Review Article

Multimodal Antiemetic Therapy and Emetic Risk Profiling

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Abstract

Introduction: Postoperative nausea and vomiting (PONV) is a common problem with no simple solution. This review highlights factors that are known to increase the risk of PONV. It examines the various data on pharmacological and non-pharmacological methods that have been used to prevent PONV. Methods: Peer-reviewed journals on the subject were covered. Conclusion: Patient, surgical and anaesthetic factors increase the risk of PONV. While patient and surgical factors are understandably difficult to control, a multimodal approach involving both pharmacological and non-pharmacological interventions has been successfully adopted to reduce the incidence of PONV. Various factors have been identified to categorise patients into different profiles to determine their risk of PONV. Perioperative strategies can then be targeted at these patient groups.

Ann Acad Med Singapore 2005;34:196-205

Key words: Nausea, PONV, Risk factors, Vomiting

Introduction

In the last few years, hundreds of papers exploring the issue of postoperative nausea and vomiting (PONV) have been published. It has been estimated that the overall incidence of PONV for all surgeries and patient populations is between 25% and 30%, with severe, intractable PONV estimated to occur in approximately 0.18% of all patients.[1] In high-risk groups, PONV occurs in as many as 70% of patients. Despite advances in surgical techniques and the introduction of less emetogenic anaesthetic techniques and drugs, PONV remains an important cause of delayed discharge from the recovery room and decreased patient satisfaction. It is also associated with complications such as tension on suture lines, wound bleeding and dehiscence, increased intracranial pressure, pulmonary aspiration, dehydration and electrolyte imbalance.[1]

Anatomy and Physiology of Vomiting

The vomiting centre in the lateral reticular formation of the medulla oblongata coordinates the process of vomiting. It is closely related to the nucleus tractus solitarius and the area postrema. The chemoreceptor trigger zone (CTZ) is located in the area postrema. Peripheral and central stimuli can affect both the vomiting centre and the CTZ. Afferents from the pharynx, gastrointestinal tract, mediastinum, renal pelvis, peritoneum and genitalia can stimulate the vomiting centre. Central stimulation from the cerebral cortex, CTZ, higher cortical and brainstem centres, nucleus tractus solitarius, vestibular apparatus of the inner ear and the visual centre also affects the vomiting centre. The area postrema has no effective blood-brain barrier and chemicals present in the blood or cerebrospinal fluid can stimulate the CTZ.

A plethora of emetogenic receptors are found in the CTZ and nucleus tractus solitarius. The CTZ is rich in dopamine type 2 (D_2), opioid and 5-hydroxytryptamine type 3 (5-HT_3) receptors. The nucleus tractus solitarius has high concentrations of enkephalin, histaminergic and muscarinic cholinergic receptors. When stimulated, these receptors relay impulses to the vomiting centre, which then coordinates efferent impulses through the vagus, phrenic, and spinal nerves of the abdominal musculature to initiate the vomiting reflex. Thus, the multifactorial nature of PONV may necessitate combination therapy for prophylaxis and treatment.

Risk Factors for PONV

The aetiology of PONV is multifactorial, involving

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patient-, medical-, surgery- and anaesthesia-related factors.

Patient-related Factors

Patient-related risk factors are beyond our control and it becomes imperative to identify them during the preoperative anaesthesia evaluation. They include age, gender, history of motion sickness or PONV, and smoking history.[1] Obesity is no longer considered a risk factor for PONV.

Medical Factors

Some patients may have coexisting medical problems, such as gastrointestinal diseases (hiatus hernia, gastro-oesophageal reflux) and metabolic diseases (diabetes mellitus, uraemia, electrolyte abnormalities), that may predispose them to PONV. Pregnancy and preoperative anxiety also increase the risk of PONV. The underlying surgical problem for which the patient is undergoing surgery, such as intracranial stimulation (raised intracranial pressure from tumours) and sensory stimulation from acute abdomen, intestinal obstruction etc., can also initiate the vomiting reflex. Patients undergoing chemotherapy or radiation therapy are also more prone to emesis.

Surgery-related Causes

Certain types of surgery are associated with a higher risk of PONV. Otolaryngological surgery, dental surgery, breast augmentation surgery, orthopaedic shoulder surgery, laparoscopy, strabismus surgery and varicose vein stripping were found to have a higher incidence of PONV than other procedures.[2] Long operations increase the exposure time to potentially emetogenic anaesthetic drugs and are associated with a higher risk of PONV.

