Postoperative nausea and vomiting in paediatric patients

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Life-threatening complications have become very rare with modern anaesthetic techniques. This safety record has encouraged practising anaesthetists to provide greater attention to the management of the postoperative symptoms that distress patients. During the past decade, much effort has been placed correctly on ensuring patients have adequate pain relief after surgery. However, postoperative nausea and vomiting (PONV) are still viewed as minor problems by some physicians, even though they are leading causes of morbidity in paediatric surgical patients.[16 25 41 48 92] In contrast with the attitudes of some physicians, most patients view PONV as very unpleasant experiences. Some investigators report that these complications are undertreated, even though severe PONV may be associated with wound dehiscence, pulmonary aspiration of gastric contents, bleeding, dehydration and electrolyte disturbance.[125 127] Even mild PONV may result in delayed hospital discharge, decreased parental satisfaction and increased use of resources, including medical and nursing care, i.v. fluids, drugs and other supplies.[15 73 101 120] PONV remain major causes of unanticipated admission to hospital after day-case surgery and hence prevention and management is of increasing importance.[74]

The interchangeable use of the terms nausea and vomiting has led to much confusion, as the symptoms do not always accompany each other in severity. For example, some patients have stated that a single episode of vomiting had relieved the associated nausea. Drugs may be more effective in controlling one of the two symptoms, and some of the reported differences in results of studies with the same drug may be secondary to failure to differentiate between the incidence of nausea and vomiting. Nausea is a subjective phenomenon, and the smaller child often may not be able to describe or gauge the severity of this symptom. Studies of this complication in children have therefore used the more objective symptoms of retching and vomiting as the end-point. These reports should be considered as studies of postoperative vomiting only (POV). A comparison of the incidence of vomiting in a paediatric study with the incidence of both nausea and vomiting in adults may not be valid.

In several recent large studies, POV occurred in 13% to 42% of all paediatric surgical patients.[16 41 54 80 92] Fortunately, severe or intractable POV is less common, occurring in 1–3% of paediatric patients, and the incidence of unanticipated admission for its management is even lower (1 in 3000).[74 80] However, there are subsets of patients at high risk (30–80% probability) of vomiting after anaesthesia. In this article we have reviewed the physiology of emesis, the factors associated with increased POV and the measures available to reduce its incidence. We have also described the ideal features of a good study into this problem.

Physiology of emesis

Vomiting is a complicated response mediated by the emetic centre located in the lateral reticular formation of the medulla.[125] This centre receives input from several areas within the central nervous system, including the chemoreceptor trigger zone (CTZ), vestibular apparatus, cerebellum, higher cortical and brainstem centres, and solitary tract nucleus. These structures are rich in dopaminergic, muscarinic, serotoninergic, histaminic and opioid receptors, and block of these receptors may be the mechanism of the antiemetic action of drugs. The emetic centre coordinates efferent impulses through the vagus, phrenic and spinal nerves of the abdominal musculature during the act of vomiting. At the present time, there are no drugs known to act directly on the emetic centre. However, a new class of antiemetic drugs (NK1 receptor antagonists) may act on the final common pathway from the emetic centre, as this class of drugs has been shown to provide protection in animal models against emetogenic stimuli from motion, cisplatin, irradiation, morphine, ipecacuaha and copper sulphate.[32 58 90 109] These stimuli use different pathways to reach the emetic centre and other antiemetic drugs are usually effective against only a few of these stimuli.

Study design

Factors associated with increased POV may or may not be under the control of the anaesthetist. They have been

Table 1 Checklist for study design of postoperative nausea and vomiting

A. Randomized, double-blind, dose-ranging or different drug comparison

B. End-points of study

Primary end-point
- (1) Complete freedom from both nausea and vomiting
- (2) Freedom from vomiting or need for rescue medications

Secondary end-point
- (1) Freedom from vomiting
- (2) Severity of symptoms
  - (a) Need for rescue antiemetics
  - (b) Number of episodes
  - (c) Hospital admission rate
- (3) Time to discharge
- (4) Time to return to work
- (5) Patient satisfaction

C. Statistics
- (1) Power analysis before study starts
- (2) Logistic regression or other analysis to ensure groups are comparable
- (3) Separate analysis for nausea, vomiting and PONV—Fisher's exact test or chi-square with Yates' continuity correction
- (4) Separate analysis for time-based events—early, late and for entire duration of study
- (5) Provide *P* values, 95% CI and NNT in results
- (6) Provide Kaplan–Meier survival curves for study groups

identified in several controlled clinical studies, but conclusions have not been consistent as the trials have a variable quality and there are many confounding factors that affect POV. It is therefore appropriate to first examine features of a good study design in this patient population (Table 1).

An ideal study of POV should be randomized and double-blind where all known confounding factors are evenly distributed between study groups. This is best achieved by limiting the study to a standardized surgical procedure during a standardized anaesthetic. The calculated probability of POV by logistic regression analysis may be useful for balancing patient treatment groups and allow between-study comparisons.[71] Many of the older published studies did not balance the study groups. The older studies that did not show significant differences in emesis rates between two groups may also be criticized for failure to perform an *a priori* power analysis to determine the number of patients that should be enrolled to avoid a type II error in the conclusions.[129] Comparisons of two drugs or of different doses of the same drug provide more useful information to clinicians than a single-dose comparison with placebo, although the latter study design is favoured by drug companies and regulatory agencies. If a study is designed to compare the efficacy of two drugs or two doses of the same drug, the power analysis should be based on differences in emesis rates between the two drug groups and not between one study drug and a placebo group.

