Etiologies of Postoperative Nausea and Vomiting

P ostoperative nausea and vomiting (PONV) can lead to significant adverse physical, metabolic, and psychologic consequences for the surgical patient. When Bellville examined this complication 35 years ago, the researcher noted an incidence ranging from 18% to 30%. Data from more recent studies show that PONV still occurs at similar rates—despite the introduction of new anesthetic medications—because of the growth of ambulatory surgery.

For ambulatory surgery, PONV has taken on added significance. It can delay discharge from the surgical facility. Melnick and Johnson reported that PONV increased the mean time until discharge from 120 to 170 minutes. Morbidity occurs after discharge as well. In our series of patients primarily undergoing ambulatory laparoscopic surgery, 21% experienced nausea after discharge and 9% vomited. PONV is also a leading cause of unanticipated admission to the hospital. Gold et al reported that severe vomiting resulted in the hospitalization of 0.18% of 9616 subjects and accounted for 17% of all post-surgery admissions. The detrimental impact of PONV in ambulatory surgery is also seen through its effects on total procedural costs, and has a negative impact on patient satisfaction. These issues are well addressed in several literature reviews.

**PATHOPHYSIOLOGY**

All vomiting is coordinated through the vomiting center, which is thought to be located in the medulla in the area of the lateral reticular formation close to the tractus solitarius. The physical act of vomiting is produced by a collection of efferent neural pathways that include cranial nerves V, VII, IX, X, and XII; spinal nerves to the diaphragm and abdominal muscles; and sympathetic and parasympathetic motor responses.

A variety of factors contribute to triggering PONV. Stimuli
that activate mechanoreceptors in the gut wall muscle and chemoreceptors in the mucosa may be transmitted to the vomiting center through visceral-vagal (X) afferents. In addition, vestibular afferents (VIII) are activated primarily through motion stimuli, as well as pharyngeal (IX), auricular (X), and cardiac (X) ventricular afferents. In addition to the cranial nerve afferents, PONV may be modulated through cerebral responses to nauseating sights, smells, and tastes, or by activation of the chemoreceptor trigger zone (CTZ). The CTZ is thought to lie in the highly vascularized area postrema on the floor of the fourth ventricle, where it is outside the blood-brain and cerebrospinal fluid (CSF)-brain barriers. The CTZ is replete with opioid, dopamine, muscarinic-cholinergic, histamine, and 5-hydroxytryptamine (serotonin) receptors, and serves as the general chemoreceptor for emetic substances in the blood and CSF.

Numerous perioperative stimuli can activate vomiting. They may be divided into five categories: patient factors, surgical factors, anesthetic agent factors, anesthetic process factors, and postoperative factors (Table).

**PATIENT FACTORS**

The incidence of PONV increases from infancy through adolescence and remains fairly stable throughout adulthood until age 70, when it appears to decrease. Lerman reported emesis rates of 5% in infants, 20% in children, and 34% to 51% in teenagers. It is unclear whether differences noted in this study resulted purely from age or involved age-related differences in anesthetic agents used and surgical procedures performed.

Obesity increases the risk of PONV. Its effect may be partly explained by difficulties in managing the airway in overweight individuals and a greater risk of introduction of air into the stomach. In addition, obese patients may have an increased residual gastric volume and may have more gastroesophageal reflux. Further, increased body fat serves as a larger reservoir for lipid-soluble, emetogenic anesthetic agents.

Women are two to three times more likely than men to experience PONV. Female susceptibility to it has been attributed to hormonal differences and, more specifically, to the higher plasma concentrations of progesterone, estrogen, and gonadotropins in women. The incidence of PONV is higher in women aged 11 to 70, higher during pregnancy, and particularly elevated among women who have received exogenous hormone therapy in order to undergo ovum retrieval for fertility procedures. In addition, there are phasic changes in PONV rates throughout the menstrual cycle. Honkavaara et al recorded PONV during the first 24 hours after surgery and found the highest rates among women in the luteal phase (third and fourth weeks) of their menstrual cycle. Older observations support this finding. In contrast, a cohort of women studied by Beattie et al appeared most susceptible to this complication during the menses, although the postoperative observation period for this group was only 2 to 4 hours. Neither study determined plasma concentrations of female sex hormones at the time of surgery.