Anaesthesia-related Causes

While anaesthetists have little control over surgical factors, they do have control over factors such as premedication, anaesthetic technique, choice of anaesthetic drugs [nitrous oxide, volatile anaesthetics, intravenous (IV) agents, opioids and reversal agents], IV hydration and postoperative pain management. A >35% reduction in systolic blood pressure during anaesthesia, and especially during induction, has been associated with an increased incidence of PONV.[3]

Premedication

Midazolam is frequently used as a sedative for premedication. Splinter et al[4] reported a lower incidence of vomiting in children after tonsillectomy with the use of midazolam. Di Florio[5] reported 3 cases of persistent PONV that responded to midazolam. They also demonstrated a reduction in PONV and the use of rescue antiemetics using a 1-mg/h midazolam infusion.[6] In addition to its anxiolytic effect, midazolam probably enhances the inhibitory effects of gamma amino butyric acid (GABA) and decreases dopaminergic neuronal activity and 5-hydroxytryptamine (5-HT) release.[5] Midazolam may also decrease adenosine reuptake, leading to an adenosine-mediated reduction in synthesis, release and postsynaptic action of dopamine at the CTZ.[7] It has also been shown that midazolam reduces catecholamine levels and contributes to less PONV.[8]

Choice of Anaesthetic Technique

The use of volatile anaesthetics during general anaesthesia (GA) was a strong risk factor for the development of postoperative vomiting.[9] It appeared to be restricted to the first 2 hours post-operation and also depended on the duration of exposure.[9] There was no apparent difference in the incidence of postoperative vomiting when isoflurane, enflurane and sevoflurane were compared.

N_2O stimulates the vomiting centre directly and interacts with opioid receptors, the sympathetic nervous system and peripheral pathways. It causes distension of air spaces in the middle ear, stomach and small and large intestines. Various studies have shown a higher incidence of PONV with the use of N_2O.[10,11] Some studies[12,13] have reported no increase in the incidence of PONV with N_2O. The difference observed may be related to different surgery, use of opioids for premedication or intraoperative administration of opioids. Moreover, the underlying incidence of PONV (control event rate) in the studies varied by a large degree and it is possible that other confounding factors might be present. Hartung[14] reviewed 27 studies between 1969 and 1995 to compare the incidence of vomiting in patients who received N_2O with that in patients who received anaesthetics or analgesics without N_2O. Twenty-four out of 27 studies reported an absolutely higher incidence of vomiting in patients who received N_2O. Recently, the large multi-centre IMPACT trial demonstrated that the use of nitrogen (N_2), instead of N_2O, reduced the incidence of PONV by 12%. However, this did not reach statistical significance.[15] Propofol or omission of N_2O is less effective than giving an antiemetic agent such as ondansetron, dexamethasone or droperidol, but their combination may reduce PONV risk significantly.[15]

Administration of a regional anaesthetic technique has advantages over GA. The incidence of PONV may be reduced, as the use of N_2O, neostigmine and opioids is avoided. However, PONV can still occur if opioids are injected into the epidural or intrathecal space. The use of more lipid-soluble opioids, such as fentanyl or sufentanil, limits the rostral spread of opioids and lowers the risk of emesis. Postural hypotension secondary to sympathetic blockade in central neuraxial blocks can also contribute to PONV.

Choice of Anaesthetic Drugs

Propofol is commonly used for the induction and maintenance of GA. There is strong evidence to suggest that total intravenous anaesthesia (TIVA) with propofol reduces the incidence of PONV.[15-17] Meta-analyses have also shown that propofol is associated with a lower incidence of PONV than inhalational anaesthesia.[18] Propofol may act by reducing 5-HT levels in the area postrema.[19] However, propofol given for induction alone has no relevant effect on PONV.[16] This has led to a suggestion that the difference between propofol and volatile anaesthesia is caused mainly by the emetogenic effects of volatile anaesthetics, rather than by the antiemetic effect of propofol.[9] The use of patient-controlled antiemesis with subhypnotic doses of propofol may also effectively reduce the incidence of PONV with a high level of patient satisfaction.[20]

Neostigmine has been implicated as a cause of PONV due to its muscarinic action on the gastrointestinal tract.[21-23] The first group of investigators[21] used a combination of neostigmine and atropine while the other 2 groups[22,23] used neostigmine-glycopyrrolate for reversal. On the contrary, Janhunen and Tammisto[24] reported a decreased incidence of emesis with the use of neostigmine-atropine. Boeke et al[25] administered neostigmine and atropine as well and demonstrated no difference in the incidence of PONV. In fact, the need for antiemetic therapy was lower in this group of patients. More recently, Hovorka et al[26] and Joshi et al[27] demonstrated that the use of neostigmine and glycopyrrolate did not increase the incidence of PONV.