The primary efficacy end-point should be the number of patients completely free of any symptoms of PONV. Many studies in adults have used a modified end-point of the number of patients free from emesis or the need for rescue antiemetics. This end-point considers therapy to be successful if the patient has milder forms of nausea and does not request antiemetic therapy. Nausea is a subjective symptom and in most paediatric studies the more objective symptom of emesis is used as an end-point. Secondary end-points make an assessment of the severity of emesis by determining the number of episodes of emesis and the need for rescue antiemetic medication. However, studies that limit evaluation to the number of patients with symptoms during the first 24 h have been criticized for evaluating 'surrogate' end-points and not 'true' outcome measures.[24 25] These critics state that duration of stay in the PACU, incidence of unplanned hospitalizations after ambulatory surgery, cost of antiemetic therapy or overall anaesthetic care, and patient or parent satisfaction are more important end-points.[24] Others believe that an episode of vomiting is a valuable outcome measure as it has an impact on patient well being.[33]

Data for the primary and secondary end-points should be analysed separately for symptoms of nausea, vomiting and both nausea and vomiting (PONV). Separate time-based analyses should be performed for the early (0–6 h), delayed (6–24 h) and 24-h postoperative periods. Statistical analysis results (Fisher's exact test and chi-square tests with Yates' continuity correction) should include both *P* values and 95% confidence intervals. A Kaplan–Meier survival analysis is useful in determining the duration of effect of a drug. Some investigators have emphasized that statistically significant differences may not always be of clinical importance and recommended using the numbers-needed-to-treat (NNT) method as a useful tool in guiding clinical practice.[115] This technique involves calculating the number of patients needed to be treated with a specific regimen to avoid an undesired problem in one patient, who would otherwise have developed the problem if treated with an alternative regimen.[116]

Factors associated with increased POV

Only some of the factors associated with increased POV can be influenced by the anaesthetist (Table 2).

Factors not under the control of the anaesthetist

Patient-related factors associated with increased POV in children, but not under the control of the anaesthetist, include age, sex, and previous history of POV or motion sickness.[16 41 80 93] Paediatric patients have a higher incidence of POV than adults, with a peak incidence of 34–50% in school children. The lowest incidence occurs in infants (5%), while preschool children have an incidence of 20%.[16 125]

Although female sex is consistently associated with an increased risk of PONV in adult subjects, this association has not always been observed in pre-pubertal children.[80 93] In paediatric patients more than 13 yr of age, girls vomited significantly more often than boys after general anaesthesia.[41] The type of surgery performed also has an influence on the occurrence of emetic sequelae that is independent of other patient and anaesthetic factors.[41 80 92 125] Children undergoing adenotonsillectomy, strabismus repair, orchio-

Table 2 Factors affecting the incidence of PONV

Factors not under the control of the anaesthetist
(1) Age
(2) Sex
(3) History of previous PONV or motion sickness
(4) Surgical procedure
(5) Duration of surgery
(6) Patient and parental anxiety
Factors under the control of the anaesthetist
(1) Premedication—clonidine or midazolam
(2) Nitrous oxide
(3) I.v. agents—propofol
(4) Potent inhalation agents
(5) Antagonists of non-depolarizing neuromuscular blocking drugs
(6) Postoperative management
(a) Pain management
(i) Local anaesthetics
(ii) NSAID
(iii) Opioids
(b) Movement
(c) Timing of oral intake
(d) Non-pharmacological—acupressure/acupuncture
(7) Antiemetics

pexy, herniorrhaphy, middle ear surgery and laparotomy are at increased risk of POV.[12 80] The risk of POV increases with duration of surgery and anaesthesia, possibly because of greater accumulation of emetogenic anaesthetic agents.[80 125] Rowley and Brown reported that POV occurred in 34% of paediatric patients when anaesthesia was less than 30 min duration *vs* 48% if it was longer than 30 min.[80] As in adult patients, children with a history of previous motion sickness or previous surgery complicated by POV are at greater risk of POV.[41]

Unlike the patient and surgical factors mentioned above, there are anaesthetic-related factors under the control of the anaesthetist that have an impact on the incidence and severity of POV.

Factors under the control of the anaesthetist

Anaesthetic-related factors that affect the incidence of POV include preoperative sedation, choice of intraoperative anaesthetic drugs and postoperative factors.

Premedication

These are administered to provide anxiolysis, sedation and analgesia, and to reduce airway secretions and cardiovascular responses during induction. With the advent of sevoflurane, the routine use of anticholinergic premedication in children for its vagolytic and antisialogogue actions may be questioned. Prophylactic transdermal scopolamine has been used effectively to reduce POV in children.[43] The major reasons given by many anaesthetists for the routine administration of drugs to children in the preoperative period are to ease anxiety, facilitate separation of the child from the parents and increase acceptance of the face mask during induction. Benzodiazepines, particularly midazolam, are used widely for this purpose, and these drugs also reduce POV in children after strabismus repair and adenotonsillectomy.[51 97] The mechanism of action is unknown, but does not involve reduction of gastric volume or increase in gastric pH.[36] The α_2 agonist clonidine, another drug used as a sedative premedication in children, has also been shown to reduce POV after strabismus repair. This action of clonidine may be secondary to its ability to reduce anxiety and decrease requirements for anaesthetic and analgesic drugs.[64 65]

