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Special REPORT

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Antiemetic Drugs in the Prevention and Treatment of Postoperative Vomiting in Children

NEEDS STATEMENT

Postoperative nausea and vomiting (PONV) remains among the most unpleasant complications of surgery, especially in children. Fewer data are available for children than for adults on the preven-

tion and treatment of PONV. This activity was created to educate clinicians about state-of-the-art methods to prevent and treat this multifactorial complication in the pediatric patient.

ACCREDITATION STATEMENT

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LEARNING OBJECTIVES

At the end of this activity, participants should be able to:

- 1 Describe the incidence of and major risk factors for postoperative vomiting (POV) in children.
- 2 Review the neurochemical receptors involved in nausea and vomiting.
- 3 List the pharmacologic therapies, including doses, available for preventing and treating POV in children.

- 4 Describe the efficacy of combination therapies that have been evaluated for the prophylaxis of pediatric POV.
- 5 Discuss the available cost-effectiveness data for antiemetics used in the prevention and treatment of pediatric POV.

TARGET AUDIENCE

This activity is intended for pharmacists, nurses, nurse anesthetists, and physicians.

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METHOD OF PARTICIPATION

This activity should take approximately 1.5 hours to complete. The participant should, in order, read the objectives and monograph, answer the multiple choice post-test, and complete the answer form, registration, and evaluation. A score of at least 80% is required to successfully complete this program. Retests are NOT available for CRNAs. Participants will be sent their corrected answer sheet for comparison with course information. This credit is valid through April 30, 2005. No credit will be given after this date.

CE grading is available online at: CMEZone.com. Enter the project number "SR345" in the keyword field to directly access the activity.

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Introduction

Postoperative nausea and vomiting (PONV) is a common unpleasant complication of surgery in both adults and children, occurring in up to 80% of pediatric patients after some procedures.¹⁻³ Persistent PONV may result in delayed hospital discharge, unanticipated hospital readmission, decreased parental satisfaction, and higher healthcare costs. Severe, persistent vomiting has been reported to be associated with bleeding, dehydration, electrolyte disturbances, pulmonary aspiration, and wound dehiscence.¹⁻³

Unlike adults, children may not be able to describe the subjective feeling of nausea. Hence, the end point in pediatric studies is limited to vomiting and retching, and the term *postoperative vomiting* (POV) is used instead of *PONV*. Because drugs may have different effects on nausea and vomiting, data from adults cannot be applied to

children. This article reviews the most recent data on POV in children with regard to incidence and pathophysiology, risk factors, and prevention and treatment.

Incidence of and Risk Factors for Pediatric POV

Incidence

The overall incidence of POV is higher in children (11%–73%) than in adults (20%–30%).^{1,4} In fact, in children aged 3 years and older, the average incidence of POV ($\geq 40\%$) is almost twice that in adults.⁵ Fortunately, severe or intractable vomiting is rare, occurring in only 1% to 3% of children.⁶ Factors that may increase the risk for the development of POV in children are listed in Table 1.^{2,6-9} Not all of these factors are under the control

Table 1. Risk Factors for Pediatric POV^{2,6-9}

Risk Factor	Increases Risk	Decreases Risk
Patient-Related Factors		
Age	Older (>3 years to puberty)	Younger (≤ 2 years)
Gender*	Females (postpubertal)	Males
History of POV or motion sickness	Positive history	No history
Patient or parental anxiety	Yes [†]	No
Anesthetic-Related Factors		
Premedications	Opioids	Benzodiazepines, clonidine, transdermal scopolamine
Potent inhalation agents	Cyclopropane, ether	Desflurane, enflurane, halothane, isoflurane, sevoflurane have similar risk, but a lower risk than cyclopropane and ether
Nitrous oxide	Use of nitrous oxide	Avoidance of nitrous oxide
I.V. agents	Etomidate, ketamine	Propofol
Postoperative pain management	Opioids alone	Combination and/or multimodal analgesic therapy
Ambulatory surgery	Early postoperative movement	Inpatient admission
Timing of postoperative oral intake	Insist that patient drink before discharge	Let the patient decide when to drink
Surgery-Related Factors		
Type of surgery	Adenotonsillectomy, dental extraction, herniorrhaphy, laparotomy, laparoscopy middle ear surgery, orchiopexy, strabismus correction	Other
Duration of surgery	>30 min	<30 min

*Gender not a risk factor in prepubertal children.

[†]Historically considered a risk factor, but prospective clinical trial data supporting the claim are lacking. **POV**, postoperative vomiting

