nucleus tractus solitarius (NTS) in the brainstem. Another mechanism for their action is through inhibition of substance P, a neuropeptide that binds in the area postrema and throughout the GI tract to cause nausea. The most commonly used NK_1 antagonist is aprepitant. The typical dose is 40 mg orally preoperatively, most commonly given within 3 h of surgery. Research has shown that aprepitant is most effective when combined with other antiemetics, particularly corticosteroids and $5HT_3$ receptor blockers.

Aprepitant has few side effects, is nonsedating, and has been shown to be longer acting than other commonly used antiemetics. Thus, it may be particularly beneficial in patients undergoing same-day surgeries for which postdischarge nausea and vomiting is a concern. Aprepitant does have a higher cost than other antiemetics, which may limit its use in some situations. Aprepitant also affects the hepatic metabolism of many drugs. Importantly, oral contraceptive serum hormone levels may decrease, and therefore, alternative nonhormonal contraception is recommended when using this drug. This

interaction may somewhat limit the use of aprepitant in young women at risk for PONV. Another oral NK_1 receptor antagonist, rolapitant, is currently in clinical trials.

Emetogenic Trigger Avoidance

Opioids and volatile anesthetics are two drug classes that have been implicated as risk factors for PONV, and, thus, avoidance of these triggers has been shown to decrease the risk of PONV in at-risk patients. One technique in minimizing the use of volatile anesthetics is the maintenance of anesthesia with an IV infusion of agents such as propofol or dexmedetomidine. In addition to its benefit in sparing the use of volatile anesthetics, propofol by itself is an antiemetic. The mechanism of action behind propofol's antiemetic properties is likely multifactorial. Activation of gamma-aminobutyric acid (GABA) receptors by propofol directly inhibits neurons in the area postrema and decreases serotonin levels in this same region, resulting in a breakdown in the pathways causing nausea and vomiting. Studies have shown that a single induction dose of propofol alone does not result in effective prevention of PONV. However, combining a single induction dose of propofol with an intraoperative maintenance infusion does decrease the risk of PONV.

Many patients experience PONV in association with opioid use. There are numerous opioid-sparing techniques that can be utilized in such patients to decrease their risk of PONV. Certain regional anesthetic techniques can reduce a patient's need for postoperative opioids. Similarly, perioperative use of nonopioid analgesics such as ketorolac, acetaminophen, ketamine, clonidine, and dexmedetomidine can decrease opioid requirements. Many patients with a history of PONV experience significant anxiety regarding the recurrence of this complication, which itself can trigger nausea and vomiting. Benzodiazepines, such as lorazepam and midazolam, can be used for the prevention of anticipatory nausea and vomiting in the perioperative period.

Nonpharmacological Techniques

Electroacupuncture and acupressure are nonpharmacological techniques that have been extensively studied in the prevention and treatment of PONV. Electroacupuncture involves electrical stimulation with a needle that administers about 1 Hz of stimulation either as a single twitch, double burst, tetanus, or train-of-four. Recent studies have shown that tetanic stimulation is most effective in the prevention of PONV. Acupressure involves a bracelet containing a magnet or an electrical stimulator that is applied to the wrist at the P6 acupoint, which is located along the distal wrist over the median nerve. These techniques can be applied as prophylaxis either preoperatively or intraoperatively. Electroacupuncture is effective postoperatively as rescue for PONV. Evidence suggests that electroacupuncture and acupressure may decrease opioid requirements postoperatively.

Clinical Review

1. The following drug does *not* prolong the QTc interval on the electrocardiogram:
   A. Ondansetron
   B. Dolasetron
   C. Droperidol
   D. Palonosetron
2. Metoclopramide is contraindicated in patients with:
   A. Asthma
   B. Parkinsonism
   C. Depression
   D. Rheumatoid arthritis
3. Aprepitant prevents nausea and vomiting by inhibiting the following receptors:
   A. Neurokinin
   B. Bradykinin
   C. Cytokinin
   D. Kallikrein
4. Use of the following agent intraoperatively may prevent postoperative nausea and vomiting:
   A. Desflurane
   B. Etomidate
   C. Propofol
   D. Remifentanil

Answers: 1. D, 2. B, 3. A, 4. C

Further Reading

1. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441–51.
2. Cechetto DF, Diab T, Gibson CJ, Gelb AW. The effects of propofol in the area postrema of rats. Anesth Analg. 2001;92:934–42.
3. Doran K, Halm MA. Integrating acupressure to alleviate postoperative nausea and vomiting. Am J Crit Care. 2010;19:553–6.
4. George E, Hornuss C, Apfel CC. Neurokinin-1 and novel serotonin antagonists for postoperative and postdischarge nausea and vomiting. Curr Opin Anaesthesiol. 2010;23:714–21.
5. Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg. 2005;101:1634–42.
6. McKeage K, Simpson D, Wagstaff AJ. Intravenous droperidol a review of its use in the management of postoperative nausea and vomiting. Drugs. 2006;66:2123–47.

7. Mizrak A, Gul R, Ganidagli S, Karakurum G, Keskinkilic G, Oner U. Dexmedetomidine premedication of outpatients under IVRA. Middle East J Anesthesiol. 2011;21:53–60.
8. Schnabel A, Eberhart LH, Muellenbach R, Morin AM, Roewer N, Kranke P. Efficacy of perphenazine to prevent postoperative nausea and vomiting: a quantitative systematic review. Eur J Anaesthesiol. 2010;27:1044–51.
9. Song D, Whitten CW, White P, Song YY, Zarate E. Antiemetic activity of propofol after sevoflurane and desflurane anesthesia for outpatient laparoscopic cholecystectomy. Anesthesiology. 1998;89:838–43.