CHAPTER **2**

POSTOPERATIVE AND POSTDISCHARGE NAUSEA AND VOMITING: Risk Assessment and Treatment Strategies

Joshua J. Mann, DPM

INTRODUCTION

Postoperative nausea and vomiting (PONV) relates to the immediate postoperative period, and continues to be one of the most common complaints following anesthesia in the surgical setting. In fact, it is one of the postsurgical complications that patients would most like to avoid (1). Its incidence has been reported to occur in more than 30% of surgeries, and it can occur in 70% to 80% of surgeries dealing with high-risk populations without prophylaxis (2). Although PONV is usually self-limiting, it can lead to serious medical consequences. Emesis increases the risk of aspiration, and has been associated with electrolyte imbalances, dehydration, esophageal rupture, and painless loss of vision due to retinal detachment (3-7). PONV also can impact patient satisfaction, quality of life, and lead to increased health-care costs as a result of delayed discharge, prolonged nursing care, and unanticipated admissions (8, 9).

Increasing attention has been directed towards nausea and vomiting that occurs beyond the immediate post-operative period, better known as postdischarge nausea and vomiting (PDNV). Caroll et al (10) found that 35% of patients will experience PDNV, and delayed resumption of their normal daily activities because of it. PDNV has not been fully recognized, and the literature on the subject is scarce.

In the recent literature, there has been an emphasis on risk stratification and prophylactically treating those patients at a moderate to high risk for developing PONV. This may help decrease both the risk of developing PONV, and also PDNV. The 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists are currently considered the mainstay of antiemetic therapy, but newer approaches involving multimodal management, and the use neurokinin-1 antagonists, a longer-acting serotonin receptor antagonist, is gaining attention.

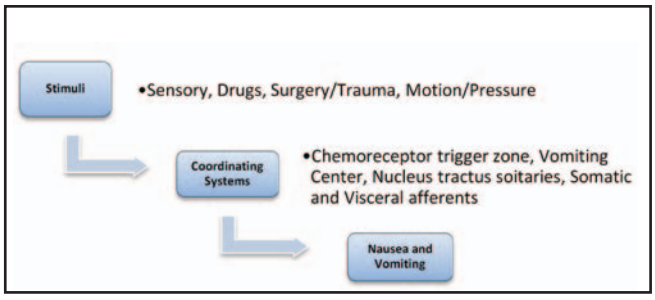

Figure 1. Mechanism of nausea and vomiting.

NAUSEA AND VOMITING PATHOPHYSIOLOGY

Nausea and vomiting are controlled by the vomiting center, which is an ill-defined area of the lateral reticular formation in the brainstem (11, 12). It is not a discrete center as much as it is a central pattern generator (CPG) that initiates a specific sequence of neuronal activities throughout the medulla to result in vomiting (13). There are several areas throughout the body including higher cortical centers, cerebellum, vestibular apparatus, vagal, and glossopharyngeal nerve afferents that influence the complex motor response of emesis (14). A very important afferent is the chemoreceptor trigger zone (CTZ). The CTZ is located at the base of the fourth ventricle in the area postrema, and is outside the blood-brain barrier (15). The CTZ is richly vascularized, and interprets chemical stimuli from the bloodstream and cerebrospinal fluid. It communicates with the adjacent nucleus tractus solitaries (NTS), which projects into the emesis center (16). There are several neurotransmitter receptors including serotonergic, dopaminergic, histaminergic, cholinergic, and neurokininergic that mediate signals between the anatomic areas. Antiemetic agents are directed towards these receptors. Exogenous substances such as opioid analgesics, chemotherapeutic agents, and cardiac glycosides can also induce nausea and vomiting (Figure 1) (17, 18).

RISK FACTORS FOR PONV AND PDNV

In the recent literature, there has been an emphasis on risk stratification for determining which patients to prophylactically treat with antiemetics. There are several surgical, anesthetic, and individual factors that have been considered predictors for PONV. In adults, Apfel colleagues

(19) identified four highly predictive risk factors for PONV: female sex, history of motion sickness or PONV, nonsmoker, and use of perioperative opioids. The presence of 0, 1, 2, 3, or 4 of these factors corresponded to an incidence of PONV of 10%, 21%, 39%, 61%, and 79%, respectively. In the pediatric population, Eberhart and colleagues (20) identified four independent risk factors for postoperative vomiting (POV). These factors were duration of surgery 30 minutes or longer, age 3 years or older, strabismus surgery, and a positive history of POV in the child or POV/PONV in immediate relatives. The presence of 0, 1, 2, 3, and 4 of these risk factors corresponded to an incidence of POV of 9%, 10%, 30%, 55%, and 70% respectively. Other studies have implied that the use of volatile anesthetics, nitrous oxide, and administration of intraoperative and postoperative opioids are also significant risk factors for PONV (21-24). There are a few studies that have attempted to identify specific PDNV risk factors. To date, it is not clear whether PDNV and PONV risk factors are the same (25).