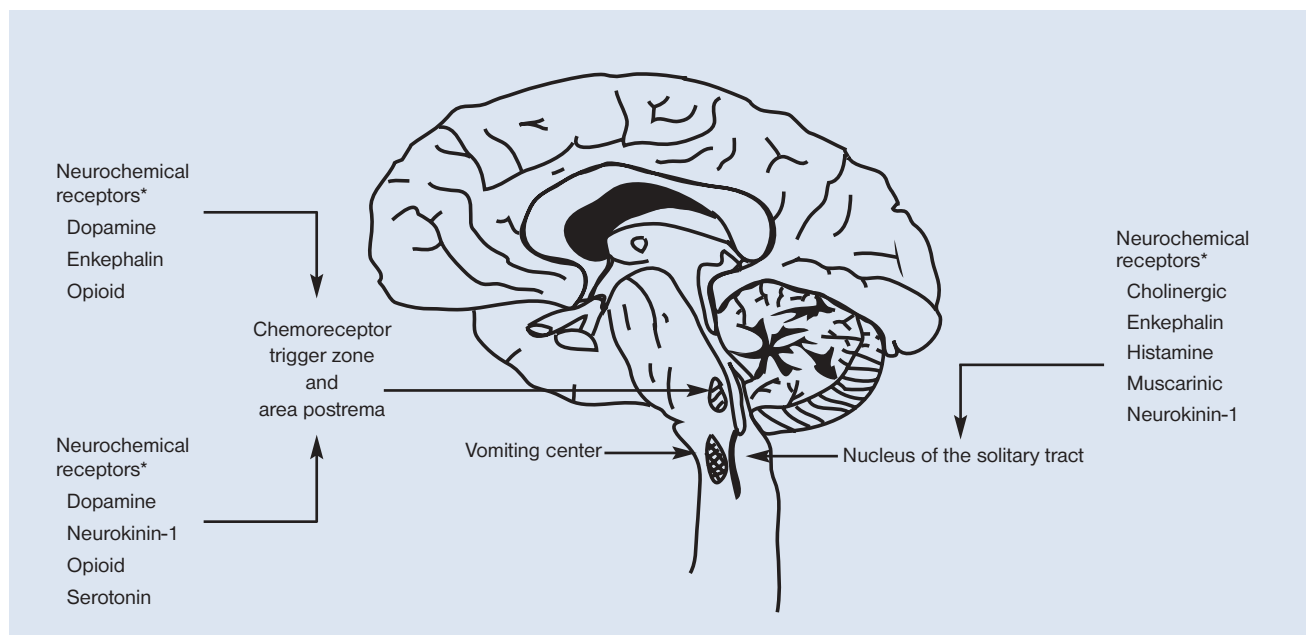


Figure 1. Midbrain neurochemical emetogenic receptor locations.^{1,4,9-11}

*Vomiting center coordinates impulses from these receptors to initiate the emetic reflex. Adapted and modified, with permission from Donnerer.¹⁰

of the anesthesiologist. The risk factors may be associated with the preoperative, intraoperative, or postoperative period.

Pathophysiology of Emesis

The vomiting center, which is located in the lateral reticular formation of the medulla, controls and coordinates the complex process of vomiting (Figure 1).^{1,4,9-11} This area receives input from other areas within the central nervous system (CNS), including the chemoreceptor trigger zone (CTZ), cerebellum, vestibular apparatus, cortical and brain stem centers, and solitary tract nucleus. These areas are rich in serotonergic, muscarinic, histamine, opioid, and dopaminergic receptors, the blockade of which has been postulated to be the mechanism of action of antiemetic drugs. The efferent output from the emetic center travels via the phrenic and spinal nerves of the abdominal wall musculature during the act of vomiting. No class of drugs has been determined to act on the emetic center. A new class of antiemetic drugs, neurokinin-1 (NK-1)-receptor antagonists, inhibit emetogenic stimuli from motion, irradiation, cisplatin, morphine, ipecac, and copper sulfate. This suggests that the NK-1-receptor antagonist class of drugs may act on the final common pathway from the emetic center.¹¹

Antiemetic Agents

Several antiemetics have been used for the prevention and treatment of POV, including anticholinergics; antihistamines; corticosteroids; and dopamine-, NK-1-, and serotonin type 3 (5-HT₃)-receptor antagonists.^{1,2,4,6,9,12-14} Although many of these agents have not been approved for this specific indication in children, a large body of data supports current practices. The literature is more extensive for adults. However, similar to studies in adults,

studies in children often contain contradictory data, as well as more data on the efficacy of a drug for the prophylaxis of POV than for its treatment.

During the last few years, a concerted effort has been made to summarize these data in systematic reviews in order to reach valid conclusions. When such systematic reviews apply advanced statistical techniques of meta-analysis to synthesize the results of multiple studies, the overall conclusions have greater precision. Indirect comparisons of various therapeutic regimens can be made by using the number-needed-to-treat approach, in which the investigator determines the number of patients that would need to be treated with a particular regimen to achieve the desired effect in 1 patient in whom the effect would not have been achieved with an alternative regimen.

Anticholinergic Agents

Anticholinergic agents are potent inhibitors of cholinergic and muscarinic receptors located in the nucleus of the solitary tract and vestibular apparatus.^{2,9} These drugs are effective in reducing both POV and motion sickness in adults.^{5,9} In children, however, only transdermal scopolamine has been shown to be effective in the prevention of POV in abdominal, prominent ear, and strabismus repair surgery.^{1,9} This agent is not approved for the prevention or treatment of POV in children, but it is approved for the prevention of PONV in adults. The development of delayed POV and adverse effects of scopolamine, however, may limit its use.⁹ Adverse effects of anticholinergic agents include dry mouth, visual disturbances, sedation, dysphoria, and hallucinations.²

Antihistamines

Antihistamines block histamine receptors in the nucleus

Table 2. Commonly Used Antiemetic Doses for Children^{1,2,4,6,7,9,21}

Drug	Receptor Antagonism Site	Dose (Route)	Common Adverse Effects
Anticholinergic Agent Scopolamine*	Muscarinic	1–1.5 mg every 72 h (transdermal patch)	Sedation, dry mouth, visual disturbances, dysphoria, hallucinations
Antihistamine Dimenhydrinate†	Histamine	0.5 mg/kg (I.V.) [‡]	Sedation, extrapyramidal effects, dry mouth, restlessness
Corticosteroid Dexamethasone†	Unknown	150 mcg/kg up to 8 mg (I.V.) [‡]	Cutaneous flushing, perineal itching
Dopamine Receptor Antagonists Droperidol	Dopamine	50–75 mcg/kg up to 1.25 mg (I.V.) [‡]	Drowsiness, sedation, extrapyramidal effects
Metoclopramide*	Dopamine	0.1–0.25 mg/kg (I.V.)	Sedation, extrapyramidal effects
Perphenazine‡	Dopamine	70 mcg/kg (I.V.) [‡]	Extrapyramidal effects, sedation (less than promethazine)
Promethazine	Dopamine	0.5–1 mg/kg (I.V./IM)	Sedation (more than perphenazine), extrapyramidal effects
5-HT ₃ -Receptor Antagonists Dolasetron	Serotonin	350 mcg/kg up to 12.5 mg (I.V.) [‡]	Headache, dizziness
Granisetron [§]	Serotonin	0.04 mg/kg (I.V.)	Headache, dizziness
Ondansetron	Serotonin	50–100 mcg/kg up to 4 mg (I.V.) [‡]	Headache, dizziness

*Not FDA-approved for prevention or treatment of POV in children, but approved for prevention of PONV in adults.