Anxiety may be another patient-related risk factor for PONV. The link between anxiety and PONV involves an alpha-adrenergic mechanism, with increased levels of circulating catecholamines. Supporting this theory are the results of a cat study in which vomiting was produced by instillation of epinephrine and norepinephrine directly into the fourth ventricle. Vomiting was prevented by pretreatment with the alpha blocker phentolamine, but not by pretreatment with the beta blocker propranolol. Alpha1- and alpha2-adrenergic receptors are found in the area postrema. It has been theorized that anxious patients are more likely to swallow air and to have reduced gastrointestinal motility; however, one study failed to find any
difference in gastric volumes between anxious patients and controls.16

Patients with a history of motion sickness or previous episodes of postoperative vomiting are also at increased risk for PONV. The reflex arc in these individuals may be sensitized by their earlier experience; subsequently, lower-intensity stimuli may induce vomiting.

Ingestion of solid food before surgery increases emesis risk via distension of the gut and release of GI hormones that can sensitize the reflex arc. It has been shown recently that intake of clear liquids before surgery is not associated with increased rates of PONV.17 In fact, several studies have shown that patients given clear liquids have lower gastric volumes than fasted subjects.18,19 Furthermore, overnight fasting is itself a risk factor for nausea. In one series, 56% of women and 38% of men who abstained from all food and drink overnight were nauseated in the morning when they arrived for surgery.10

SURGICAL FACTORS

Surgery is accompanied by increased vasopressin release, as well as delayed gastric emptying and decreased intestinal motility. Surgical site also influences PONV risk. Emesis rates are particularly high after abdominal surgery, because bowel manipulation stimulates vagal and splanchnic mechanoreceptor afferents, resulting in the release of serotonin, prostaglandins, and other peptides that can trigger vomiting. Gynecologic procedures are also associated with a high incidence of PONV. Stimulation of afferents from the uterus and cervix may play a role, as well as bowel manipulation. Other procedures with increased PONV include those involving the ear, nose, throat, or eyes.20 Traction on the extraocular muscles sensitizes the vomiting center via ciliary ganglion afferents.

ANESTHETIC AGENT FACTORS

The drugs used for inducing, maintaining, and supplementing anesthesia have varying effects on the risk of PONV. All opioids, regardless of their route of administration, can produce nausea and vomiting. This effect is partly due to stimulation of μ-opioid receptors in the area postrema. Opioids also contribute to nausea and emesis via delayed gastric emptying, sensitization of vestibular-induced emesis, and release of vasopressin. Opioid administration also stimulates serotonin release, although this is not a major pathway.21

Among the hypnotic drugs used for surgical patients, both etomidate and ketamine have been associated with high rates of emesis. Fragen and Caldwell reported a 55% emesis rate among subjects given etomidate versus 15% for those given the barbiturate thiopental.22 Thompson et al compared ketamine with thiopental and found emesis rates of 30% for ketamine and 10% for thiopental.23

Propofol, a fast-acting, rapidly eliminated agent used in the induction and maintenance of anesthesia, can reduce PONV in procedures that have a high baseline incidence of emesis. In a study reported by Korttila et al involving gynecologic surgery patients, the incidence of nausea and vomiting was reported as 37% among women receiving propofol for induction and maintenance versus 75% among those given thiopentone and isoflurane.24 Another study, which compared propofol with methohexital for induction and maintenance, reported emesis rates of 17% with propofol and 43% with methohexital.25 The
beneficial effect of propofol on PONV has also been seen in children. Propofol appears to offer no significant benefit for reducing the overall incidence of vomiting among patients undergoing surgeries associated with a low emetogenic potential.

Administration of propofol (for anesthesia induction) may itself protect patients against PONV, through stabilization of the afferent triggering pathways. In our study, patients underwent induction with propofol and were then randomized to maintenance with propofol or isoflurane. Propofol was associated with a 27% incidence of PONV, versus 29% for isoflurane. Fredman et al reported similar results.

Propofol can also be given postoperatively for its direct antiemetic effect. Using a sedative at a dose of 10 to 20 mg, Borgeat et al reported reduction of vomiting in 81% of patients versus 35% of placebo-treated controls.

Although nitrous oxide does produce nausea in normal volunteers, its effect in adult surgery patients is less clear. In their study of women undergoing laparoscopy with enflurane as the anesthetic, Lonie and Harper reported that the postoperative vomiting rate was 49% in patients given adjunctive nitrous oxide and 17% in those receiving air. However, subsequent studies have failed to confirm a highly emetic potential for nitrous oxide. The vomiting rate for patients receiving isoflurane with adjunctive nitrous oxide during laparoscopy was 54%, compared with a 52% vomiting rate for those patients receiving air. Data from pediatric studies indicate that nitrous oxide increases PONV rates after strabismus surgery. Watcha et al reported postoperative vomiting in 60% of children given propofol and nitrous oxide, compared with 23% given propofol and oxygen.