ANTIEMETIC CLASSES

Antiemetics act on specific neurotransmitter receptors. The CTZ contains dopamine, muscarinic, histamine-1 (H1), serotonin, neurokinin-1 (NK1), and opioid receptors. The NTS contains dopamine, serotonin, histamine, and muscarinic receptors. No individual antiemetic has been found to block all receptor types, and therefore no single agent is completely effective against PONV in all cases. Hence, there is a need to be familiar with the broad range of drug classes and agents available.

Serotonin Antagonists

Serotonin antagonists have become one of the mainstay treatments for PONV since their debut in the early 1990s to treat chemotherapy-induced nausea and vomiting (26). Serotonin is released from the gastrointestinal tract and central nervous system to stimulate the CTZ or vagal afferents to activate the vomiting center (27). The 5-HT3 receptor antagonists include odansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet), and most recently palonosetron (Aloxi). These inhibit the action of serotonin in 5-HT3 receptor-rich areas of the brain, and have all been approved by the Food and Drug Administration (FDA) for use in PONV.

Serotonin antagonists are generally safe and effective. All have been shown to be equally effective for the treatment of PONV (28). Ondansetron (Zofran) has been the most studied. The most common side effects are headache, dizziness, constipation, and diarrhea. These are usually short term, and only mild to moderate in intensity. Most available data suggests that these are most effective when administered at the end of surgery (29-33).

Tramer and colleagues (33) found that ondansetron 4 mg had a number needed to treat (NNT) of 4.4 for the prevention of both nausea and emesis in the first 48 hours postoperatively. Risk of severe side effects was generally low, with a number needed to harm (NNH) of 23 for constipation, 31 for elevated liver enzymes, and 36 for headache. The usual recommended dose of ondansetron is 4 mg intravenously (IV) given at the end of surgery (18). Ondansetron is also available as an orally disintegrating tablet (ODT), which seems to be as effective as the IV form (34). Ondansetron is the only serotonin antagonist that has been approved for pediatric patients less than 2 years old (35).

Palonosetron is the newest serotonin antagonist, and has a relatively long duration of action. Some studies have suggested that the long half-life of palonosetron may have an antiemetic effect for several days following administration (36). However, further studies are needed to confirm that palonosetron has any advantage over the other available serotonin antagonists.

Corticosteroids

Dexamethasone is beneficial in the management of PONV. It is believed that dexamethasone acts centrally to inhibit prostaglandin synthesis or controls endorphin release (37). According to studies it is most effective when administered at induction, and is particularly effective in combination with 5-HT3 receptor antagonists (37, 38). Dexamethasone may reduce levels of serotonin by diminishing its precursor tryptophan, preventing the release of serotonin in the gut, and sensitizing the 5-HT3 receptor to other antiemetics. The Society for Ambulatory Anesthesia Guidelines, published in 2007, recommended that a prophylactic dose of dexamethasone of 4 to 5 mg IV administered at induction seemed to be as effective as ondansetron 4 mg IV in preventing PONV (18).

Anticholinergics

Transdermal scopolamine and atropine are among the oldest antiemetics. Atropine has weak antiemetic effects (39), and generally is not used because of its cardiovascular effects (40). Most studies have looked at transdermal scopolamine designed to release 1.5 mg over three days. Premedication with scopolamine has been shown to be as effective as odansetron and droperidol in the prevention of early and late PONV/PDNV. There is a greater risk of dry mouth associated with scopolamine (41). It may be a great adjunct with other therapies. It should be applied either the evening before surgery, or four hours before the end of anesthesia due to it taking two to four hours before having an effect.

Dopamine Antagonists (Benzamides, Butyrophenones, Phenothiazines)

There are three types of dopamine antagonists that act at the D2 receptors in the CTZ and area postrema to suppress nausea and vomiting. These are benzamides, butyronphenones, and phenothiazines.