†Not FDA-approved for prevention or treatment of PONV in adults or POV in children.

‡Not FDA-approved for prevention or treatment of POV in children, but approved for treatment of severe nausea and vomiting in adults.

§Not FDA-approved for prevention or treatment of POV in children, but approved for the prevention and treatment of PONV in adults.

[‡]Dose recommended for POV prophylaxis in the consensus panel guidelines.⁷

FDA, Food and Drug Administration; 5-HT₃, serotonin type 3; IM, intramuscular; I.V., intravenous

of the solitary tract and acetylcholine in the vestibular apparatus.⁹ These drugs may be effective in preventing or controlling emesis following vestibular stimulation, which occurs during middle ear surgery and postoperative motion sickness, but their overall weak antiemetic properties and the profound sedation caused by antihistamines make these drugs less suitable for the management of POV.^{1,2,6}

The only antihistamine that has been evaluated as prophylaxis for POV in pediatric patients is dimenhydrinate, which has been shown to be effective in preventing POV in children when administered at a dose of 0.5 mg/kg I.V. or 2 to 3 mg/kg rectally.^{1,15} In addition, the recently published consensus guidelines for managing POV, which were developed by a multidisciplinary panel of experts, recommend administering dimenhydrinate at a dose of 0.5 mg/kg I.V.⁷ The most common adverse effects of dimenhydrinate include sedation, dry mouth, extrapyramidal symptoms, and restlessness.^{1,9} This agent is not approved for the prevention or treatment of PONV in adults or POV in children.

Corticosteroids

The antiemetic mechanism of action of corticosteroids

is unknown. Proposed mechanisms include prostaglandin antagonism, tryptophan depletion, endorphin release, reduction of 5-HT₃ levels in the brain and gastrointestinal tract, psychological effects, and anti-inflammatory and membrane-stabilizing effects.^{1,4} Although corticosteroids have been highly effective in preventing and treating chemotherapy-induced nausea and vomiting, their role in the prevention and treatment of POV is less well understood.

The results of several studies have shown that dexamethasone, administered alone or in combination with a 5-HT₃-receptor antagonist, successfully prevents the development of POV in children undergoing tonsillectomy or strabismus repair surgery.^{1,16,17} The recent consensus guidelines recommend using dexamethasone 150 mcg/kg to 8 mg I.V. in children.⁷ This agent is not approved for the prevention or treatment of PONV in adults or POV in children.

The most common adverse effects of dexamethasone are injection-related (cutaneous flushing and perineal itching).⁴ These effects, however, are most likely caused by the phosphate in the injectable solution.⁴ Delayed wound healing and suppression of the hypothalamic-pituitary-adrenal axis are not observed with the preoperative administration of corticosteroids.^{1,4}

Dopamine-Receptor Antagonists

Dopamine-receptor antagonists that are effective in preventing and treating pediatric POV include the benzamides (metoclopramide), butyrophenones (droperidol), and phenothiazines (promethazine, perphenazine). Each of these drugs exerts an antiemetic effect primarily by blocking dopamine receptors in the CTZ.

BENZAMIDES

Metoclopramide, a benzamide derivative, blocks dopamine receptors in the CTZ, area postrema, and gastrointestinal tract when administered at low doses, such as those used for POV prophylaxis or treatment.^{1,4,9} Additionally, metoclopramide enhances gastric motility and increases esophageal sphincter tone, which may prevent the delayed gastric emptying often caused by opioids administered as analgesics during surgery.^{1,9} At high doses, metoclopramide also inhibits 5-HT₃ receptors.⁶ Metoclopramide is not approved for the prevention or treatment of POV in children but is approved for the prevention of PONV in adults.

Metoclopramide is effective in preventing POV in children undergoing high-risk surgery; however, the results of comparative studies have shown that metoclopramide is less effective than the 5-HT₃-receptor antagonist ondansetron or droperidol.^{1,6} The short duration of effect of metoclopramide (1–2 hours) requires that this drug be administered at the end of surgery for maximal effectiveness.⁹ At the low doses (0.1–0.25 mg/kg I.V.) commonly used for the prevention of pediatric POV, metoclopramide is rarely associated with sedation and extrapyramidal symptoms.⁹ Rectal trimethobenzamide has been widely used as a rescue antiemetic, despite the lack of well-controlled studies to support this practice.

BUTYROPHENONES

Droperidol also has proven efficacy in the prevention and treatment of POV in children.⁶ This butyrophenone exerts its antiemetic effect by blocking dopamine receptors in the CTZ and area postrema.⁹ Additionally, droperidol may occupy γ -aminobutyric acid (GABA) receptors, resulting in an imbalance of dopamine (increased) and acetylcholine (decreased) and subsequent alteration in the normal transmission of impulses to the vomiting center and CTZ.¹ The drug is indicated to reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in adults and children. According to the prescribing information, it is not recommended for any use other than the treatment of PONV in patients for whom other treatments are ineffective or inappropriate.