In contrast, premedication with opioid analgesics increased the risk of PONV. Oral transmucosal fentanyl citrate (OTFC) in doses of 5–20 μg kg^{-1} facilitated anaesthetic induction, and produced sedation and analgesia before painful paediatric procedures such as bone marrow aspiration, lumbar puncture or suturing lacerations in the emergency room.[6 21 27 59 84 87 88] However, postoperative vomiting was common in most (but not all) reports of OTFC use in children and this limits its routine use in these situations.[21 22] Other opioids such as sufentanil have also been administered intranasally for pre-induction sedation, but there was more POV in these children compared with those who received midazolam (34% *vs* 6%, respectively).[132]

Intraoperative anaesthetic drugs and POV

Nitrous oxide. Early reports of the effect of nitrous oxide on PONV provided conflicting results, perhaps because these investigators did not differentiate between the effects of nitrous oxide for nausea and vomiting. Three independent meta-analyses of studies in adults have concluded that omission of nitrous oxide reduced the incidence of vomiting, but only in subjects at high-risk for this complication.[40 112 113] However, these meta-analyses also suggested that there was no reduction in the incidence of nausea when nitrous oxide was omitted.[113] Similar results were noted in paediatric patients, where omission of nitrous oxide was associated with a small reduction in early POV after restorative dentistry (15% *vs* 24%), but not after myringotomy and grommet placement.[96 105] Late POV was not affected in either study. Physiological mechanisms invoked to explain this observation include diffusion of nitrous oxide into the middle ear and bowel, resulting in stimulation of the vestibular apparatus and bowel distension, activation of the medullary dopaminergic system and increased endogenous cerebrospinal opioids.[67] Tramer, Moore and McQuay have emphasized that omitting nitrous oxide in 100 patients at high risk for emesis would avoid the problem in 20, but at the risk of intraoperative awareness in two patients.[112]

Potent inhalation agents. Modern potent inhalation anaesthetics are associated with a much lower incidence of PONV than ether and cyclopropane, which are agents that caused release of endogenous catecholamines.[125] However, differences in the incidence of POV with halothane, enflurane, isoflurane, desflurane and sevoflurane have not been well studied. There are some reports of a lower incidence of POV in children undergoing ENT and endoscopic procedures during anaesthesia with sevoflurane than with halothane.[47 63] These observations need to be confirmed in other investigations.

I.v. agents. Propofol, an i.v. hypnotic agent, is an alkylphenol compound that has been used for induction and maintenance of general anaesthesia, short- and long-term sedation, and as an antiemetic in sub-hypnotic doses. Studies in children and adults suggest that postoperative emetic sequalae occur less frequently with propofol.[39 60 68 106 116 123 128] However, questions have been raised about the efficacy of propofol for preventing emesis after paediatric squint surgery, specially when opioids have not been used. The limited improvement in early POV with propofol infusions during strabismus repair has to be balanced against an increased risk of stimulating the oculocardiac reflex.[111 123] In a systematic review of 84 studies of propofol involving more than 6000 patients, Tramer and colleagues stated that a single induction dose of propofol was effective in controlling only early nausea and vomiting. The best results were achieved when propofol was used for both induction and maintenance of anaesthesia.[46] More consistent results were noted when study comparisons were limited to those where the control rate of symptoms was 20–60%. A single dose of propofol may have greater effects on the control of nausea than on vomiting. Within the 20–60% control event rate, the NNT for nausea was 5 compared with an NNT of 7 for vomiting. However, when propofol was used for both induction and maintenance, approximately five patients would need to be treated to prevent early symptoms in one, and eight patients to prevent late symptoms in one (NNT=5 for early events and 8 for late events).[46]

Sub-hypnotic doses of propofol were effective in reducing nausea and vomiting associated with general anaesthesia, intrathecal opioids and cancer chemotherapy in adult subjects.[10 31 42 85] In contrast, no antiemetic benefits were observed when sub-hypnotic doses of propofol were administered to children after adenotonsillectomy.[133] The mechanism of the antiemetic effect of propofol is not clear. It does not appear to be related to anxiolysis, sedation, or interaction with D_2 dopamine or 5-HT_3 receptors.[4 5 7] The short duration of antiemetic action of a single dose of propofol makes it unlikely that it will be a first-line drug for the management of established PONV in the PACU.

Other i.v. drugs. Etomidate is a useful sedative–hypnotic agent for anaesthetic induction in patients with compromised cerebral perfusion or limited cardiovascular reserve. It has also been used as a total i.v. anaesthetic in paediatric oncology patients undergoing painful procedures. But etomidate is more emetogenic than propofol.[61] Similarly, the dissociative anaesthetic *ketamine* is associated with increased POV.[61 125] The emetogenic potential of *barbiturates* is difficult to determine as anaesthesia is usually maintained with other agents after induction with a barbiturate. Nevertheless, administration of thiamylal, methohexital or sodium pentothal for induction of anaesthesia was associated with a higher incidence of PONV than propofol in adults.[9 68 83]

Antagonists of neuromuscular block (anticholinesterases). Non-depolarizing neuromuscular blocking drugs are an important component of many general anaesthetics and routine antagonism of residual neuromuscular block has become standard practice. However, the muscarinic actions of cholinesterase inhibitors on the gastrointestinal tract may increase POV. The concomitant use of atropine with neostigmine or edrophonium may decrease POV during the early recovery period, but not during the entire postoperative period.[122] Others have questioned this relationship even for the early recovery phase.[46] Antagonism of neuromuscular block is not required when patients are allowed to breathe spontaneously via a laryngeal mask airway, and if tracheal intubation is performed under deep anaesthesia or facilitated by ultra-short acting neuromuscular blocking agents (e.g. mivacurium).