Benzamides. Metoclopramide (Reglan) is the most commonly used antiemetic in this group. It is a procainamide derivative that blocks D2 receptors centrally at the CTZ and area postrema, and peripherally in the gastrointestinal tract (39). Metoclopramide slows esophageal clearance, accelerates gastric emptying, and shortens bowel-transit time. These properties may make it useful in preventing the delayed gastric emptying caused by opioids (42). Adverse side effects associated with metoclopramide are akathisia, dystonia, and tardive dyskinesia. Metoclopramide has not been recommended as an effective antiemetic (43).

Butyrophenones. Butyrophenones, haloperidol and droperidol, are strong D2 receptor antagonists, but are also α-blockers that contribute to their adverse effects of sedation and extrapyramidal symptoms (39). Extrapyramidal symptoms are rare at the low doses administered for PONV. In 2001, the FDA issued a black box warning for droperidol, due to reports of severe cardiac arrhythmias, and rare cases of sudden cardiac death (44). Many experts and anesthesia providers still believe that droperidol at low doses remains a safe antiemetic (44-46). The use of droperidol has significantly declined since then, and if used the FDA recommends that all elective surgical patients receiving droperidol be placed on continuous electrocardiographic monitoring for two to three hours following administration. Its use in ambulatory surgical patients is not practical.

Haloperidol has since received increased interest as an antiemetic. This agent has been used as an antipsychotic since the 1960s, and has a faster onset of antiemetic action than droperidol. The effect of haloperidol is not as long acting, possibly due to a weaker binding affinity to D2-receptors (39, 47). Additional studies are needed before haloperidol can be recommended for prophylaxis or treatment of PONV.

Phenothiazines. This class is one of the most commonly used in the world. These include promethazine, chlorpromazine, prochlorperazine, perphenazine, and thiethylperazine. There are many adverse effects associated with these agents including sedation, restlessness, diarrhea, agitation, central nervous system depression, hypotension, supraventricular tachycardia, neuroleptic syndrome, and extrapyramidal effects (17). Due to these effects usage has become less favorable. It should also be noted that there are black box warnings suggesting that promethazine could cause respiratory depression or soft tissue necrosis with possible gangrene if administered in the IV form. Strong data are lacking to recommend these as first-line antiemetics. Promethazine has been noted to be a useful alternative if patients fail to respond to ondansetron (18).

Antihistamines

Diphenhydramine, dimenhydrinate, and promethazine are antihistamines that have antiemetic properties. They block histamine H1 receptors in the NTS, vestibular system, and vomiting center. There is little or no direct action at the CTZ (27). Common side effects that can occur with these agents are sedation, blurred vision, urinary retention, and dry mouth due to them also having some anticholinergic activity. They are relatively inexpensive, but have not been well studied for use in PONV (62).

Innovative Antiemetic Therapies (Neurokinin-1 Antagonists, Opioid Antagonists)

Neurokinin-1 Antagonists. This is a new class of antiemetics that competitively bind substance P. Substance P is a ligand for neurokinin-1 receptors located in the gastrointestinal tract and the area postrema (50). Neurokinin-1 receptor antagonists work centrally on the neurotransmission between the NTS and CPG, which is believed to suppress nausea and vomiting (51). These may also decrease the strength of emetogenic signals sent to the emetic center from vagal terminals in the gut (52). Encouraging data have shown aprepitant, the first neurokinin-1 receptor antagonist to be approved by the FDA, to be as effective as ondansetron in the treatment of PONV (54). The most common side effects are asthenia, diarrhea, dizziness, and hiccups (55).

Aprepitant is available in both an oral form and IV form (fosaprepitant). Further studies need to be performed in the PONV setting. In the future, these may be good options for patients who have failed treatment with other antiemetic classes.

Opioid Antagonists

Naloxone is an opioid reversal agent that may have antiemetic efficacy. Perioperative administration of opioids have been shown to cause an increased risk of PONV due to decreasing gastric motility and delaying gastric emptying by inhibiting central μ-opioid receptors (56). Low dose naloxone (0.25 μ/kg/h) has been shown to be effective in decreasing the incidence of PONV in adults (57) and children (58). However, there is scarcity of research on this type of use, and further study is required before this can be recommended in the treatment of PONV.