Droperidol is a highly effective antiemetic for the prevention of POV, particularly in children undergoing strabismus repair surgery.² Consensus guidelines recommend using a dose of 50 to 75 mcg/kg, up to 1.25 mg I.V. in children.⁷ Higher doses appear to be more effective in preventing POV than lower doses, but the higher doses are associated with more sedation and extrapyramidal reactions.¹ In fact, the consensus guide-

lines recommend that droperidol be reserved for patients who have failed all other therapies and are being admitted to the hospital.⁷ For outpatient procedures or surgeries in which minimal sedation and drowsiness are preferred, low doses (≤ 50 mcg/kg) of droperidol may be optimal.¹ Repeated low doses of droperidol may be preferred over single high doses because of increased anti-nausea efficacy, reduced sedation and extrapyramidal symptoms, and increased protective effects against post-operative headache.¹

Droperidol controversy. Recent reports of electrocardiogram (ECG) rhythm changes with the use of droperidol led the FDA to insert a black box warning in the package insert. Initial reports were based on the use of large doses (>25 mg) for managing manic-depressive patients during the manic phase. However, there were 7 reports of cardiac arrest, with 3 deaths, in patients who were given <2.5 mg of droperidol. Two cases of cardiac arrest, with 1 death, occurred in patients receiving <1 mg. The FDA-approved black box warning calls for a 12-lead ECG before a patient receives droperidol and a 3-hour post-administration period of continuous observation of the ECG.^{18–22} The warning emphasizes that the use of benzodiazepines, volatile anesthetics, and opioids increases the risk for prolonged QT syndrome.

These steps by the FDA caused many institutions to stop using droperidol, despite the fact that experts in the field have pointed out that the drug has been used safely for more than 30 years. Interestingly, not a single case has been reported in a peer-reviewed journal in which droperidol at doses used for the management of PONV was associated with QTc prolongation, arrhythmias, or cardiac arrest.²²

The data used as the basis for the FDA ruling were obtained by some investigators through the Freedom of Information Act.¹⁸ A review of the cases showed that the vast majority of arrhythmias followed the administration of very large doses (25 mg) in psychotic patients. In 19 cases in which dysrhythmias were allegedly associated with doses <10 mg, many confounding factors made it difficult to pinpoint droperidol as the likely cause of the adverse event.²²

PHENOTHIAZINES

Although phenothiazines are primarily CNS dopamine-receptor antagonists, they also have modest anticholinergic and antihistaminergic effects.⁹ These drugs are effective in preventing and treating POV by countering the effects of drugs that stimulate the CTZ (eg, opioids), have less efficacy in preventing motion-induced nausea and vomiting than antihistamines and anticholinergics, and have no effect on gastric emptying.⁹ Both perphenazine and promethazine have been shown to be effective in preventing POV in children.^{1,6} Perphenazine 70 mcg/kg oral has been shown to be more effective than dexamethasone 150 mcg/kg oral, as effective as ondansetron 150 mcg/kg oral, and less effective than granisetron 40 mcg/kg oral in preventing POV in pediatric patients undergoing tonsillectomy.^{1,9,23} Perphenazine is not approved for the prevention

or treatment of POV in children but is approved for the treatment of severe nausea and vomiting in adults. Promethazine is approved for PONV in adults and POV in children.

Adverse effects of phenothiazines include extrapyramidal symptoms and sedation. Extrapyramidal symptoms, such as akathisia, acute dystonia, pseudoparkinsonism, and tardive dyskinesia, are more common with perphenazine than promethazine; however, promethazine is associated with more sedation.^{6,9} These adverse effects may complicate postoperative care or prolong hospitalization, limiting their use in POV prophylaxis.⁶ The consensus guidelines note that the use of these agents is limited in the ambulatory setting because of their sedative effects.⁷

NK-1–Receptor Antagonists

Aprepitant is the first NK-1–receptor antagonist approved for the treatment of chemotherapy-induced nausea and vomiting.^{11,24,25} NK-1–receptor antagonists may be effective in preventing POV by blocking input from emetic stimuli in the vomiting center.¹¹ In adults, investigational NK-1–receptor antagonists, such as CP-122,721 and GR205171, have been shown to reduce POV effectively.^{11,25} Currently, no studies evaluating NK-1–receptor antagonists for the prevention of POV in children have been reported. The role of this drug remains to be determined.

5-HT₃– Receptor Antagonists

5-HT₃–receptor antagonists such as ondansetron, granisetron, and dolasetron produce antiemetic activity by selectively inhibiting 5-HT₃ receptors located in both the central (area postrema and CTZ) and peripheral (vagus nerve within the gastrointestinal tract) nervous systems.^{1,10} According to the consensus guidelines, there are no differences in the efficacy and safety profiles of the 5-HT₃–receptor antagonists in the prophylaxis of PONV in adults.

The most commonly reported adverse effects of these agents are mild and transient headache and dizziness.^{4,9} Because 5-HT₃–receptor antagonists can block sodium and potassium channels, mild, transient, and asymptomatic ECG changes have been observed.⁹ However, these ECG changes have been shown to be clinically insignificant.²⁶

The development of these drugs is considered a major advance in the management of pediatric POV because they are effective and free of sedative effects.^{4,7} Furthermore, 5-HT₃–receptor antagonists are considered to be the drugs of first choice for the prophylaxis of POV in children because these agents are more effective in preventing vomiting than in preventing nausea.⁷

ONDANSETRON

Ondansetron was the first 5-HT₃–receptor antagonist available for the prevention and treatment of pediatric POV and hence is the most widely studied drug of its class.^{6,14} When administered before or immediately after induction of anesthesia, ondansetron is effective in preventing POV in children undergoing high-risk procedures, such as ade-

notonsillectomy; ear, nose, and throat (ENT) surgeries; herniorrhaphy; orchiopexy; strabismus repair; tonsillectomy; and craniofacial operations.^{14,27}

Tramer and colleagues performed a meta-analysis of 53 trials of ondansetron prophylaxis in 13,000 patients, with a subset of 1,000 pediatric patients.²¹ In this subset, the data supported the use of 50 mcg/kg as the lowest effective dose. However, the results of more recent studies have shown that ondansetron 50 mcg/kg may not be as efficacious as higher doses (eg, 75–150 mcg/kg).¹⁴ The consensus guidelines recommend a pediatric dose of 50 to 100 mcg/kg I.V. (maximum, 4 mg). Information about ondansetron use in children younger than 2 years of age is limited.¹⁴