Nitrous oxide has the potential to increase postoperative emesis by several mechanisms. It diffuses into the middle ear, increasing pressure and thereby stimulating vestibular afferents for PONV. It also may diffuse into the intestines, resulting in distension. Nitrous oxide is also known to stimulate the sympathetic nervous system and may interact with endogenous opioid receptors.

The potent inhaled agents ether and cyclopropane are associated with increased endogenous catecholamines and have long been recognized for a high incidence of associated postoperative vomiting. At deeper anesthetic levels, the newer agent isoflurane also increases sympathetic stimulation. This drug has been associated with a higher incidence of PONV than enflurane or sevoflurane. Desflurane also can induce high levels of sympathetic stimulation and has anecdotally been linked to increased postoperative vomiting.

Use of acetylcholinesterase inhibitors, such as neostigmine, for reversal of neuromuscular blockade may also increase a patient's risk for PONV. Compared with controls allowed to recover spontaneously from muscular blockade, King et al reported that patients treated with neostigmine had significantly higher rates of both nausea (68% vs 32%, respectively) and vomiting (47% vs 11%). These agents may increase vomiting risk by muscarinicholinergic-induced increases in GI motility as well as by direct activation of central cholinergic pathways at the area postrema.

Anticholinergic agents such as atropine and glycopyrrolate are often given in combination with the acetylcholinesterase-inhibiting drugs to minimize unwanted effects on GI motility. In a comparative study, patients given atropine had less nausea than those treated with glycopyrrolate (8% vs 28%) and a lower requirement for droperidol in the first 2 hours postsurgery (6% vs 24%). Atropine is more effective in reducing PONV because it crosses the blood-brain barrier and can block the cholinergic afferents centrally, whereas glycopyrrolate acts only peripherally.

The use of regional anesthetic techniques reduces the risk of PONV relative to general anesthetic techniques but does not eliminate it.
general anesthetic techniques but does not eliminate it. Nineteen percent to 22% of patients undergoing spinal or epidural anesthesia may experience nausea and vomiting, and the rate is 9% for patients receiving peripheral blocks.\textsuperscript{38,39} Bridenbaugh et al reported a definite reduction in PONV with epidural anesthesia over general anesthesia in their comparative study of laparoscopy patients (4% versus 38%).\textsuperscript{40} but the reduced PONV in this series may reflect the fact that laparoscopy done under epidural anesthesia often is associated with changes in surgical technique, such as abdominal distension and less positional change.

Overall, PONV incidence in patients receiving local or regional anesthetic techniques is determined by the procedure being performed and the sedative/analgesic drugs used. Even patients receiving local anesthesia may experience high rates of nausea and vomiting. Monk et al reported in two studies that 4% to 11% of patients undergoing extracorporeal shock wave lithotripsy with monitored anesthesia required antiemetic therapy.\textsuperscript{41,42} The combination of regional plus general anesthesia can result in an additive effect on PONV: 59% with the combined technique versus 22% with regional anesthesia and 31% with general anesthesia.\textsuperscript{38}

**ANESTHETIC PROCESS FACTORS**

It has long been thought that mask ventilation is associated with a higher risk of emesis than is intubation, but this concept appears to be more belief than reality. The study by Bellville et al, which is usually cited as the reference for this theory, favored intubation over mask ventilation only in the subset of patients who received the highly emetogenic ether or cyclopropane anesthetics.\textsuperscript{43} In the overall patient population, however, emesis rates were similar for mask ventilation and intubation. A difference in PONV may occur if the mask ventilation is administered by a trainee, who may be more likely than an experienced anesthesiologist to introduce air and distend the patient's stomach, increasing emesis risk. Hovorka et al reported vomiting during the first 2 hours after surgery in 54% of subjects receiving mask ventilation administered by a trainee but in only 35% of those cared for by an experienced specialist.\textsuperscript{44}

The success of gastric suctioning in preventing emesis is also more widely believed than substantiated. Most studies evaluating this method report no difference in vomiting rates during the recovery process between patients suctioned and controls. In fact, Trépanier and Isabel found that suctioning increased the incidence of postdischarge vomiting, probably secondary to orogastric tube-induced pharyngeal stimulation.\textsuperscript{45}

**POSTOPERATIVE FACTORS**

Sedation suppresses PONV. On the other hand, rapid awakening may enhance the risk of this complication. Awake patients are more likely to experience nausea, which occurs before the emetogenic anesthetic effects have waned. Movement also plays a role in producing PONV, through a variety of mechanisms. Prolonged recumbency may increase vestibular discharge. Furthermore, surgical patients may be relatively hypovolemic, which places them at risk for postural hypotension, dizziness, and nausea triggered by decreased blood flow to the CTZ when they stand up.\textsuperscript{46} In addition, ambulation may precipitate nausea and vomiting in patients who have received opioids, which sensitize motion-induced vestibular system afferents to the CTZ.