Postoperative factors

Pain management and PONV. Pain can prolong gastric emptying time and contribute to the occurrence of emetic symptoms after surgery. Kotiniemi and colleagues have shown that the incidence of POV increases with the severity of postoperative pain in children.[54] Patient-controlled analgesia (PCA), neuroaxial opioids and continuous epidural analgesia have improved the quality of postoperative analgesia. However, opioid therapy for pain management can also increase POV. Opioid-related nausea and vomiting can be so distressing to some children and adults who are using a PCA device that they reduce the number of demands for the drug, preferring to experience pain than the nausea and dysphoria associated with opioid analgesics. When administered in equi-analgesic doses, all opioids are capable of eliciting emetic symptoms. However, as the emetogenic profile of opioids varies considerably from one patient to another, it is often possible to reduce the severity of opioid-related POV by selecting a different opioid. Proposed mechanisms for this action include direct stimulation of the CTZ and vestibular apparatus, and decreased motility of the stomach, and small and large intestine.[77]

The incidence and severity of opioid-related side effects can be reduced by balanced or multimodal analgesia, where combinations of systemic opioids, regional nerve block and adjuvants such as non-steroidal anti-inflammatory drugs (NSAID) and clonidine are administered.[49 64 65 126] Ketorolac, an i.v. NSAID, has the same analgesic effect as conventional doses of morphine, but may be associated with increased bleeding during the first 24 h after tonsillectomy.[49 121]

Regional anaesthetic blocks are used frequently to supplement general anaesthesia in children.[34] Theoretical benefits of this approach include reduction in the amount of general anaesthetics and opioids required during operation, residual analgesia in the early postoperative period, reduced consumption of opioid analgesics after operation and a reduction in the incidence of side effects associated with opioids.[8] Children who had general anaesthesia supplemented with local anaesthetic injected into the caudal epidural space or infiltrated into the wound during hernia repair vomited less

frequently than children who had general anaesthesia and morphine in the PACU.[94] In a study of children undergoing circumcision, those who received only a dorsal penile nerve block had a lower incidence of vomiting in addition to reduced operating room and post-anaesthesia care unit times compared with those having general anaesthesia supplemented with a dorsal penile nerve block.[89] In another study of children during hernia repair, general anaesthesia and local anaesthetic infiltration of the wound, supplemented with intraoperative ketorolac 1 mg kg^{-1} i.v., resulted in a lower incidence of vomiting (15% *vs* 29%), earlier ambulation (130±35 min *vs* 149±45 min) and earlier micturition (150 *vs* 291 min) than children whose anaesthetic was supplemented with caudal epidural block.[98] Thus it can be seen that the judicious use of regional anaesthesia as the sole anaesthetic or as a supplement to general anaesthesia in children can result in a reduction in postoperative emetic sequelae.

Other factors. Gastric distension has been associated with increased PONV in adults.[125] In one study, patients experienced a higher incidence of PONV if their lungs were ventilated before tracheal intubation by inexperienced rather than experienced anaesthesia personnel.[45] However, routine evacuation of the stomach via orogastric suctioning has either no effect or increases the risk for PONV.[44 117]

Nursing procedures in the PACU and POV. Motion, including ambulation or transportation on a stretcher, wheelchair or by car during the recovery phase can precipitate POV. This is particularly true for patients who have received opioids. The vestibular apparatus may become sensitized by nitrous oxide diffusion into the middle ear or by opioids, resulting in activation of the emetic reflex. Many anaesthetists recommend that patients with POV restrict their activities until their need for opioid analgesics is over.

Control of environmental factors can be important in reducing the incidence and severity of POV. Noise, activity, motion and light can aggravate symptoms of nausea and vomiting. A quiet, darkened environment with little activity can reduce vestibular stimulation and emetic symptoms in patients with a history of previous POV or motion sickness, and in those with established POV.

Many patients who vomit in the early postoperative period do so immediately after taking their first drink.[118] The once common practice of requiring paediatric day-case surgery patients to drink without vomiting before discharge actually increased the incidence of POV and prolonged hospital stay.[86] This practice has been abandoned by most paediatric anaesthetists. Patients should chose when they want to start drinking liquids, and if no vomiting ensues after they have accepted oral liquids, the diet can be advanced to solids. It should be noted that restricting children to a soft diet for the first 12 h after tonsillectomy did not result in a parental perception of quicker recovery or a reduction in emesis and pain.[37]

Large fluid deficits are uncommon in paediatric patients undergoing elective surgery after the liberalization of *nil per os (*NPO) guidelines. Nevertheless, it is still common practice to administer i.v. fluids in excess of maintenance requirements during surgical procedures, to avoid postoperative hypovolaemia, orthostatic hypotension, dehydration and dizziness, all of which can result in POV. Although there are no studies to support this practice in paediatric patients, i.v. administration of a high volume of crystalloid solution (20 ml kg^{-1}) compared with a low volume (2 ml kg^{-1}) reduced postoperative emetic sequelae and dizziness in adult ambulatory surgery patients.[131] The need to ensure patients are well hydrated before discharge is even greater now that anaesthetists no longer insist patients drink before discharge from the day-case surgery unit.