NONPHARMACOLOGIC OPTIONS

Acupuncture, transcutaneous electrical stimulation, and acupressure have all been studied as nonpharmacological options in the treatment of PONV. Acupuncture is the most studied, and it has been shown that acupuncture of point pericardium 6 (P6) is effective in prevention of PONV with few side effects. P6 is located four centimeters proximal from the wrist crease between the tendons of the palmaris longus and flexor carpi radialis muscles (59). It is thought that acupuncture influences the release endogenous opioids, or inhibits gastric acid secretion and normalizes dysrhythmia (60). Possible side effects include fainting, exacerbation of symptoms, and lost or forgotten needle (61).

ANTIEMETIC STRATEGIES

Prophylactic strategies need to be tailored to an individual patient's risk. Baseline risk reductions consist of the avoidance of volatile anesthetics (21), using propofol for induction and maintenance of anesthesia (2), avoiding the use of nitrous oxide, (2, 19) using doses of neostigmine less than 2.5 mg, (66) minimizing the use of perioperative opioids (19, 21, 65, 67) and using regional anesthesia over general anesthesia when appropriate (64). Adequate hydration should be achieved due to hypotension compromising intestinal perfusion and possibly leading to gastrointestinal intolerance (68).

Prophylaxis is not recommended for low risk patients (0-1 risk factor present). If rescue therapy is needed