These contradictory findings may be related to factors such as age of patients (adult versus child), type of surgery (peripheral versus gynaecologic), use of different induction agents (thiopentone versus propofol), different doses of neostigmine and different anticholinergic agents (glycopyrrolate versus atropine) administered. Children and women are more prone to PONV and laparoscopic surgery is associated with a higher risk of PONV. Atropine, unlike the quaternary anticholinergic glycopyrrolate, crosses the blood-brain barrier and is known to possess some antiemetic property.[28] Thus, the possibility that the differing results were due to the anticholinergic drug, rather than the anticholinesterase, could not be excluded.

The use of shorter-acting muscle relaxants such as mivacurium will decrease the need for reversal drugs. However, it should not be assumed that it is safe to avoid reversal of residual neuromuscular blockade as potentially life-threatening postoperative respiratory obstruction may occur. Even a minor degree of residual paralysis (train-of-four ratio of 0.9) can cause visual disturbances, decreased grip strength, inability to maintain incisor teeth apposition, inability to sit up without assistance, severe facial weakness and overall weakness and tiredness.[29] Therefore, reversal drugs should be used in appropriate doses when necessary.

Traditional versus New Antiemetic Therapy

Older drugs used for preventing or treating PONV include the anticholinergics (glycopyrrolate, scopolamine), phenothiazines (promethazine, prochlorperazine), antihistamines (hydroxyzine, diphenhydramine), butyrophenones (droperidol), benzamides (metoclopramide) and steroids (betamethasone, dexamethasone). Some of these antiemetics are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extrapyramidal symptoms and dystonic effects. Three major groups of drugs that remain in use for PONV are the benzamides, butyrophenones and steroids.

Metoclopramide

Metoclopramide is a benzamide that has been widely used in clinical practice for many decades. It blocks D_2 receptors centrally (vomiting centre, CTZ) and peripherally (gastrointestinal tract). However, it has fallen out of favour because of its weak antiemetic efficacy at the typical prophylactic dose. A systematic review of 66 studies showed that prophylactic metoclopramide did not appear to be effective in preventing PONV in both adults and children at the commonly used doses of 10 mg to 20 mg (adults) and 0.25 mg/kg (children).[30] Metoclopramide seemed to have better antiemetic efficacy when given in the immediate postoperative period.[31] Nevertheless, its ineffectiveness for prophylaxis may be a result of underdosage. However, the use of higher doses has to be weighed against the greater risk of extrapyramidal symptoms.

Droperidol

Droperidol is the only commonly used butyrophenone. Its mechanism of action is through antagonism of D_2 receptors centrally. Droperidol was reported to be more effective as an antiemetic when given at the end of surgery when compared with the same dose given at induction.[32] A meta-analysis of 54 studies by Domino et al[33] showed that droperidol was as effective as ondansetron when given prophylactically. At doses <1.25 mg droperidol, the incidence of central nervous system (CNS) side effects was comparable to that of ondansetron. In contrast to adults, droperidol is less effective than ondansetron in paediatric patients.[33]

In December 2001, the US Food and Drug Administration (FDA) issued a "black box" warning on droperidol for antiemesis based on a number of anecdotal reports of QTc prolongation and torsades de pointes associated with its use.[34] It recommended that droperidol should not be used as a first-line drug for PONV, and electrocardiographic

monitoring should be performed before treatment and continued for 2 to 3 hours after treatment to monitor for arrhythmias. However, no report of adverse cardiac events or cardiac deaths caused by droperidol has ever been published in peer-reviewed journals since its introduction for the management of PONV.[34] This announcement has led to the withdrawal of droperidol from many countries.

Dexamethasone

Dexamethasone has been shown to be effective in reducing the incidence of PONV in numerous studies. Its mechanism of action is likely to be related to the inhibition of prostaglandin synthesis[35] and the stimulation of endorphin release, resulting in mood elevation, a sense of well-being and appetite stimulation.[36]

In a systematic review, Henzi et al[37] combined data from 4 trials in adults and 3 trials in children and showed that dexamethasone had antiemetic efficacy when compared with placebo. Efficacy was similar in adults and children. Goldman et al[38] demonstrated a 27% reduction in postoperative vomiting with the use of dexamethasone in a meta-analysis.