Antiemetic therapy for the prevention and management of established POV

Routine administration of antiemetic agents to all children undergoing surgery is not justifiable as the majority do not experience POV or have at most 1–2 episodes. Some authors believe the benefits of routine prophylactic antiemetic therapy have not been proved, even in children at high risk of POV.[111] In addition, the commonly used antiemetics can produce significant side effects, including sedation, headache, dysphoria, extrapyramidal symptoms, dry mouth and blurred vision. Although the serotonin antagonists are relatively devoid of side effects, high costs limit their availability in many institutions. In this section, we discuss the drugs available for the prevention and treatment of POV and the basis for a rational choice of a therapeutic strategy. Greater emphasis will be placed on the newer drugs in this review. Readers are referred to a previous review for details of the use of the older drugs.[125]

The emetic response may be elicited by a wide variety of stimuli at dopaminergic, muscarinic, histaminic, serotonergic and opioid receptors. Block of these receptors is the mechanism of action of antiemetic drugs. However, none of the agents available today is known to antagonize all of these receptors, to exert their antiemetic effect directly on the emetic centre or to eliminate all nausea and vomiting associated with anaesthesia and surgery. The NK1 antagonists probably act on the final common pathway of the emetic reflex.

Butyrophenones

Droperidol is the only commonly used butyrophenone, which are a class of heterocyclic neuroleptic antagonists of central dopamine receptors. It is effective in the treatment or prevention of POV in children in doses of 20–75 μg kg^{-1} i.v. However, sedation, lethargy, agitation and extrapyramidal effects have been reported with these doses. Lethargy and delayed discharge are major concerns in the ambulatory (day-case) surgery population.[17] Nevertheless, in a recent meta-analytic study of antiemetic prophylaxis for children undergoing strabismus repair, droperidol 75 μg kg^{-1} i.v. had the greatest antiemetic benefit with an

estimated NNT of 4.[111] Furthermore, it was estimated that fewer than 1% of children who received droperidol would experience extrapyramidal symptoms and 16% would have less serious adverse effects. In adults, droperidol in doses as low as 0.625–1.25 mg (10–20 μg kg^{-1}) has been shown to be as effective as ondansetron 4 mg without increasing sedation, agitation, anxiety or delaying discharge.[26]

Phenothiazines

The phenothiazines, in common with the butyrophenones, are believed to exert their antiemetic effects primarily by antagonism of central dopaminergic receptors in the CTZ. Low doses of chlorpromazine, promethazine, perphenazine and dixyrazine are effective in preventing and controlling POV.[93 100 104] However, all phenothiazines are capable of producing extrapyramidal symptoms and sedation and this may complicate postoperative care, resulting in prolonged hospitalization. The degree of sedation varies between phenothiazines, with little sedation produced by perphenazine compared with the other phenothiazines.[100 104]

Benzamides

The benzamide and benzimidazole derivatives, metoclopramide and trimethobenzamide, have antiemetic and prokinetic effects. Metoclopramide is the most effective antiemetic of this class. Its antiemetic effects are mediated by antagonism of central dopaminergic receptors, and at high doses it also antagonizes 5-HT_3 receptors. In the gastrointestinal tract, metoclopramide has significant dopaminergic and cholinergic actions and increases motility from the distal oesophagus to the ilieocaecal valve. High doses of metoclopramide are well tolerated by adults, but children are prone to dystonic reactions. For this reason, metoclopramide is combined frequently with diphenhydramine and/or lorazepam when used to treat chemotherapy-induced emesis in children. Although metoclopramide has been used successfully to reduce the incidence of POV in high-risk children, it is not as effective as droperidol or the newer serotonin antagonists.[23 29 111]

Histamine antagonists

The histamine (H1) receptor antagonists are weakly antiemetic drugs with profound sedative effects, which make them less suitable for use in postoperative patients. They are frequently used in drug regimens to combat chemotherapy-induced nausea and vomiting because they counteract the extrapyramidal effects of the more efficacious dopamine receptor antagonists. These drugs may be useful for controlling emesis resulting from vestibular stimulation, as occurs in patients with motion sickness or after middle ear surgery. The low costs of histamine receptor antagonists have led to a recent resurgence of interest in their use as perioperative antiemetics. Dimenhydrinate 0.5 mg kg^{-1} i.v. during induction of anaesthesia was more effective than placebo in reducing vomiting after strabismus repair but not after adenotonsillectomy in children.[38 119]

Muscarinic receptor antagonists

The vestibular apparatus and the nucleus of the tractus solitarius are rich in muscarinic and histaminic receptors. Muscarinic receptor antagonism is effective in preventing emesis related to vestibular stimulation, which may be the mechanism of morphine-induced POV. In adults, the use of glycopyrrolate, a drug that does not cross the blood–brain barrier, was associated with three times the need for rescue antiemetic therapy compared with atropine.[82 107] In this study, the anticholinergic drugs were used for both premedication and with an anticholinesterase for antagonism of residual neuromuscular block. However, neither atropine nor glycopyrrolate reduced the incidence of POV in children after strabismus surgery.[14] Interestingly, transdermal scopolamine has been used successfully to reduce POV in children receiving morphine by PCA, but was associated with a significant increase in sedation and dry mouth.[20] Other potential side effects include dysphoria, confusion, disorientation, hallucinations and visual disturbances.