I.V. ondansetron is generally administered before or immediately after the induction of anesthesia.¹⁴ However, data in adults suggest that the drug may be more effective when administered at the end of surgery. Ondansetron also may be administered orally for the prevention of POV in children; doses of 100 to 150 mcg/kg, administered 30 to 60 minutes before surgery, have been shown to be effective. The results of comparative studies suggest that the efficacy of ondansetron is similar to that of dexamethasone, perphenazine, and prochlorperazine, and greater than that of dimenhydrinate.^{14,28}

Several studies have compared ondansetron and droperidol for the prevention of POV in children undergoing surgery, including adenotonsillectomy and dental, ENT, and strabismus repair surgeries.²⁸ The results of these comparative studies were recently evaluated in a meta-analysis, and ondansetron was found to be significantly more effective than droperidol in preventing POV in children ($P=0.004$).²⁸ Additionally, many placebo-controlled, double-blind, randomized studies have compared ondansetron with metoclopramide. The results of these studies show that ondansetron 100 to 150 mcg/kg is consistently better than metoclopramide 150 to 250 mcg/kg in reducing the incidence of POV in children undergoing high-risk surgeries.¹⁴

Several studies that have compared ondansetron, metoclopramide, and droperidol for the prevention of POV in children undergoing surgery, including adenotonsillectomy and dental, ENT, and strabismus repair surgeries, were recently evaluated in a meta-analysis.²⁸ Ondansetron was found to be significantly more effective than droperidol in preventing POV in children ($P=0.004$).²⁸ In another trial, both drugs were more effective than metoclopramide 100 to 150 mcg/kg.¹⁴

Studies comparing ondansetron with dolasetron as prophylaxis for pediatric POV have shown these drugs to be equally effective and well tolerated.^{12,29} In a study in which 149 children aged 2 to 12 years undergoing tonsillectomy were randomized to ondansetron 150 mcg/kg, dolasetron 500 mcg/kg, or placebo (all patients also received dexamethasone 1 mg/kg), the two 5-HT₃–receptor antagonists had similar efficacy (success rates of 76%, 74%, and 44% for ondansetron-, dolasetron-, and placebo-treated patients, respectively; $P<0.05$).²⁹ In this study, success was defined as no retching or vomiting and no antiemetics administered in the first 48 hours after surgery. In addition,

a randomized, double-blind study by Olutoye and colleagues showed that dolasetron 350 mcg/kg and ondansetron 100 mcg/kg were equally effective in preventing POV.¹² Ondansetron has not been directly compared with granisetron in this patient population.

Ondansetron has also been shown to be effective in the treatment of established pediatric POV. In a randomized study by Khalil and colleagues, involving children undergoing outpatient surgery who experienced 2 emetic episodes within 2 hours after discontinuation of nitrous oxide anesthesia, I.V. ondansetron at a dose of 100 mcg/kg (maximum dose, 4 mg) showed a 78% success rate compared with 34% in the placebo group ($P<0.001$).³⁰ Although ondansetron became less effective over time, significantly more ondansetron-treated patients experienced a complete response 24 hours after the antiemetic was administered than did placebo-treated patients (53% vs 17%; $P<0.001$).

GRANISETRON

The efficacy of granisetron in preventing POV has been studied in children undergoing adenotonsillectomy and strabismus repair, as well as dental, eye, ENT, inguinal hernia, and phimosis surgeries, and in children with a history of motion sickness.^{18,31-35} This agent is not approved for the prevention or treatment of POV in children but is approved for the prevention and treatment of PONV in adults.

Granisetron 40 mcg/kg has been shown to be the lowest effective dose in children undergoing adenotonsillectomy,² and 20 mcg/kg has shown efficacy during strabismus repair surgery.^{23,30,34,35} Studies comparing granisetron with dexamethasone, droperidol, metoclopramide, and perphenazine have been performed, but no studies comparing granisetron with other 5-HT₃-receptor antagonists have been published. In a randomized, double-blind study evaluating I.V. administration of granisetron 40 mcg/kg, dexamethasone 150 mcg/kg, and granisetron 40 mcg/kg plus dexamethasone 150 mcg/kg, the combination regimen was significantly more effective in preventing vomiting within the first 24 hours after surgery (86%, 68%, and 98%, respectively; $P<0.05$).³³ Granisetron 40 mcg/kg I.V. is more effective than droperidol 50 mcg/kg I.V. and metoclopramide 0.25 mg/kg I.V. in preventing POV in children undergoing adenotonsillectomy or tonsillectomy.³² Similarly, oral granisetron 40 mcg/kg was reported to be more effective than oral perphenazine 70 mcg/kg in children undergoing tonsillectomy.²³

DOLASETRON

Dolasetron I.V. is approved for the prevention and treatment of PONV in adults and POV in children. According to the prescribing information for this drug as well as the consensus guidelines, the recommended I.V. dose in patients aged 2 to 16 years is 350 mcg/kg (maximum, 12.5 mg).⁷ The drug should be given as a single dose approximately 15 minutes before the cessation of anesthesia or as soon as nausea or vomiting presents. The I.V. formulation can

also be mixed in apple or apple-grape juice and administered orally 2 hours before surgery at a dose of 1.2 mg/kg (maximum, 100 mg). The drug is also available in oral form, which is indicated for the prevention of PONV in adults and POV in children. According to the prescribing information, the recommended oral dosage in pediatric patients 2 to 12 years of age is 1.2 mg/kg (maximum, 100 mg) given within 2 hours before surgery.