Dexamethasone probably has a delayed onset time of at least 2 hours and a prophylactic IV dose is best given at the time of induction rather than at the end of surgery to prevent early PONV.[39] It has a relatively long half-life of 36 to 72 hours and late efficacy of up to 24 hours is exhibited. Dexamethasone 5 mg IV appears to be the minimum effective dose for reducing the incidence of PONV in adults.[40] It has also been effectively used as prophylaxis in strabismus surgery in children.[41] It was more cost-effective than ondansetron and it had the added advantage of antiemetic efficacy in the late postoperative period. When dexamethasone was used in combination with ondansetron, the antiemetic effect was increased.[41]

Side effects with long-term administration of steroids may include glucose intolerance, adrenal suppression or wound infection. However, there was no evidence that a single dose of dexamethasone increases the incidence of postoperative infection.[42] None of the PONV studies tested the effect of dexamethasone on the hypothalamus-pituitary-adrenal (HPA) axis. But no evidence of HPA axis dysfunction was seen in ovarian cancer patients given high doses of 20 mg dexamethasone per day for 5 days for chemotherapy-induced vomiting.[43]

5-HT_3 Receptor Antagonists

The 5-HT_3 receptor antagonists are generally superior to the traditional antiemetic agents for preventing PONV. These antiemetics do not have the adverse effects of the older, traditional antiemetics. Headache and dizziness are their main adverse effects in the dosages used for PONV.

Ondansetron 4 mg IV has been reported to be the optimal dose[44] and it should be administered at the end of surgery.[45] Ondansetron has a fairly short half-life of 3 to 4 hours and may be less effective if given at the time of induction. Ondansetron 0.1 mg/kg up to 4 mg was significantly more effective than placebo for the prophylaxis of PONV in high-risk surgeries such as adenotonsillectomy and strabismus surgery in children.[46]

Dolasetron mesylate is a highly selective 5-HT_3 receptor antagonist. Dolasetron is rapidly broken down to its active metabolite, hydrodolasetron. Hydrodolasetron has a half-life of approximately 8 hours. The optimal dose of IV dolasetron is likely to be 12.5 mg.[47] The timing of dolasetron administration appeared to have little effect on its efficacy when administered as a prophylactic antiemetic.[48] No significant differences in efficacy between prophylactic doses of dolasetron 12.5 mg IV and ondansetron 4 mg IV were noted in preventing PONV in outpatient otolaryngological surgery. However, dolasetron 12.5 mg IV was more cost-effective than 4 mg of ondansetron.[49]

Newer 5-HT_3 antagonists have also been investigated for the prevention and treatment of PONV. Although a dose-finding study determined tropisetron 2 mg IV to be the lowest effective dose,[50] a recent study showed tropisetron 5 mg IV to be more effective.[51] Tropisetron may be a better choice than ondansetron because it has a longer half-life of 7 to 30 hours compared with ondansetron (3.5 hours) and both drugs have similar efficacy and side effects profiles.[52] The optimum effective dose of granisetron was found to be 40 mcg/kg IV when administered prophylactically before the start of surgery.[53,54] Ramosetron is another selective 5-HT_3 antagonist and it is more potent and longer-acting than granisetron in treating chemotherapy-induced vomiting. Fujii et al[55] demonstrated that the minimum effective dose of ramosetron for preventing PONV after gynaecologic surgery was 0.3 mg IV.

Other Drugs

Ephedrine is effective in treating emesis secondary to hypotension induced by spinal anaesthesia. It was shown to have similar antiemetic efficacy as droperidol[56] and propofol[57] in 2 separate studies when given to prevent PONV.

Clonidine, an α_2-adrenergic agonist, has been used to prevent PONV in children after strabismus surgery.[58] More recently, a group of investigators studied the use of clonidine for co-induction of GA in adult patients undergoing breast surgery.[59] The number of PONV-free patients was doubled when compared with the placebo group. A general reduction in sympathetic outflow caused by clonidine may be a possible reason. Clonidine has analgesic properties and its administration reduced the

opioid requirement, and this may have contributed to a lower incidence of PONV.

Neurokinin-1 (NK-1) receptors are found in the nucleus tractus solitarius and area postrema of the CNS, as well as in the peripheral nervous system. Substance P, a natural ligand for the NK-1 receptor, plays a role in the vomiting reflex through actions such as stimulation of gastrointestinal smooth muscle, exocrine gland secretion, afferent sensory responses to gastric distension and other visceral afferent stimuli. A preliminary study involving GR205171, an NK-1 receptor antagonist, indicated that this compound could control PONV when given postoperatively.[60] In another study, preoperative administration of 200 mg of oral CP-122,721, another NK-1 antagonist, decreased emetic episodes as effectively as ondansetron 4 mg IV during the first 24 hours after abdominal hysterectomy.[61] The combination of CP-122,721 and ondansetron prevented emesis better than either drug alone.[61]

Adjuvant Therapy

In a prospective randomised double-blinded study, Yogendran et al[62] demonstrated that perioperative hydration of ambulatory patients undergoing GA with 20 mL/kg of fluids reduced the incidence of thirst, dizziness and drowsiness up to 24 hours after surgery.