Serotonin receptor antagonists

Serotonin antagonists were discovered serendipitously when compounds structurally related to metoclopramide were found to have significant antiemetic effects, but lacked dopamine receptor affinity. These drugs produced pure antagonism of the 5-HT_3 receptor. Serotonin antagonists were first used to prevent chemotherapy-induced nausea and vomiting and were found to be superior to a variety of other antiemetics in this setting. *Ondansetron* was the first drug of this class to become available for clinical use in 1991. Since that time, granisetron, tropisetron and dolasetron have been introduced. This class of pure 5-HT_3 receptor antagonists are not associated with the side effects of dopamine, muscarinic or histamine receptor antagonists. The most serious side effects of ondansetron are rare hypersensitivity reactions.[91] Other side effects reported include headache, light-headedness, dizziness, flushing at the i.v. site, increased liver enzymes and a warm epigastric sensation.[81] Gastric emptying and small bowel transit time were not affected by ondansetron. However, colonic transit time was delayed and constipation is a known side effect.[35] Asymptomatic, brief prolongation of the PR interval and the QRS complex of the electrocardiogram have been reported in adults, but rapid i.v. infusion of ondansetron in children was not associated with changes in heart rate, arterial pressure or oxyhaemoglobin saturation.[79] Psychomotor and respiratory function were unaffected by ondansetron.

Prophylactic ondansetron 0.05–0.15 mg kg^{-1} i.v. or orally reduced the incidence of POV in children after a variety of surgical procedures, but not after craniotomy.[30 66 73 95 102 120] The number and duration of postoperative nursing interventions, need for rescue antiemetics and duration of stay in the PACU were also decreased after prophylactic administration of ondansetron.[17 66 73 78 120] Tramer and colleagues

performed a meta-analysis of 53 studies of ondansetron involving more than 13 000 patients.[115] In a subset of almost 1000 paediatric patients, the best documented regimen was 0.1 mg kg^{-1} i.v. However, these authors stated that '...the data suggested that it may not be worthwhile to increase the dose above 50 μg kg^{-1} ..'.[115] This review was remarkable for emphasizing that the antiemetic efficacy of ondansetron was consistently better than its anti-nausea efficacy. This may explain why ondansetron has been shown to be more effective than droperidol in preventing vomiting in children, but not for preventing both nausea and vomiting in adults.[17 25] Tramer and colleagues concluded that for every 100 patients receiving prophylactic ondansetron, 20 who would have vomited if they had received placebo were protected from this complication. However, three patients would develop increased liver enzymes and three would have a headache, but would not have developed these adverse events if they had not received the drug.[115] In our opinion, data presented in this manner are more useful for practising anaesthetists than a report of '*P*' values. More recent data suggest that the efficacy of ondansetron may be improved by administration at the end of a surgical procedure rather than at the beginning.[108]

There are fewer studies of the efficacy of ondansetron in controlling established PONV in the PACU compared with the multitude of studies on its prophylactic effect. Tramer and colleagues recently subjected these studies to meta-analysis and concluded that ondansetron prevented further vomiting, but four patients would need to be treated to prevent the problem in one.[114] The authors also concluded that ondansetron did not differ significantly in its antiemetic effects from droperidol or metoclopramide when given in the PACU for established emesis, but this conclusion was based on only two studies comparing ondansetron with droperidol and one with metoclopramide. However, subsequently published direct comparisons of ondansetron and metoclopramide have shown that ondansetron has greater efficacy in controlling established PONV.[18 75] There are no dose–response studies of the efficacy of ondansetron in controlling established POV in paediatric patients, but a single-dose trial showed that ondansetron 0.1 mg kg^{-1} was effective compared with placebo for treating vomiting in the PACU.[50]

Investigations of the antiemetic efficacy of other serotonin antagonists in children are limited. *Granisetron* 40 μg kg^{-1} i.v. was effective in decreasing the incidence of POV in children at high risk of this complication.[29] This drug has a longer half-life than ondansetron, but a single dose of ondansetron has been used for effective 24 h prophylaxis.[73] Some investigators report that the cost of granisetron (US$101.00 per patient free from emesis) makes its use for routine prophylaxis of POV prohibitively expensive.[15]

Dolasetron is the newest member of this class of antiemetics, and the effective dose is marketed at a lower cost than the effective dose of ondansetron. After i.v. administration, dolasetron is converted rapidly to hydrodolasetron, which is responsible for most of the antiemetic effects. Dose–response studies of dolasetron have shown that the minimum effective dose is 50 mg if given at the start of surgery, but only 12.5 mg if given at the end of surgery.[19 53] There are no published studies of the efficacy of dolasetron compared with placebo, other anti-serotonin drugs or the older antiemetics in children undergoing surgery. The half-life of hydrodolasetron is approximately 8 h, giving single-dose dolasetron a potential theoretical advantage over the other serotonin antagonists. However, this was not shown in the few comparative studies of serotonin antagonists available in the literature.[53 69]

Tropisetron is another anti-serotonin drug that is undergoing investigation. It has a longer half-life than ondansetron, but as with other anti-serotonin drugs, it is unclear if this is associated with a clinical advantage. A dose of 2 mg in adults or 0.1 mg kg^{-1} in children seems to be effective against PONV (Table 3).[1–3 13 76] This drug is available in only a few countries and is still being investigated in others.

Other drugs

The *glucocorticoid*s, dexamethasone and methylprednisolone, exert antiemetic properties by a mechanism as yet unknown. These drugs have been used for many years to prevent chemotherapy-related emesis, and are now being used in the postoperative setting. Dexamethasone in doses up to 1 mg kg^{-1} i.v. (maximum dose 25 mg) was effective in reducing postoperative vomiting in children after tonsillectomy.[66 72 103 132] However, low-dose dexamethasone 0.15 mg kg^{-1} i.v. was not as effective as perphenazine 70 μg kg^{-1} i.v. in preventing emesis after tonsillectomy in children.[72 93] This drug is better used in combination with another antiemetic than as the sole agent to prevent POV (see below).