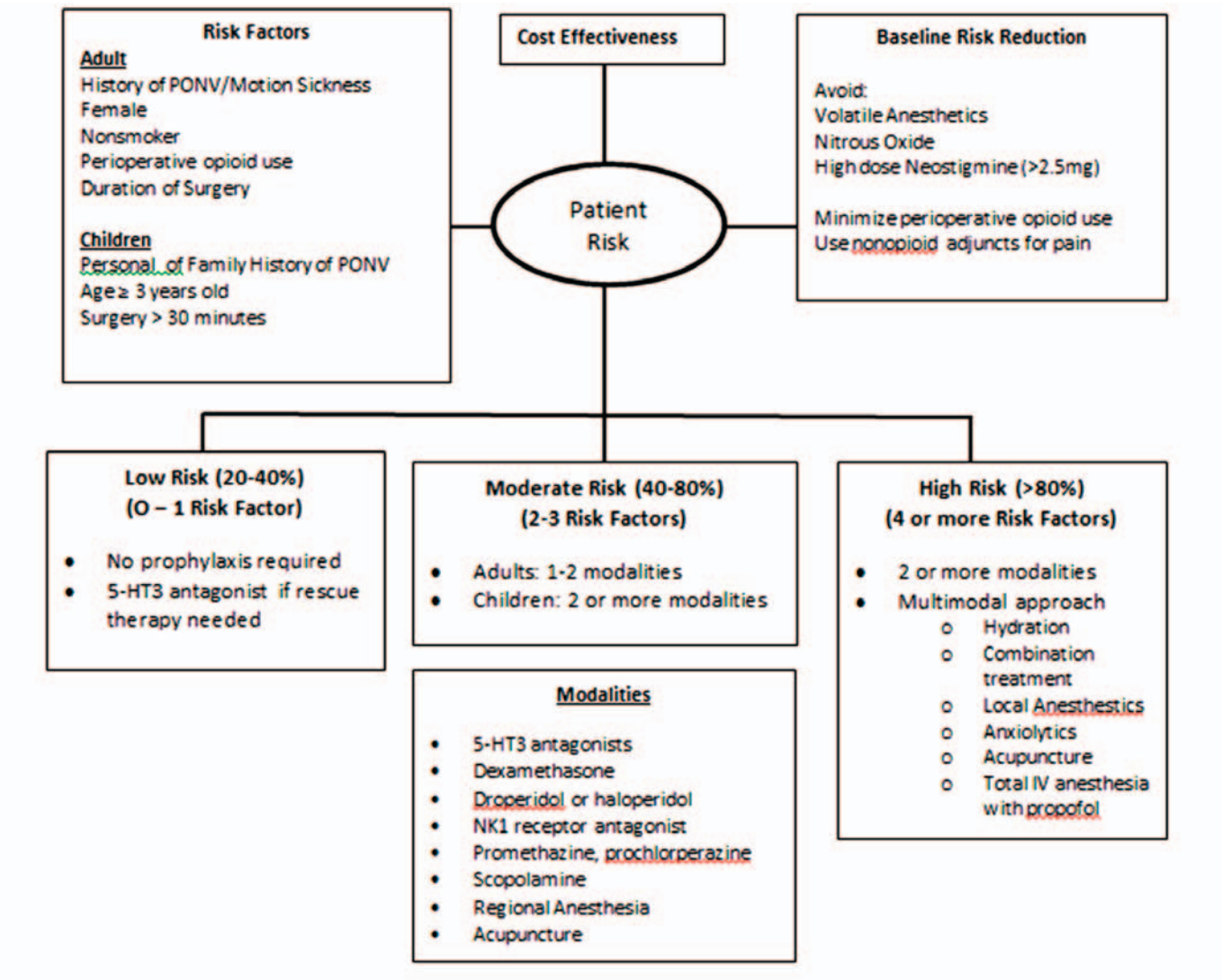

Figure 2. Treatment algorithm for postoperative nausea and vomiting.

postoperatively, ondansetron is the recommended agent at 4 mg IV. In moderate risk patients (2-3 risk factors present) one or two modalities should be performed in adults, and two or more modalities should be used for children. Possible modalities include using a 5-HT3 receptor antagonist, dexamethasone, droperidol, propofol anesthesia, regional anesthesia, a NK1 receptor antagonist, a phenothiazine, scopolamine, or acupuncture. A multimodal approach should be used for high risk patients (4 risk factors present). Multimodal approaches involve adequate hydration, combination therapy, total intravenous anesthesia with propofol, local anesthetics, anxiolytics, and nonpharmacological therapies (Figure 2) (18, 62).

RESCUE TREATMENT AND MANAGEMENT OF PDNV

It is unfortunate when PONV occurs in the hospital, but it is much worse for the patient when PDNV occurs at home where healthcare professionals are not available to provide intervention. All possible factors need to be determined before initiating rescue antiemetic drugs. Pain, mechanical reasons (blood in the throat, abdominal obstruction, etc.), and use of opioids and other medications need to be considered. Frequent intake of clear liquids in small amounts should be encouraged, along with the avoidance of milk-based products and acidic fruit juices due to these causing an increase in gastric secretions. Carbonated drinks should be avoided as well because these can distend the stomach (69). Patients who did not receive any antiemetic prophylaxis should be given a serotonin antagonist (18). Ondansetron 4 mg, by mouth is the typical dosage, however studies have shown that 1 mg is effective. If ondansetron was given prophylactically, no additional benefit will be achieved if a repeated dose is given within six hours of the initial dose (61). An alternative agent should be used in this case such as promethazine 6.25 to 12.5 mg, by mouth. Dexamethasone and transdermal scopolamine are not recommended for emetic episodes that occur longer than six hours postoperatively because of their longer duration of action (18). Pan et al (25) found that administering a single dose of IV dexamethasone 8 mg and ondansetron 4 mg, followed with an 8 mg oral disintegrating ondansetron tablet, that was taken on discharge, as well as, in the morning of postoperative days one and two significantly decreased the incidence of PDNV during the first five days of recovery in those patients at high risk.

CONCLUSION

PONV and PDNV continue to be common problems following surgery. Strategies to reduce the occurrence of these complications involve assessing patients for risk factors, and performing baseline risk reductions. A multimodal approach is most useful for high risk patients. Ultimately, healthcare costs will be reduced, and patient satisfaction will more likely be achieved if these risks are recognized and proper management is implemented.