Administration of supplemental oxygen (O_2) has also been reported to reduce the incidence of PONV. Eighty per cent O_2, balance N_2, given intraoperatively and for the first 2 hours of recovery, produced a significant reduction in the incidence of PONV when compared with 30% O_2, balance N_2, given to patients undergoing colonic resection.[63] The authors speculated that less bowel inflation occurred when a higher concentration of O_2 was used. Bowel distension releases 5-HT, which may influence PONV. Secondly, bowel ischaemia can result from surgical manipulation or splanchnic vasoconstriction secondary to anaesthesia-induced arteriovenous shunting of blood to the peripheral tissues.[63] A consequence of ischaemia is the release of 5-HT and other emetogenic factors from the intestine.

Alternative medical therapy for PONV using aromatherapy has been explored. Separate studies have reported the use of inhalational isopropyl alcohol and demonstrated a reduction in the severity of nausea and vomiting.[64,65] The mechanism of action is unclear, but may involve depressant effects on the CNS.

Postoperative Factors

Postoperative pain, especially visceral or pelvic pain, is often overlooked as a cause of PONV. Pain can prolong gastric emptying time and contribute to emesis after surgery. Use of systemic opioids or non-steroidal anti-inflammatory drugs, patient-controlled analgesia, neuraxial blocks, regional nerve blocks and local infiltration of the surgical wound can improve the quality of postoperative pain. However, opioid therapy can potentially increase PONV. Therefore, a balanced or multimodal analgesia technique employing a combination of the abovementioned methods will reduce the side effects of each method to achieve a synergistic effect.[66]

Sudden movements or changes in position during transfer of patient and ambulation can precipitate nausea and vomiting. This is particularly true in patients who have been given opioids. The vestibular apparatus may become sensitised to motion-induced nausea and vomiting by opioids or by N_2O diffusion into the middle ear.

Postdischarge Nausea and Vomiting

The treatment of nausea and vomiting is frequently neglected in the postdischarge period. Carroll et al[67] surveyed 143 patients from 6 surgical centres at 24 to 48 hours and 5 days after discharge. Postdischarge nausea and vomiting were experienced by 35.7% of patients, with >72% of this group having had no PONV in the recovery room. The study showed no correlation between the occurrences of pre- and postdischarge nausea and vomiting, and suggested that other factors such as motion, early ambulation or pain medication, in addition to the usual causes of PONV, might be responsible. A group of investigators have reported the successful administration of orally disintegrating ondansetron tablets (ondansetron ODT) in preventing postdischarge vomiting.[68] However, ondansetron ODT was not shown to be effective after gynaecologic laparoscopic surgery.[69]

The complete recovery of patients extends into the postdischarge period. Therefore, further studies should look into strategies to manage PONV after the patient has returned home.

Combination Therapy for PONV

In general, combination therapy is superior to monotherapy for PONV. Our understanding of the neuropharmacology of the vomiting centre, CTZ and their associations with multiple emetic receptors in the brain has provided evidence that the aetiology of PONV is multi-factorial and it is only logical to adopt multiple drugs to tackle it. Many studies have already shown, without doubt, that antiemetics given in combination are more effective than each individual antiemetic. The combination of droperidol and ondansetron proved to be superior to using each drug alone.[70] Droperidol has greater anti-nausea efficacy, whereas ondansetron has better anti-vomiting efficacy.[71] In addition, droperidol effectively protects against postoperative headaches that may occur as a side effect of ondansetron. The combination of

dexamethasone and ondansetron was more effective than each drug given individually.[72]

In a study by Scuderi et al,[73] a multimodal prophylactic antiemetic algorithm was advocated in outpatient gynaecologic laparoscopy. It consisted of TIVA with propofol and remifentanil, avoidance of N_2O and neuromuscular blockade, aggressive IV hydration (25 mL/kg) triple prophylactic antiemetics (ondansetron, droperidol and dexamethasone), and ketorolac for analgesia. The study group had a 98% complete response rate and no incidence of vomiting. Although this study did not result in earlier patient discharge or show any difference in the time to return to normal activities, it is encouraging to know that PONV can be eliminated if necessary measures are taken.