Combinations of drugs

Given the vast number of drugs and the relatively limited efficacy of any individual drug, it seems reasonable to examine if a combination of antiemetics from different pharmacological classes would provide enhanced antiemetic efficacy with a reduced side effect profile. Combinations of drugs have become a proven strategy for combating emesis in chemotherapy patients and adult surgical patients, but there are few studies which have evaluated this approach for the prevention of POV in paediatric surgical patients. In both adults and children, the combination of dexamethasone with a serotonin antagonist improved antiemetic efficacy compared with the use of a serotonin antagonist only.[28 57 62 99] Combinations of oral droperidol and metoclopramide in children and droperidol with ondansetron in adults have been shown to be more effective than any one drug alone.[52 55] However, the efficacy of i.v. ondansetron was not improved by addition of oral metoclopramide.[56]

Table 3 Properties of antiemetic drugs. *No paediatric dose-ranging data available. †Not yet released for use in the USA. Costs unknown

Drug	Receptor antagonism site	Usual dose (mg kg^{-1})	Antiemetic efficacy	Relative costs	Side effects and comments
Butyrophenones	Dopamine				Drowsiness, sedation, dysphoria, anxiety and restlessness reported with higher doses. For adults, 0.625–1.25 mg seems to be ideal
Droperidol		0.025–0.075	++++	Cheap	
Phenothiazines	Dopamine				Variable anticholinergic effect. For sedation, chlorpromazine ⩾ promethazine > hydroxyzine >perphenazine > cyclizine. Extrapyramidal symptoms reported most often with prochlorperazine and perphenazine
Chlorpromazine		0.5–1.0	++++	Very cheap	
Perphenazine		0.025–0.07*			
Prochlorperazine		0.13			
Promethazine		0.25–0.5			
Benzamides	Dopamine				In usual doses, not associated with drowsiness. Extrapyramidal symptoms reported with high doses
Metoclopramide	↑GI motility	0.1–0.25	++	Cheap	
Antihistaminics	Histamine				These drugs have anticholinergic effects also, making the basis of their antiemetic effect unclear. Sedation is prominent with hydroxyzine and diphenhydramine but not with cyclizine or dimenhydrinate
Cyclizine		1.0	+++	Very cheap	
Dimenhydrinate		0.5	++++		
Diphenhydramine		1.0–1.25	++		
Hydroxyzine		1.0	++++		
Anticholinergics	Acetylcholine			Cheap, but scopolamine patch expensive	Reduces PONV when used with opioids. Can cause unpleasant dry mouth, irritable behaviour. Scopolamine patch expensive
Atropine		0.01	++		
Scopolamine		0.006	++		
Anti-serotonins	5-HT$_3$				Headache, abdominal pain, constipation reported. No drowsiness. Very effective, but also very expensive
Ondansetron	Peripheral	0.05–0.1	++++	Expensive	
Granisetron	and central	0.04	++++	most expensive	
Tropisetron†		0.1	++++	expensive	
Dolasetron		0.035*	++++	expensive	

Non-pharmacological approaches

In addition to the pharmacological strategies discussed to prevent POV, several non-pharmacological techniques may be of benefit. Concerns over the cost of newer antiemetics and the side effects associated with older agents have resulted in increased interest in some of these techniques. Acupuncture, acupressure and electrical stimulation of the P6 or Neiguan point located on the anterior surface of the wrist approximately three finger breadths above the distal skin crease of the wrist joint and between the tendons of the flexor carpi radialis and palmaris longis muscles, has been used to prevent POV in adults with mixed results.[125] In children, 5 min of acupressure after induction of anaesthesia was ineffective in preventing vomiting after strabismus repair.[130] The antiemetic efficacy of this technique may depend on the timing and duration of therapy and on the placebo effect. The technique may also have greater effect on controlling nausea than vomiting. Until further studies in children are performed, it is unclear if this non-pharmacological intervention will ever play a significant role in the prevention or treatment of POV.

Clinical strategies in the prevention and control of PONV

Given the varying patient population, drug efficacy and costs, it is appropriate for anaesthetists to develop systematic strategies for the management of this problem. Some centres have been successful in developing treatment algorithms and education programmes to provide better management of PONV.[70] These programmes have been modelled after the highly successful acute pain management services provided by some institutions. Management procedures for PONV should take into consideration the institutional incidence of the problem for the proposed surgical procedure, PACU discharge plans (day-case or inpatient) and the costs of all resources used if the patient develops PONV (Table 4). When practice guidelines are being formulated, the following questions should be answered:

(1) Which patients, if any, should receive routine prophylactic antiemetic therapy?

(2) What should be the preferred drug for prophylaxis?

(3) When should rescue antiemetic drugs be given and what drug should be used?

The answers to these questions may vary from institution to institution, depending on the risk of emesis without prophylaxis, the costs of the drugs and on practice patterns in the healthcare system. Decisions may also differ for the same procedure performed on a day-case and on an inpatient basis. These practice guidelines do not constitute a cookbook approach to patient management, and the acceptance of such a programme depends on demonstration of continual improvement in outcome, including patient satisfaction. An example is provided in Table 4.