Dolasetron is effective in preventing POV in children undergoing herniorrhaphy, orchiopexy, and strabismus repair, as well as penile, superficial plastic, and umbilical hernia surgeries.^{12,36} Additionally, dolasetron combined with dexamethasone is an effective prophylactic antiemetic regimen in children undergoing tonsillectomy.²⁹

A recent dose-finding study confirmed that 350 mcg/kg is the optimal weight-based I.V. dose of dolasetron for preventing POV in children.¹² In this study, children undergoing ambulatory surgeries were randomized to either ondansetron 100 mcg/kg I.V. or dolasetron 45, 175, 350, or 700 mcg/kg I.V. Patients who received dolasetron 45 mcg/kg were more likely to experience early (0–6 hours) and 24-hour emesis than patients who received higher doses of dolasetron or ondansetron.¹² In addition, repeated POV occurred more frequently in patients who received dolasetron <350 mcg/kg than in patients who received the 2 largest doses of dolasetron (24% vs 2%, respectively; $P<0.001$). No differences were observed between the 350- and 700-mcg/kg groups in terms of complete response rate (i.e., no emesis at 24 hours) or incidence of repeated POV. The researchers concluded that dolasetron 350 mcg/kg is the smallest dose that achieves efficacy and patient satisfaction scores equivalent to those of ondansetron 100 mcg/kg I.V.¹²

Wagner and colleagues recently reported that a 12.5-mg fixed dose of I.V. dolasetron for children undergoing strabismus repair surgery was as safe and effective as a 350-mcg/kg dose of dolasetron in reducing the incidence of POV.³⁶ In this randomized study, the rate of a complete response—defined as no emetic episodes and no rescue medication within 24 hours of drug administration—was 62% for the 350-mcg/kg dose, 64% for the 12.5-mg dose, and 33% for placebo.

Comparative studies have shown that dolasetron and ondansetron are equally effective and well tolerated in the prevention of POV (see ondansetron section).^{12,29}

Other Drugs

Oral clonidine is often used as a preanesthetic medication in children for sedation and analgesia, but it does not have antiemetic properties; however, a reduction in POV in children undergoing strabismus repair surgery and receiving preoperative clonidine and inhalation anesthesia has been observed.³⁷ To confirm this observation, Handa and Fujii³⁷ conducted a prospective, randomized, double-blind study comparing oral clonidine 4 mcg/kg with diazepam 400 mcg/kg for the prevention of POV in children undergoing propofol-nitrous oxide anesthesia for strabismus repair surgery. These investigators found that clonidine, relative to diazepam, significantly

increased the antiemetic effects of propofol ($P=0.024$).^{1,37}

Another drug without any known antiemetic properties that has recently been evaluated for pediatric POV is isopropyl alcohol administered by nasal inhalation.³⁸ Wang and colleagues established that up to 3 treatments with this regimen after surgery reduced the severity of nausea or frequency of vomiting, but the effects were transient. These results suggest that isopropyl alcohol may not be an effective therapy for pediatric POV.

Combination Therapy

Because several neurochemical receptors are involved in the pathogenesis of emesis, using a combination regimen for preventing POV is a rational approach. In fact, the consensus guidelines note that combination therapy is superior to monotherapy for PONV prophylaxis.⁷ Ondansetron has been evaluated in combination with droperidol, metoclopramide, dexamethasone, and propofol for pediatric POV prophylaxis. Conflicting results have been reported for I.V. ondansetron plus droperidol, and the combination of ondansetron plus metoclopramide has not been shown to be more effective than ondansetron alone.¹⁴ Oral droperidol (300 mcg/kg) administered with metoclopramide (0.15 mg/kg) has been shown to be highly effective in reducing POV in children undergoing strabismus repair surgery.¹ The droperidol-ondansetron combination is more effective than either agent alone in preventing POV in children undergoing strabismus repair surgery, but not in children undergoing orthopedic surgery.¹ These conflicting findings may be a result of the different doses of both

droperidol and ondansetron administered in each study.

Two comparative studies showed that a dexamethasone-plus-ondansetron combination is highly effective in preventing pediatric POV, with 91% of patients receiving the combination in each study not experiencing POV within the first 24 hours after surgery, compared with 72% and 79% of patients receiving ondansetron and dexamethasone alone, respectively.¹⁴ Similarly, the combination of ondansetron and propofol—an I.V. anesthetic with antiemetic properties used for induction and maintenance of anesthesia—has been shown to be highly effective in preventing POV.^{14,39}

Cost-effectiveness

Studies evaluating the pharmacoeconomics of antiemetics used for the prevention and treatment of POV in children are limited. Older antiemetics—such as anticholinergics and dopamine-receptor antagonists—are less expensive than newer agents—such as the 5-HT₃-receptor antagonists.¹ However, acquisition costs are not the only costs associated with the use of a POV antiemetic regimen.⁹ The cost of an antiemetic regimen should include 1) drug acquisition costs; 2) pharmacy supply costs; 3) costs associated with managing therapy failure (eg, additional treatment costs and hospital costs associated with delayed discharge or hospital readmission); and 4) non-drug-related costs, such as costs of resources for emesis cleanup, labor costs, and lost caregiver income because of a patient's prolonged illness.^{9,12} Only a few studies have evaluated the cost-effectiveness of antiemetic therapies by using these cost indicators.