In the IMPACT trial, the investigators found that droperidol, dexamethasone and ondansetron possessed similar antiemetic efficacy.[15] Successive interventions to further reduce the incidence of PONV were effective, but the additional antiemetic benefit was lower. This was more apparent in patients with few risk factors for PONV.

Prophylaxis versus Treatment of PONV

The issue of prophylaxis versus treatment of PONV remains controversial. A truly effective antiemetic regimen should increase a patient's comfort and shorten his or her stay in the recovery room or hospital. In an editorial, Fisher[74] questioned the value of measuring the antiemetic efficacy of a drug using surrogate end points, such as PONV, in many studies. Instead, true (nonsurrogate) outcomes that measure the time spent in recovery, incidence of unplanned hospital admissions, occurrence of adverse events (morbidity), patient satisfaction with treatment and quality-of-life indicators should be used.

Scuderi et al[75] examined both true and surrogate outcomes with the use of prophylactic ondansetron. Although the incidence of PONV was less with ondansetron prophylaxis, patient satisfaction (a true outcome) showed only a 4% improvement – less than the 10% improvement defined by the authors as clinically significant. There were no clinically or statistically significant differences in objective measures of other true outcomes. Unfortunately, failure to control for the type of surgery, anaesthetic technique and timing of ondansetron administration may have contributed to the negative findings in the study. However, the authors did show that patient satisfaction was higher with prophylaxis (versus treatment) in a subset of women with a history of motion sickness and PONV undergoing highly emetogenic procedures. Tramer et al[76] demonstrated, in a meta-analysis, that treatment of PONV with ondansetron 1 mg IV was more cost-effective than ondansetron prophylaxis. However, direct comparisons were not made between the prophylactic and therapeutic efficacy of 1-, 4- and 8-mg doses, but between the ondansetron doses and placebo. The authors also highlighted that ondansetron prophylaxis is associated with a finite risk of adverse reactions and recommended therapeutic ondansetron as being effective and cheap.[77]

Other studies have also demonstrated higher levels of patient satisfaction when ondansetron 4 mg IV was administered for prophylaxis.[45,78,79] Two recent editorials have also recommended routine antiemetic prophylaxis for outpatients at risk of PONV.[80,81] The contention against symptomatic treatment of PONV is that higher costs may be incurred if a patient's stay in the recovery room is prolonged, especially in patients at high risk of PONV.

Patients with PONV, despite antiemetic prophylaxis, should be given rescue therapy with a drug from a different class. Repeating ondansetron in Post-anaesthesia Care Unit (PACU) after failed prophylaxis with intraoperative ondansetron did not improve efficacy.[82] Interestingly, using a different member of the same 5-HT_3 antagonist class showed increased efficacy for treating chemotherapy-induced nausea and vomiting.[83] This may be related to the side chain differences and the consequent differences in receptor binding and half-life among the 5-HT_3 antagonists.

Non-pharmacologic Techniques

Non-pharmacologic techniques, such as acupuncture, electroacupuncture, transcutaneous electrical nerve stimulation, transcutaneous acupoint electrical stimulation, acupoint injection and acupressure, have been described for the treatment of PONV.[84] It is believed that stimulation of the *Nei-Guan* Pericardium 6 (P6) acupoint may be associated with activation of serotonergic and noradrenergic fibres, or the release of β-endorphin in the cerebrospinal fluid, potentiating the antiemetic actions at the μ-receptor. P6 is the sixth point on the pericardial meridian, located about 5 cm proximal to the palmar aspect of the wrist between flexor carpi radialis and palmaris longus tendons.

Many studies that were performed to determine the efficacy of nonpharmacologic techniques in preventing PONV had various shortcomings. Some of these were factors such as different surgeries or type of anaesthesia, small study sizes, absence of placebo or sham-controlled groups, different methods of acupoint stimulation, absence of blinding, absence of a relevant comparator, or a combination of these. Lee and Done[85] attempted to pool data from these studies in a systematic review and concluded that nonpharmacologic techniques appeared to be superior to placebo in preventing early nausea and vomiting, but not thereafter. This held true only in adult patients and not in children. Unfortunately, the results of the meta-analysis might be affected by such diversity in the abovementioned factors and would potentially magnify the differences and

result in invalid comparisons.