Most anaesthetists agree that routine prophylaxis for all surgical patients is not indicated, but also agree that some patients would benefit from prophylaxis rather than a strategy of waiting for symptoms to be established in the PACU before treatment. Logistic regression analysis has been used to determine the risk of POV for a given patient at a specific institution.[71 110] Patients at highest risk are those with a previous history of the problem and undergoing operations known to be associated with a high incidence of PONV (e.g. strabismus surgery, dental treatment or tonsillectomy). The cost-effectiveness of a strategy of prophylaxis for all patients was examined by Watcha and Smith using a decision analysis model.[124] Mutually exclusive outcomes were identified, depending on the incidence of PONV after prophylaxis, need for rescue antiemetic therapy, incidence of side effects of therapy and need for hospitalization.[124] The costs for each outcome were calculated together with the probability of reaching that outcome. These costs included those for drugs, 'clean-up of emesis', rescue antiemetic therapy and management of side effects.[124] In this study, prophylactic ondansetron was more cost-effective than metoclopramide but not as cost-effective as droperidol. The prophylactic use of ondansetron was cost-effective only when the frequency of inhospital emesis exceeded 33%, whereas prophylactic droperidol was cost-effective even if the frequency was only 10%. These authors also stated that the expected frequency of PONV, and local drug acquisition costs, would significantly influence whether a particular antiemetic was cost-effective when given prophylactically or only as therapy for established PONV.[124]

This model was used in cost-effectiveness estimates of other antiemetics. Some have objected to the use of nursing labour costs in these estimates, on the grounds that these are semi-fixed and not variable costs. The same model has been used where results were presented separately with the inclusion and exclusion of nursing labour costs.[15 108] The prophylactic use of granisetron was not cost-effective compared with using the drug for treatment of established PONV.[15]

Many institutions have questioned the routine use of anti-serotonin drugs for prophylaxis and prefer to reserve them for the management of established POV.[70] The treatment of established POV is more challenging, particularly if it occurs after discharge from the day-case unit and despite prophylactic antiemetic therapy. It is important to note the dose, route and time of administration of antiemetics together with hydration status, severity and frequency of symptoms, and presence of other precipitating factors (e.g. movement, car journey, pain, analgesic therapy, forced oral intake). Often conservative measures such as dietary instructions or control of environmental factors may be all that is required. When symptoms persist, despite parental adherence to these instructions, antiemetic medications are required. An antiemetic drug from a different class should be given if the patient has failed prophylactic antiemetic therapy. This is important as additional doses of the same antiemetic may not be effective. If there is intractable POV or dehydration, it is necessary to have the patient return to

Table 4 Proposed management procedure for POV. This is based on the risk of POV, costs and efficacy of drugs and whether the patient is admitted to hospital or is a day case. †Use a drug from a class other than one already used in this patient. ¶Consider adding sub-hypnotic dose of propofol, acupressure or midazolam

Inpatient/day-case	Risk of POV	Prophylaxis	First episode	Second episode	Third episode	Fourth episode
Inpatient	<10%	None	None or metoclopramide or perphenazine or dimenhydrinate	Droperidol	Metoclopramide or prochlorperazine or dimenhydrinate†	Antiserotonin
	10–30%	Metoclopramide or perphenazine or dimenhydrinate	Droperidol	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate†	Antiserotonin	Metoclopramide or prochlorperazine or dimenhydrinate¶
	30–50%	Droperidol or perphenazine	Antiserotonin	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate†	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate¶	Metoclopramide or prochlorperazine or dimenhydrinate¶
	>50%	Antiserotonin ± steroids + metoclopramide or perphenazine	Droperidol	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate†	Metoclopramide or prochlorperazine or dimenhydrinate†	Metoclopramide or prochlorperazine or dimenhydrinate¶
Day-case surgery	<10%	None	Metoclopramide	Antiserotonin	Droperidol	Prochlorperazine
	10–30%	Metoclopramide or dimenhydrinate or perphenazine	Antiserotonin	Droperidol	Metoclopramide or prochlorperazine or dimenhydrinate†	Metoclopramide or prochlorperazine or dimenhydrinate¶
	30–30%	Antiserotonin ± steroids ± metoclopramide	Droperidol	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate†	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate¶	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate†¶
	>50%	Antiserotonin + steroids + metoclopramide or perphenazine	Droperidol	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate†	Metoclopramide or perphenazine or prochlorperazine or dimenhydrinate¶	Admit to hospital

the hospital for further evaluation. I.v. fluid and electrolyte therapy may also be required to combat POV.

Summary

The past decade has witnessed the introduction of several significant innovations to combat POV, particularly the introduction of serotonin antagonists and the use of combinations of drugs for analgesia and control of POV. Based on current knowledge, the anaesthetic plan for a patient with a previous history of severe PONV and undergoing a procedure known to be associated with a high incidence of this problem should include premedication with a benzodiazepine and/or clonidine and the preferential use of regional anaesthetic techniques. If general anaesthesia is essential, anaesthetists should consider the use of propofol for both induction and maintenance of anaesthesia, together with avoidance of nitrous oxide, opioids and neuromuscular antagonists. Pain control is extremely important, and a peripheral regional block should be used if possible. A combination of prophylactic antiemetics such as dexamethasone, a 5-HT_3 antagonist and an antiemetic of a different class (e.g. perphenazine or dimenhydrinate) should be administered. Non-pharmacological measures such as acupressure and suggestion should also be considered, together with nursing measures to avoid sudden movement from one position to another during the postoperative period. A quiet environment, adequate i.v. fluids and not forcing the patient to drink before discharge all contribute to decreased emesis. It is possible that the advent of a new class of antiemetic agents, the NK1 antagonists, may have major effects on the incidence of this complication. Drugs in this group differ from other currently available drugs in having the ability to effectively block the emetic response to many stimuli in experimental animals.[11] Postoperative vomiting remains a significant problem, resulting in patient suffering and prolonged recovery from anaesthesia. Our aim should be to eliminate this complication in all children who require surgery. It should not be considered merely as the 'big, little problem'. [48]

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