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Prevention and Treatment of Postoperative Nausea and Vomiting

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Abstract

Pain, nausea and vomiting are frequently listed by patients as their most important perioperative concerns. With the change in emphasis from an inpatient to outpatient hospital and office-based medical/surgical environment, there has been increased interest in the 'big little problem' of postoperative nausea and vomiting (PONV). Currently, the overall incidence of PONV is estimated to be 25 to 30%, with severe, intractable PONV estimated to occur in approximately 0.18% of all patients undergoing surgery. PONV can lead to delayed postanaesthesia care unit (PACU) recovery room discharge and unanticipated hospital admission, thereby increasing medical costs.

The aetiology and consequences of PONV are complex and multifactorial, with patient-, medical- and surgery-related factors. A thorough understanding of these factors, as well as the neuropharmacology of multiple emetic receptors [dopaminergic, muscarinic, cholinergic, opioid, histamine, serotonin (5-hydroxy-

tryptamine; 5-HT)] and physiology [cranial nerves VIII (acoustic-vestibular), IX (glossopharyngeal) and X (vagus), gastrointestinal reflex] relating to PONV are necessary to most effectively manage PONV. Commonly used older, traditional antiemetics for PONV include the anticholinergics (scopolamine), phenothiazines (promethazine), antihistamines (diphenhydramine), butyrophenones (droperidol) and benzamides (metoclopramide). These antiemetics have adverse effects such as dry mouth, sedation, hypotension, extrapyramidal symptoms, dystonic effects and restlessness.

The newest class of antiemetics used for the prevention and treatment of PONV are the serotonin receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron). These antiemetics do not have the adverse effects of the older, traditional antiemetics. Headache and dizziness are the main adverse effects of the serotonin receptor antagonists in the dosages used for PONV.

The serotonin receptor antagonists have improved antiemetic effectiveness but are not as completely efficacious for PONV as they are for chemotherapy-induced nausea and vomiting. Older, traditional antiemetics (such as droperidol) compare favourably with the serotonin receptor antagonists regarding efficacy for PONV prevention. Combination antiemetic therapy improves efficacy for PONV prevention and treatment.

In the difficult-to-treat PONV patient (as in the chemotherapy patient), suppression of numerous emetogenic peripheral stimuli and central neuroemetic receptors may be necessary. This multimodal PONV management approach includes use of: (i) multiple different antiemetic medications (double or triple combination antiemetic therapy acting at different neuroreceptor sites); (ii) less emetogenic anaesthesia techniques; (iii) adequate intravenous hydration; and (iv) adequate pain control.

1. Incidence of Postoperative Nausea and Vomiting (PONV)

With the change in emphasis from an inpatient to an outpatient and office-based medical/surgical care environment, postoperative nausea and vomiting (PONV) has been called the 'big little problem'.[1] The overall incidence of PONV has been difficult to assess because often there is no single initiating stimulus and multiple aetiologies (patient-related, medical, surgical, and anaesthesia-related) are involved. The incidence of PONV ranged from 75 to 80% during the ether era to approximately 9 to 43% over the past 40 years. Presently, the overall incidence of PONV for all surgeries and patient populations is estimated to be 25 to 30%.[2,3] Furthermore, it is estimated that approximately 0.18% of all patients who have surgery may experience intractable PONV, leading to a delay in postanaesthesia care unit (PACU) recovery room discharge and/or unanticipated hospital admission, thereby increasing medical costs.[4]

1.1 Anatomy and Physiology of Vomiting

Vomiting (emesis) is the forceful expulsion of gastrointestinal (GI) contents through the mouth. Retching is the rhythmic action of respiratory muscles preceding vomiting. Both retching and vomiting are objective patient experiences. Nausea is a subjective personal patient experience which may or may not be associated with vomiting. The vomiting reflex was hypothesised by Borison and Wang[5,6] to be a complex act that is coordinated by the vomiting centre. The vomiting centre is located in the lateral reticular formation of the medulla oblongata of the mid-brainstem CNS in close proximity to the nucleus of the solitary tract and area postrema at the level of the dorsal motor nucleus of the vagus nerve. The chemoreceptor trigger zone

(CTZ) is located in the area postrema near the vomiting centre at the bottom of the fourth ventricle (fig. 1).[7-9]