Dundee and Ghaly[86] suggested that P6 stimulation had to be administered preemptively before the start of surgery to be effective. A recent study involving children, however, demonstrated that P6 acupoint injections with 0.2 mL of 50% dextrose solution at the conclusion of surgery was as effective as droperidol 10 mcg/kg IV in controlling early PONV.[87]

A separate multicentre study examined the antiemetic efficacy of the ReliefBand® device (Woodside Biomedical, Inc., Carlsbad, CA, USA) for P6 acustimulation before the end of laparoscopic cholecystectomy.[88] It included both placebo (inactive device) and sham (device applied in a non-P6 location) groups, in addition to the study group. The incidence and severity of nausea was significantly reduced, but not vomiting.

Only 2 recent studies attempted to compare the efficacy of nonpharmacologic techniques with commonly used prophylactic antiemetic drugs. Agarwal et al[89] demonstrated similar reduction in the incidence of PONV and the need for rescue therapy in the first 6 hours after laparoscopic cholecystectomy when P6 acupressure was compared with ondansetron 4 mg IV. However, there was no significant difference in PONV and antiemetics requirement 24 hours postoperatively. Wang and Kain[87] demonstrated similar efficacy with P6 acupoint injection and droperidol IV. Acupoint stimulation may also enhance the effects of antiemetic medication.[90] Further randomised controlled studies with standardisation in the type of surgery, technique of P6 acupoint stimulation, onset and duration of stimulation should be carried out to determine the effectiveness of nonpharmacologic techniques.

Risk Profiling

With a better understanding of the contributing factors of PONV, investigators have created various risk prediction tools to stratify patients into high-, medium- and low-risk groups for PONV. Palazzo and Evans[91] were the first to use logistic regression analysis to quantify the relative impact of patient, anaesthetic and surgical factors to predict PONV. They identified female gender, history of previous PONV, postoperative opioids and a history of motion sickness as factors associated with an increased risk of PONV. Apfel et al[92] identified 4 risk factors: being of female gender, prior history of motion sickness or PONV, non-smoking status and the use of postoperative opioids. If none, one, two, three, or four of these risk factors are present, the incidences of PONV are 10%, 21%, 39%, 61% and 79%, respectively. In addition to these risk factors, Sinclair et al[2] classified age, nature of surgery and duration and type of anaesthesia as independent risk factors. Koivuranta et al[93] developed a simple scoring system that can be used to determine the risk of PONV based on gender, previous history of postoperative sickness, longer duration of surgery, nonsmoking and a history of motion sickness. These risk scores were comparable. Simplified scoring methods by Apfel et al[92] and Koivuranta et al[93] were superior to the more complex logit models for clinical use in daily practice because equal weight was given to each of the predictive risk factors.[94,95]

Junger et al[96] utilised an Anaesthesia Information Management System (AIMS) to collect various patient-related, surgical, anaesthetic and postoperative data over a 3-year period. Using a logistic regression approach, they demonstrated that the female gender, increased age, nonsmoking status, increased duration of surgery, intraoperative opioid administration and intraoperative use of N_2O were associated with an increased risk of PONV. On the other hand, the use of IV propofol had a protective effect. Variables such as previous history of PONV and motion sickness were not evaluated because they were not documented in AIMS.

Based on a patient's risk profile, well-defined evidence-based guidelines for the prophylaxis and therapy of PONV should form the framework for the management of PONV. Recently, a set of guidelines were drawn up by Gan et al,[97] with the goals of identifying primary risk factors and reducing the baseline risks for PONV, in an attempt to find the optimal approach to PONV prevention and treatment. Taking into consideration the costs of prophylactic treatment and the potential side effects of antiemetics, prompt treatment of PONV when it occurs may be as efficacious and cost-effective as prophylaxis in low-risk patients. In medium- or high-risk groups, baseline risk should be reduced[97] and the cheapest and safest drug should be used first. One reasonable approach is to use dexamethasone and TIVA as first-line and second-line methods of prophylaxis against PONV.[15] Combination prophylactic therapy that includes the more expensive ondansetron can be considered for high-risk groups. A regional anaesthetic technique should be used if there are no contraindications.

Measurement of Cost-effectiveness and Outcome

Establishing the true cost of an intervention is more important than ever in this era of cost containment. The cost of anaesthetic drugs accounts for a large portion of total hospital drug costs, but drug costs alone form only a minor proportion of total patient costs. Watcha and Smith[98] used a decision analysis treatment model and demonstrated that prophylactic use of ondansetron (versus therapeutic) was only cost-effective when the incidence of PONV exceeds 33%, whereas the prophylactic use of droperidol (versus therapeutic) was cost-effective when the incidence was as low as 10%. Hill et al[79] found that it was more cost-effective for PONV prophylaxis when compared with placebo.