REFERENCES

1. Gan T, Sloan F, Dear Gde L, et al. How much are patients willing to pay to avoid postoperative nausea and vomiting? Anesth Analg 2001;92:393-400.
2. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2441-51.
3. Atallah FN, Riu BM, Nguyen LB, et al. Boerhaave's syndrome after postoperative vomiting. Anesth Analg 2004;98:1164-6.
4. Eroglu A, Kurkcuoglu C, Karaoglanoglu N, et al. Spontaneous esophageal rupture following severe vomiting in pregnancy. Dis Esophagus 2002;15:242-3.
5. Komenaka IK, Gandhi SG, deGraft-Johnson JB, et al. Postoperative vomiting causing esophageal rupture after antiemetic use. A case report. J Reprod Med 2003;48:124-6.
6. Zhang GS, Mathura JR Jr. Images in clinical medicine. Painless loss of vision after vomiting. N Engl J Med 2005;352:e16.
7. Nanji GM, Maltby JR. Vomiting and aspiration pneumonitis with the laryngeal mask airway. Can J Anaesth 1992;39:69-70.
8. Williams KS. Postoperative nausea and vomiting. Surg Clin N Am 2005;85:1229-41.
9. Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology 2000;92:958-67.
10. Carroll NV, Miederhoff P, Cox FM, et al. Postoperative nausea and vomiting after discharge from outpatient surgery centers. Anesth Analg 1995;80:903-9.
11. Wang SC, Borison HL. A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides. Gastroenterology 1952;22:1-12.
12. Wang SC, Borison HL. The vomiting center; a critical experimental analysis. Arch Neurol Psychiatry 1950;63:928-41.
13. Hornby PJ. Central neurocircuitry associated with emesis. Am J Med 2001;111(Suppl 8A):106S-12.
14. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162-84.
15. Borison HL. Area postrema: chemoreceptor circumventricular organ of the medulla oblongata. Prog Neurobiol 1989;32:351-90.
16. Leslie RA. Neuroactive substances in the dorsal vagal complex of the medulla oblongata: nucleus of the tractus solitarius, area postrema, and dorsal motor nucleus of the vagus. Neurochem Int 1985;7:191-211.
17. Gan TJ. Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. CNS Drugs 2007;21:813-33.
18. Gan TJ, Meyer TA, Apfel CC, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007;105:1615-28.

19. 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.
20. Eberhart LH, Geldner G, Kranke P, et al. The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients. Anesth Analg 2004;99:1630-7.
21. Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth 2002;88:659-68.
22. Roberts GW, Bekker TB, Carlsen HH, et al. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesth Analg 2005;101:1343-8.
23. Leslie K, Myles PS, Chan MT, et al. Risk factors for severe postoperative nausea and vomiting in a randomized trial of nitrous oxide-based vs nitrous oxide-free anaesthesia. Br J Anaesth 2008;101:498-505.
24. Mraovic B, Simurina T, Sonicki Z, et al. The dose-response of nitrous oxide in postoperative nausea in patients undergoing gynecologic laparoscopic surgery: a preliminary study. Anesth Analg 2008;107:818-23.
25. Pan PH, Lee SC, Harris LC. antiemetic prophylaxis for postdischarge nausea and vomiting and impact on functional quality of living during recovery in patients with high emetic risks: a prospective, randomized, double-blind comparison of two prophylactic antiemetic regimens. Anesth Analg 2008;207:429-38.
26. Hesketh PJ, Gandara DR. Serotonin antagonists: a new class of antiemetic agents. J Natl Cancer Inst 1991;83:613-20.
27. Scuderi PE. Pharmacology of antiemetics. Int Anesthesiol Clin 2003;41:41-66.
28. Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. BMC Anesthesiol 2001;1:2.
29. Zofran (ondansetron hydrochloride) injection [prescribing information]. GlaxoSmithKline. 2009. URL: http://us.gsk.com/products/assets/us_zofran.pdf.
30. Kytril (granisetron hydrochloride) injection [prescribing information]. Roche Laboratories. 2009. URL: http://www.gene.com/gene/products/information/kytril/pdf/pi_injection.pdf.
31. Anzemet injection (dolasetron mesylate injection) [prescribing information]. Sanofi-Aventis; 2006. URL: http://products.sanofi-aventis.us/Anzemet_Injection/anzemet_injection.html.
32. De Leon A. Palonosetron (Aloxi): a second-generation 5-HT(3) receptor antagonist for chemotherapy-induced nausea and vomiting. Proc Bayl Univ Med Cent 2006;19:413-6.
33. Tramer MR, Reynolds DJ, Moore RA, et al. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997;87:1277-89.
34. Grover VK, Mathew PJ, Hegde H. Efficacy of orally disintegrating ondansetron inpreventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study. Anaesthesia 2009;64:595-600.
35. Olutoye O, Jantzen EC, Alexis R, Rajchert D, Schreiner MS, Watcha MF. A comparison of the costs and efficacy of ondansetron and dolasetron in the prophylaxis of postoperative vomiting in pediatric patients undergoing ambulatory surgery. Anesth Analg 2003;97:390-6
36. Kovac AL, Eberhart L, Kotarski J, et al. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. Anesth Analg 2008;107:439-44.
37. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000;90:186-94.
38. Wang JJ, Ho ST, Tzeng JI, et al. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth Analg 2000; 91:136-9.
39. Kovac Al. Prevention and treatment of postoperative nausea and vomiting. Drugs 2000;59:213-43.
40. Cameron D, Gan TJ. Management of postoperative nausea and vomiting in ambulatory surgery. Anesthesiol Clin N Am 2003;21:347-65.
41. White PF, Tang J, Song D, et al. Transdermal scopolamine: an alternative to ondansetron and droperidol for the prevention of postoperative and postdischarge emetic symptoms. Anesth Analg 2007;104:92-6.
42. Harrington RA, Hamilton CW, Brogden RN, et al. Metoclopramide. An updated review of its pharmacological properties and clinical use. Drugs 1983;25:451-94.
43. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, Kovac A, Philip BK, Sessler DI, Temo J, Tramer MR, Watcha M. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg 2003;97:62-71.
44. White PF. Droperidol: a cost-effective antiemetic for over thirty years. Anesth Analg 2002;95:789-90.
45. Habib AS, Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. J Clin Anesth 2008;20:35-9.
46. Dershwitz M. Droperidol: should the black box be light gray? J Clin Anesth 2002;14:598-603.
47. Granger B, Albu S. The haloperidol story. Ann Clin Psychiatry 2005;17:137-40
48. Habib AS, Reuveni J, Taguchi A, et al. A comparison of ondansetron with promethazine for treating postoperative nausea and vomiting in patients who received prophylaxis with ondansetron: a retrospective database analysis. Anesth Analg 2007;104:548-51.
49. Apfel CC, Malhotra A, Leslie JB. The role of neurokinin-1 receptor antagonists for the management of postoperative nausea and vomiting. Curr Opin Anaesth 2008;21:427-32.
50. Saito R, Takano Y, Kamiya HO. Roles of substance P and NK(1) receptor in the brainstem in the development of emesis. J Pharmacol Sci 2003;91: 87-94.
51. Minami M, Endo T, Kikuchi K, et al. Antiemetic effects of sendide, a peptide tachykinin NK1 receptor antagonist, in the ferret. Eur J Pharmacol 1998;363:49-55.
52. Diemunsch P, Joshi GP, Brichant JF. Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. Br J Anaesth 2009;103:7-13.
53. Gan TJ, Apfel CC, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of post-operative nausea and vomiting. Anesth Analg 2007;104:1082-9.
54. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003;97:3090-8.
55. Tsuchida D, Fukuda H, Koda K, et al. Central effect of mu-opioid agonists on antral motility in conscious rats. Brain Res 2004;1024:244-50.
56. Gan TJ, Ginsberg B, Glass PS, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997; 87:1075-81.
57. Maxwell LG, Kaufmann SC, Bitzer S, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. Anesth Analg 2005;100:953–8.

58. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev 2009;2: CD003281.
59. Rowbotham DJ. Recent advances in the non-pharmacological management of postoperative nausea and vomiting. Br J Anaesth 2005;95:77-81.
60. White A, Hayhoe S, Hart A, et al. Adverse events following acupuncture: prospective survey of 32 000 consultations with doctors and physiotherapists. Clinical research ed. BMJ 2001; 323 :485-6.
61. Kovac AL, O'Connor TA, Pearman MH, et al. Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled multicenter trial. J Clin Anesth 1999;11:453-9.
62. Le TP, Gan TJ. Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. Anesthesiology Clin 2010;28:225-49.
63. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? Anesthesiology 1999; 91:109-18.
64. Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesth Analg 2005;101:1343-8.
65. Khalil SN, Farag A, Hanna E, Govindaraj R, Chuang AZ. Regional analgesia combine with avoidance of narcotics may reduce the incidence of postoperative vomiting in children. Middle East J Anesthesiology 2005;18:123-32.
66. Tramer MR, Fuchs-Buder T. Omitting antagonism of neuromuscular blockade: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. Br J Anaesth 1999; 82:379-86.
67. Apfel CC, Kranke P, Eberhart LH, Roos A, Roewer N. Comparison of predictive models for postoperative nausea and vomiting. Can J Anaesth 2002;49:237-42.
68. Scuderi PE, James RL, Harris L, Mims GR. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. Anesth Analg 2009;91:1408-14.
69. Odom-Forren J, Fetzer S. Moser D. Evidence based interventions for post discharge nausea and vomiting: a review of the literature. J Perianesth Nurs 2006;21:411-30.
70. McGlamry ED. Postoperative nausea and vomiting. Update 1993. Tucker (GA); Podiatry Institute; 1993. p. 332-6.
71. Krakauer EL, et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.