The process of nausea, retching and vomiting is coordinated by the vomiting centre. Stimulation can be initiated from the periphery (oropharynx, mediastinum, GI tract, renal pelvis, peritoneum and genitalia) and centrally from the CNS (cerebral cortex, labyrinthine, otic, vestibular apparatus). Stimuli are relayed from the periphery to the vomiting centre by the autonomic nervous system afferent neurons of the vagus nerve. There is afferent input to the area postrema from the glossopharyngeal and vagal nerves. Central cerebral sensory stimuli occur directly and are transmitted by the CTZ, area postrema and nucleus of the solitary tract in the lateral reticular formation of the medulla to the vomiting centre (fig. 1).[5,7-9] Chemicals in the CSF and blood have a direct stimulating effect at the vomiting centre.[6]

The areas in the CNS associated with balance, vasomotor activity, salivation, respiration and bulbar control are located near, and have innervation to, the vomiting centre. The close proximity of these areas to the vomiting centre corresponds to the physiological reactions often seen with PONV, such as salivation, increased swallowing, sweating, pallor, tachypnea, tachycardia, cardiac dysrhythmias and motion sickness.[2]

The CTZ contains high concentrations of enkephalin, opioid and dopamine D_2 receptors. The area postrema has high concentrations of opioid, D_2 and serotonin (5-hydroxytryptamine; 5-HT) receptors. The nucleus of the solitary tract has a pre-

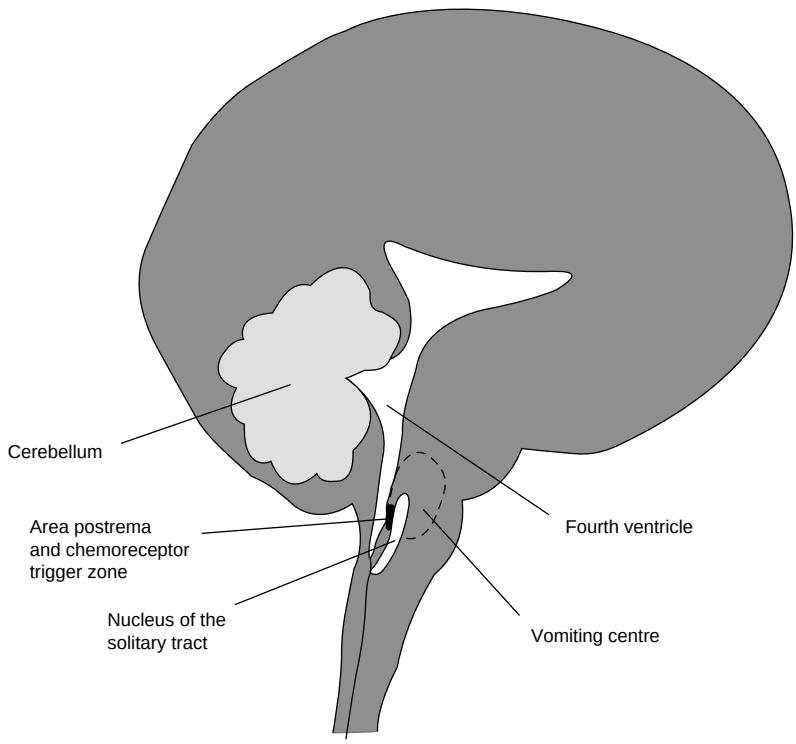

Fig. 1. Anatomical location of brain postoperative nausea and vomiting receptor areas: vomiting centre, nucleus of the solitary tract, area posterma and chemoreceptor trigger zone.

dominance of enkephalin, histamine, muscarinic and cholinergic receptors. These emetic neuroreceptor areas serve as sensors and are stimulated by drugs, electrolytes and metabolic chemicals, causing impulses to be relayed to the vomiting centre, thereby initiating the vomiting reflex (table I).[6,9-14] Blockade of these neurochemical receptor sites is the mechanism of action of the antiemetic medications commonly used for PONV.[2]

2. Consequences of PONV

The consequences of PONV are patient-, physiological-, medical-, surgical-, anaesthesia-, hospital- and cost-related (table II). Prolonged vomiting may lead to electrolyte imbalances (hypokalaemia, hypochloraemia, hyponatraemic metabolic alkalosis) and dehydration. Aspiration of gastric contents in the perioperative period is an important anaesthesia-related concern and consequence of PONV.[15] A Mallory Weis tear, oesophageal rupture, wound dehiscence and haematoma formation beneath skin flaps are important postoperative surgical-related concerns that may occur with PONV following abdominal, vascular, eye or plastic surgeries.[16-19] Patient-related concerns are the postoperative pain and discomfort from PONV. Hospital and increased nursing care time contribute to the economic-related consequences of PONV.