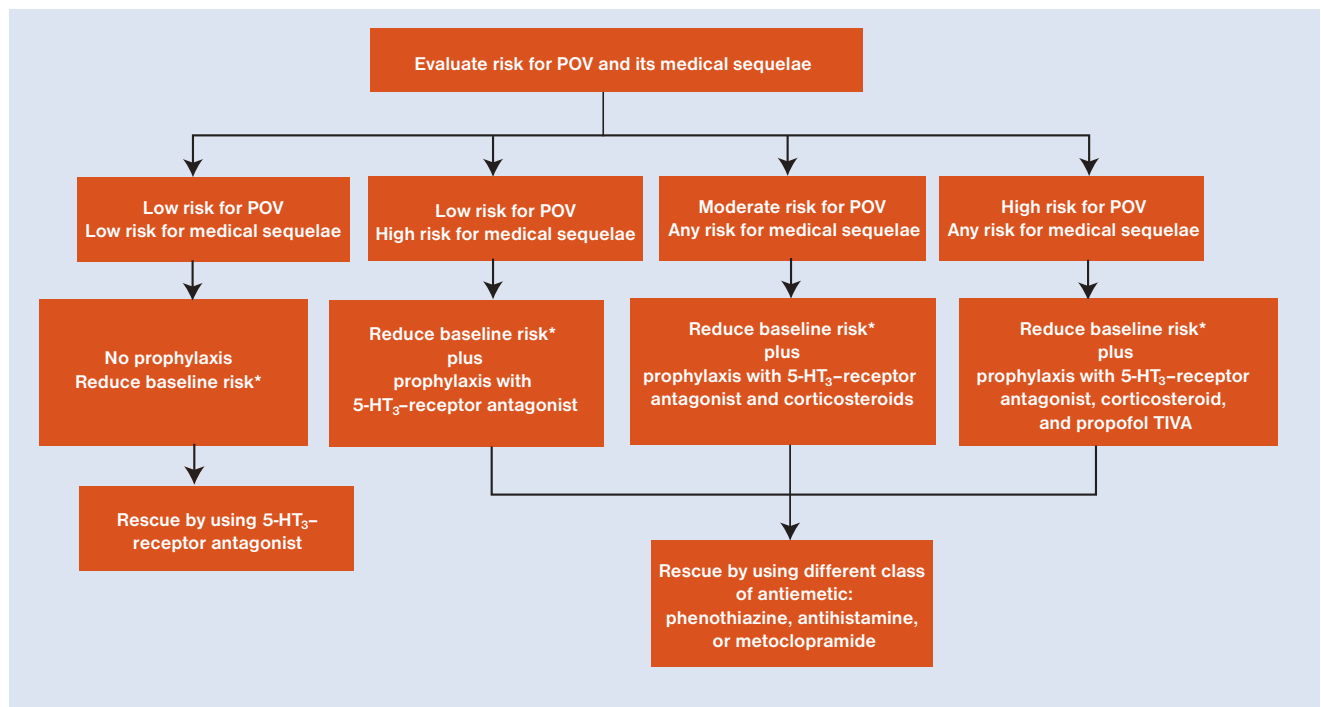


Figure 2. Algorithm for the prophylaxis and treatment of POV in children.

*Reduce baseline risk as suggested in Table 3.

POV, postoperative vomiting; 5-HT₃, serotonin type 3; TIVA, total intravenous anesthesia

Adapted from Gan et al.⁷

This pharmacoeconomic model has been used in cost-effectiveness studies of granisetron, in which the authors concluded that the high cost associated with granisetron prophylaxis may not justify its routine use in all high-risk pediatric patients undergoing surgery.³¹ Two other studies used a similar model to compare the cost-effectiveness of ondansetron with that of other antiemetics (dexamethasone and dolasetron) for the prophylaxis of POV.^{12,40} These studies concluded that dexamethasone and ondansetron are equally effective in decreasing the incidence and severity of POV in the first 24 hours after surgery. However, the cost-to-benefit ratio for each child was 22.4 times higher with ondansetron, suggesting that dexamethasone is more cost-effective than ondansetron for the prevention of POV in children.

Similarly, in the study by Olutoye and colleagues showing that dolasetron 350 mcg/kg and ondansetron 100 mcg/kg were equally effective in the prevention of POV in children, dolasetron was linked to a lower cost.¹² The total institutional cost for the dolasetron regimen was shown to be lower than the total cost of ondansetron therapy (\$6.58±3.95 and \$9.94±4.87, respectively). Although the actual direct and indirect costs of each regimen may vary from institution to institution, this model suggests that dolasetron for pediatric POV prophylaxis is more cost-effective than ondansetron. Further studies are warranted to determine the most cost-effective antiemetic regimen for the prophylaxis and treatment of POV in children.

Guidelines for the Management of POV

The routine administration of prophylactic antiemetics for POV in children is controversial.^{6,7} Some clinicians recommend routine POV prophylaxis only for high-risk children, whereas other clinicians prefer to reserve antiemetics for the treatment of established POV.^{6,7}

Prevention of POV

The consensus guidelines recommend that prophylactic antiemetic therapy be administered only to children with known risk factors for POV, and that, if feasible, efforts to reduce the baseline risk for POV be made.⁷ More children than adults may be candidates for POV prophylaxis, given that the rate of POV in children is almost twice that in adults. Prophylactic regimens in children should include a 5-HT₃-receptor antagonist and a second drug, such as dexamethasone.⁷ Commonly used antiemetic doses for children are shown in Table 2 (page 4).^{1,2,4,6,7,9,21} Strategies for reducing baseline POV risk are shown in Table 3.⁷

Treatment of POV

Studies evaluating antiemetics for the treatment of established POV are limited. Generally, antiemetics that are effective in the prevention of POV are also effective in the treatment of POV. Although the consensus guidelines provide an algorithm for the treatment of established POV, the data used to develop the guidelines were

Table 3. Strategies for Reducing Baseline POV Risk⁷

- Use of regional anesthesia
- Use of propofol for induction and maintenance anesthesia
- Use of intraoperative supplemental oxygen
- Use of hydration
- Avoidance of nitrous oxide and/or volatile anesthetics
- Minimization of intraoperative and postoperative opioid use
- Minimization of neostigmine use

derived from the results of adult POV clinical trials and may not be applicable to the treatment of POV in children.⁷ An algorithm for the management of POV in children is shown in Figure 2.