PONV resulted in increased costs of drug acquisition, materials, prolonged PACU stay, unanticipated hospital admission and personnel.

Nursing costs account for about 70% to 80% of total costs and its inclusion in such cost-effectiveness analyses make comparison among studies difficult. The hospital, ambulatory surgery centre and the office-based clinic have nurses that work on different shift systems with varying overtime pay arrangements. In general, it is reasonable to assume that nursing labour costs increase when patients with PONV require more attention and spend more time in PACU. In practice, the nurse-patient ratio is rarely changed and no extra cost is incurred. However, intangible opportunity costs, such as nurses having to give less attention to the other patients to concentrate on patients with PONV, will be hard to quantify.

Many other direct and indirect costs are peculiar to every study and may not be easily replicated and compared with another study. The expected frequency of PONV, drug acquisition and labour costs will vary from hospital to hospital and these factors will ultimately influence whether it is more cost-effective to give antiemetics prophylactically or to treat established PONV when they occur.

End points such as nausea and vomiting should be analysed separately as they are biologically different phenomena. An antiemetic may have more anti-nausea and less anti-vomiting efficacy (e.g., droperidol), or more anti-vomiting and less anti-nausea efficacy (e.g., ondansetron). The immediate and late postoperative periods should be defined and standardised internationally so that antiemetic efficacy during each of these periods can be reported and analysed. This will allow comparisons among different studies.

Conclusion

With a better understanding of the risk factors of PONV, emetic risk profiles of every patient can be established during the preoperative anaesthetic visit. Although the underlying baseline risk of PONV remains unpredictable, we can still identify patients who are at high risk of suffering from PONV. Routine antiemetic prophylaxis is not required in all patients. However, antiemetic prophylaxis will undeniably improve patient satisfaction in these high-risk groups. Prophylactic antiemetic monotherapy is no longer acceptable because of poor efficacy.

None of the drugs tested so far can be considered "gold standard" and none good enough to be used on its own. Instead, a multimodal stratagem comprising the use of anxiolytic premedication, avoidance of emetogenic anaesthetic techniques, combination pharmacological antiemetic therapy, nonpharmacologic therapy, adequate IV hydration, avoidance of hypotension, adequate pain relief and gentle transfer of patient from operating room to recovery area should be adopted. With greater emphasis on costs, the decision to select the most cost-effective antiemetic(s) for prophylaxis should be based on the expected frequency of PONV, the emetic risk profile of the patient, and the costs and intrinsic efficacy of the antiemetic drugs.

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Anti-emetic therapy administered concurrently with ORT (WHO recommended ORS) Double-blind RCT. Patients aged 6 months â€“ 12 years. (N = 145).Â The number of patients enrolled in the comparative trials was too small to appropriately establish the risk profile of anti-emetics in children with acute gastroenteritis. Leung & Robson (2007) reviewed the results from physician surveys and studies reporting on anti-emetic prescription patterns in children with acute gastroenteritis. Conclusions: Multimodal-antiemetic therapy; a regimen including total intravenous anaesthesia with propofol and remifentanil, prophylactic antiemetic (dexamethasone at induction and tropisetron at end of surgery), and multimodal analgesia with parecoxib sodium could significantly reduce the incidence of PONV after gynecological laparoscopy.Â Paper: [Effect of multimodal-antiemetic therapy on postoperative nausea and vomiting in patients undergoing gynecological laparoscopy: a randomized controlled study]. To: Xian Su, Zhi-yu Geng, Yi-lin Zheng. From (Name) Adults treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate). Antineoplastic combinations.Â If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate). High-emetic-risk radiation therapy. This review highlights factors that are known to increase the risk of PONV. It examines the various data on pharmacological and non-pharmacological methods that have been used to prevent PONV. Methods: Peer-reviewed journals on the subject were covered. Conclusion: Patient, surgical and anaesthetic factors increase the risk of PONV. While patient and surgical factors are understandably difficult to control, a multimodal approach involving both pharmacological and non-pharmacological interventions has been successfully adopted to reduce the incidence of PONV. Various factors have been identifie The previous version of the Antiemetic Guidelines was based on the Consensus Guideline Meeting held in Perugia, Italy, June 2009. Guideline Update for MASCC and ESMO in the Prevention of Chemotherapy- and Radiotherapy-Induced Nausea and Vomiting: Results of the Perugia Consensus Conference. F. Roila, J. Herrstedt, M. Aapro, R. J. Gralla, L. H. Einhorn, E. Ballatori, et al.