Table II. Consequences of postoperative nausea and vomiting

Parameter	Consequences
Patient	Delay in fluid and food intake
Physiological	Sweating, increased, swallowing, pallor, tachycardia, salivation, cardiac dysrhythmias
Medical	Interruption of diet, nutrition and/or oral drug therapy, dehydration, orthostatic hypotension, electrolyte imbalance (hypochloraemia, hyponatraemia, hypokalaemia, metabolic akalosis)
Surgical	Oesophageal tears, injury, disruption of vascular anastomosis, graphs and/or flaps, wound bleeding and dehiscence, increased intraocular pressure, haematoma formation, increased intracranial pressure
Anaesthesia	Aspiration pneumonia
Hospital/cost	Increased medical/nursing care time, delayed discharge from phase I and II postanaesthesia care unit recovery, inadvertent/unexpected hospital admission

3. Risk Factors for PONV

3.1 Factors Unrelated to Anaesthesia

Risk factors for PONV that are unrelated to anaesthesia are labyrinthine factors, metabolic factors, intracranial stimulation and sensory stimulation.

Table I. Midbrain neurochemical emetogenic receptor locations

Midbrain location	Receptors[a]
Area postrema	Opioid, dopamine (D_2), serotonin (5-hydroxytryptamine; 5-HT)
Chemoreceptor trigger zone	Enkephalin, opioid, dopamine (D_2)
Nucleus of solitary tract	Enkephalin, histamine, muscarinic, cholinergic

a The vomiting centre is the coordinator for these receptors to initiate the vomiting reflex.

Patients who have a history of motion sickness have a higher incidence of PONV. Motion sickness occurs following stimulation of the vestibular apparatus of the inner ear and is due to movement of endolymph in the semicircular canals, stimulating otolith cells in the utricle. Following this stimulation, transmission of impulses to the CTZ and vomiting centre occurs, relaying to the CNS the sensation of nausea and motion sickness. Vomiting may then occur. Motion sickness or vertigo can be a consequence of middle ear surgery as a result of vestibular stimulation.[20]

Metabolic factors that are mediated by the vomiting centre and CTZ include biochemical and environmental causes. These include uremia, diabetes mellitus (hypo- or hyperglycaemia), electrolyte disturbances (sodium, potassium), hormonal imbalances (estrogen, progesterone), pregnancy (hyperemesis gravidarum), chemotherapy and radiation therapy.[2,21,22]

Intracranial stimulation occurs from increased intracranial pressure (i.e. tumours, CSF obstruction), which can cause PONV by direct pressure on, and stimulation of, the vomiting centre.[2,16,21]

Sensory stimulation includes tactile stimulation of the posterior pharynx (from airway devices, oral or nasal airway, nasogastric or endotracheal tube), as well as stretching, inflammation or injury to the airway, upper abdomen, GI tract, renal pelvis, bladder, testes or uterine cervix that can cause sensory stimulation initiating the nausea and/or vomiting reflex.[22-24]

3.2 Patient-Related Factors

Many patient-related risk factors can affect the incidence of PONV and should be noted during the preoperative anaesthesia evaluation.[21,25] These include the patient's age, bodyweight, gender and individual predisposition, a history of PONV, nonsmoking and/or motion sickness, exposure to emetogenic drugs (i.e. digoxin), the presence of pain, coexisting medical problems and diseases (i.e. GI disturbances, indigestion, hiatal hernia, peptic ulcer disease), metabolic abnormalities (i.e. renal failure, uraemia, diabetes mellitus, electrolyte disturbances), the degree of hydration, and CNS pathology (i.e. elevated intracranial pressure).[16,24-27] Psychological concerns and preoperative anxiety can increase the risk of PONV as a result of increased plasma catecholamine levels.[28,29]