Researchers have also found a strong correlation between postoperative pain and nausea. In a series of patients who had major abdominal surgery, Andersen and Krogh found that pain occurred alone as a postoperative symptom relatively rarely, affecting only 10% of their patients after abdominal surgery, whereas pain with nausea coexisted in 59% of their subjects.\textsuperscript{47} The mechanisms by which pain can induce PONV include stimulation of the visceral
nociceptors and peripheral and central sensitization of the reflex by a variety of chemical mediators. Because pain also increases central nervous system arousal, patients may be more aware of nausea caused by other factors.

Treatment with narcotic analgesics may reduce both pain and nausea. Andersen and Krogh found that 80% of patients given morphine, 4 mg, to treat pain experienced nausea relief. Nausea persisted in 10%, and was induced by the narcotic in another 4%. Morphone's beneficial effect may not occur after lesser ambulatory surgery such as arthroscopy.

Substituting the injectable nonsteroidal anti-inflammatory drug ketorolac for opioids as an analgesic agent may avert some of the undesirable features of narcotics, particularly respiratory depression. However, ketorolac produces nausea via a direct GI effect, and its effect on PONV risk is equivocal.

In adult and pediatric patients, the first oral intake after surgery often serves as the trigger for postoperative vomiting. Evidence from a pediatric study by Schreiner et al. enforces the idea that we should refrain from requiring patients to drink after surgery. In this trial, patients who were required to drink liquids experienced a higher incidence of vomiting (23% vs 14%), as well as longer times until discharge (101 vs 84 minutes), than subjects who drank only if thirsty. Allowing patients to drink as needed had no adverse effects on the incidence of postdischarge vomiting, and there were no patient admissions or readmissions.

CONCLUSION

PONV is a common problem that is growing in significance with the growth of ambulatory surgery. It is precipitated by a multitude of factors—related to the patient, the procedure, and the anestesia—that exert their effects through a variety of pathophysiologic mechanisms. Prevention and treatment of this unpleasant side effect of anesthesia require approaches that will block the spectrum of involved afferent pathways.

DISCUSSION

Dr Kris: Does the gender difference in risk for PONV reflect the fact that women undergo more emetogenic procedures than men overall?

Dr Philip: It is in many cases difficult to separate emetogenic procedure and gender, such as gynecologic procedures for women. For all procedures, women are at increased risk for PONV. We really don't see the incidence of vomiting decline in women until they're over 70 years old—past the age of menopause. This suggests that factors in addition to cycle hormonal fluctuations are influencing PONV risk.

Dr McLeskey: Nausea and vomiting are more difficult to control in women than in men and in young compared to older adults, regardless of whether these events are secondary to surgery or chemotherapy. We've found that nausea and vomiting are easier to control in patients with a history of drinking more than five units of alcohol daily for several years versus those who have a history of lower alcohol consumption.

Dr Kris: The interesting point about alcohol is that it is not current use, but a history of use, that is important. There may be a genetic predisposition to control of vomiting.

Dr McLeskey: There also may be a genetic predisposition to alcoholism, or prolonged exposure to alcohol may have changed the patient's internal environment.

Dr Philip: Alcohol may desensitize some of the pathways for nausea and vomiting. There are no data on the effect of history of alcohol use on the risk of PONV.

Dr McLeskey: Has propofol been used much as an antiemetic in patients receiving chemotherapy?

Dr Kris: Propofol is generally not
allowed outside the operating room, because it can cause significant respiratory depression. However, propofol is commonly used in oncology as a sedative in pediatric patients undergoing spinal tap, CT scan, chemotherapy, and bone marrow aspiration. There are several anecdotal examples of children, with histories of chemotherapy-induced vomiting, who did not vomit while receiving propofol.

Dr McLeskey: It would also be necessary to prove that propofol was superior to the agents currently being used, which are safe and effective as single IV or oral doses.

References