The treatment schema for established POV, however, is relatively simple. If no prophylactic antiemetic has been administered, a 5-HT₃-receptor antagonist should be initiated at the first occurrence of symptoms.⁷ If prophylaxis fails within the first 6 hours after surgery with 5-HT₃-receptor antagonists and within the first 8 hours after surgery with dexamethasone, administration of an antiemetic from a different therapeutic class is recommended. However, if POV occurs more than 8 hours after surgery, repeated administration of the same prophylactic regimen may be considered.⁷

Conclusion

The incidence of POV in children remains high despite an improved understanding of the pathophysiology of POV and the development of novel, more effective antiemetics. Risk factors for pediatric POV include age, previous history of POV or motion sickness, anesthesia type, preoperative and postoperative conditions, and the type of surgical procedure. Knowledge of a patient's risk factors can assist the clinician in determining the most appropriate POV prevention or treatment strategy.

Several antiemetics, with different mechanisms of action, are available for the prevention and treatment of POV in children. Droperidol, dimenhydrinate, and the 5-HT₃-receptor antagonists all have excellent antiemetic activity, but droperidol and dimenhydrinate are associated with many adverse effects that may limit their usefulness. 5-HT₃-receptor antagonists, however, are well tolerated and have become the treatment of first choice when used in combination with dexamethasone for the prevention of pediatric POV. For patients who do not receive antiemetic prophylaxis, treatment consists of a 5-HT₃-receptor antagonist; patients who fail antiemetic prophylaxis should receive an antiemetic from another therapeutic class. The 5-HT₃-receptor antagonists appear to be equally effective and have similar adverse effects in adult studies. Dolasetron has been shown to be more cost-effective than the other 5-HT₃-receptor antagonist options for children, although further study is warranted to confirm this result. Future clinical trials of agents to prevent and treat POV should evaluate novel antiemetic agents, combination therapy, and the cost-effectiveness of currently available antiemetic therapies.

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Post-test

Select the single-letter response that best answers the question or completes the statement.

1. **The overall incidence of POV in children aged 3 years and older is __, which is almost twice as high as the rate in adults.**
 - a. $\geq 20\%$
 - b. $\geq 30\%$
 - c. $\geq 40\%$
 - d. $\geq 50\%$
2. **Which of the following is *not* a risk factor for POV in children?**
 - a. Age >3 years to puberty
 - b. Females (postpubertal)
 - c. Positive history of POV
 - d. Lack of patient or parental anxiety
3. **Which of the following anesthetic agents reduces the risk for POV in children?**
 - a. Cyclopropane
 - b. Nitrous oxide
 - c. Propofol
 - d. Ether
4. **Which of the following pediatric surgeries increases the risk for POV?**
 - a. Adenotonsillectomy
 - b. Cardiac surgery
 - c. Craniofacial surgery
 - d. Plastic surgery
5. **In what area of the brain is the vomiting center located?**
 - a. Lateral reticular formation of the medulla
 - b. Primary motor cortex
 - c. Olfactory bulb
 - d. Central sulcus
6. **Which of the following statements regarding phenothiazines is false?**
 - a. Phenothiazines are primarily CNS dopamine-receptor antagonists.
 - b. Phenothiazines counter the effects of drugs that stimulate the CTZ.
 - c. Phenothiazines are less effective in preventing motion-induced nausea and vomiting than are antihistamines and anticholinergics.
 - d. Phenothiazines have a significant effect on gastric emptying.
7. **Neurokinin-1-receptor antagonists may be effective in preventing POV by blocking input from emetic stimuli in the vomiting center.**
 - a. True
 - b. False
8. **The antiemetic effect of dolasetron is achieved by __ receptor blockade.**
 - a. dopamine
 - b. histamine
 - c. neurokinin-1
 - d. 5-HT₃
9. **Which of the following adverse effects is commonly observed after the administration of 5-HT₃-receptor antagonists to prevent pediatric POV?**
 - a. Dry mouth
 - b. Extrapyramidal symptoms
 - c. Headache
 - d. Sedation
10. **Which of the following variables should be included in the cost analysis of antiemetic regimens?**
 - a. Drug acquisition costs
 - b. Pharmacy supply costs
 - c. Costs associated with managing therapy failure
 - d. All of the above
11. **According to the consensus panel guidelines, if prophylaxis with 5-HT₃-receptor antagonists fails within the first __ hours after surgery, administration of an antiemetic from a different therapeutic class is recommended.**
 - a. 6
 - b. 10
 - c. 15
 - d. 20
12. **In two comparative studies, dexamethasone plus ondansetron prevented POV in __ of children within the first 24 hours after surgery.**
 - a. 25%
 - b. 46%
 - c. 72%
 - d. 91%
13. **Which of the following is *not* a strategy for reducing baseline POV risk in children?**
 - a. Use of regional anesthesia
 - b. Use of nitrous oxide
 - c. Use of intraoperative supplemental oxygen
 - d. Use of propofol for induction and maintenance of anesthesia
14. **The consensus guidelines note that combination therapy is superior to monotherapy for PONV prophylaxis.**
 - a. True
 - b. False
15. **The consensus guidelines recommend that prophylactic antiemetic therapy be administered only to children with __.**
 - a. cancer
 - b. known risk factors for POV
 - c. no known risk factors for POV
 - d. no history of motion sickness

CE/CME Post-test

Antiemetic Drugs in the Prevention and Treatment of Postoperative Vomiting in Children

—Release Date: April 2004—

077-999-04-001-H01

An 80% successful completion of this examination will provide the participant with credit as listed on page 1 of this Special Report. The evaluation form and post-test must be filled out completely for you to receive credit. Statements of credit will be issued within 4 weeks of submission of post-test and evaluation. This credit is valid through April 30, 2005. Please submit your answers only once through one of the methods listed below.

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Examination

Antiemetic Drugs in the Prevention and Treatment of Postoperative Vomiting in Children

077-999-04-001-H01

Select and circle the single best answer

- | | | |
|------------|-------------|-------------|
| 1. a b c d | 6. a b c d | 11. a b c d |
| 2. a b c d | 7. a b c d | 12. a b c d |
| 3. a b c d | 8. a b c d | 13. a b c d |
| 4. a b c d | 9. a b c d | 14. a b c d |
| 5. a b c d | 10. a b c d | 15. a b c d |

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