There is a 3-fold increase in the incidence of PONV in patients who have a history of PONV or motion sickness.[21,24] Female patients have a 2 to 3 times greater incidence of PONV than males, due to increased gonadotropin, estrogen and plasma progesterone levels during their menstrual cycle.[21,30,31] Although controversial, many women are believed to be most susceptible to PONV during the first 7 days of their menstrual cycle. This is supported in some studies,[30,31] but disputed in another.[32] In adults, there is a correlation between increasing age and decreasing incidence of PONV.[21,33] PONV is a common occurrence following anaesthesia in children (strabismus repair, tonsillectomy, adenoidectomy, middle ear operations) and increases after the age of 3 years with a peak incidence (≈40%) in the 11 to 14 year age group.[3,34,35] Morbidly obese patients (>2 times their ideal bodyweight) have a higher incidence of PONV after long operations (>3 hours) than nonobese patients, possibly due to increased drug uptake and disposition in adipose tissues which serve as a storage area for lipid-soluble emetogenic anaesthetic drugs.[2,22,36,37]

3.3 Factors Related to Anaesthesia

3.3.1 Premedication

Premedication with opioids (morphine, fentanyl, alfentanil) can increase the incidence of PONV by stimulating CNS opioid receptors.[27,28] Although opioids (in high doses) depress all CNS and vomiting centres, they directly stimulate the area postrema to a greater degree, causing PONV.[12] Opioids decrease gastric and GI motility, prolonging gastric emptying time.[38,39] Opioids predispose to PONV by sensitising the otic and vestibular areas to motion. Patient movement postoperatively with stimulation of endolymph in the inner ear appears to increase the frequency of opioid-induced emesis.[39] PONV in outpatients often occurs after movement from cart to chair, chair to standing, ambulation or during the car ride home. These dose-related effects may last for up to 6 hours after opioid administration.[40]

Atropine or scopolamine (hyoscine) administered concurrently with opioids as premedication appear to decrease the incidence of PONV compared with using opioids alone. Scopolamine and atropine are tertiary amines that cross the blood-brain barrier to exert their antiemetic and anti–motion sickness effects. As glycopyrrolate is a quaternary amine that does not cross the blood-brain barrier, it does not appear to have antiemetic or anti–motion sickness effects.[39] Scopolamine is preferable to atropine when used with morphine as premedication because of its greater sedative effect.[41] Benzodiazepines (i.e. midazolam) used as premedication for sedation also decrease the incidence of PONV by decreasing the plasma levels of catecholamines.[21,28]

3.3.2 Anaesthetic Gases

Potent inhalational anaesthetic gases, such as diethyl ether and cyclopropane, produced PONV with an incidence as high as 75 to 80% and were

considerably more emetogenic than the more recently introduced potent inhalational gases (halothane, enflurane, isoflurane, desflurane and sevoflurane).[16,24,33,39] Halothane was originally thought to have minor antiemetic properties (when administered in low doses added to trichloroethylene anaesthesia) secondary to an adrenergic antagonistic effect on the CNS.[39,42] However, while potent inhalational gases contribute to PONV to some degree, the total avoidance of these volatile agents has not resulted in a marked decrease of PONV. There appears to be no difference in PONV among the new potent inhalation agents.

Nitrous oxide (N_2O) is an inhalational gas that can cause PONV (depending on the percentage end-tidal concentration administered), with an incidence ranging from 49 to 67%.[43-46] There is a significant increase in the incidence of PONV in patients anaesthetised with a balanced general anaesthesia technique (N_2O/O_2/opioid/muscle relaxant) compared with an inhalational gas technique because of the presence of N_2O and opioid.[24,46,47] N_20 causes PONV by direct CNS stimulation of the vomiting centre and interaction with opioid receptors, as well as stimulation of the sympathetic nervous system and peripheral pathways, which include distention of air containing spaces of the middle ear, gallbladder and GI tract (stomach, small and large intestine).[48] The amount of gas volume increase equals the percentage of N_2O divided by (1.0-N_2O fractional percentage). Thus, a 50% N_2O concentration would produce a maximum volume increase of 100% [50/(1.0-0.5)]. The volume of GI tract air-filled spaces increases by approximately 0.5 litres per hour in the presence of an alveolar N_2O gas concentration of 75%. N_2O can increase the volume of GI bowel gas by 80 to 100% after 2 hours.[48,49] While several investigators[50,51] have disputed the increased incidence of PONV with N_2O, a recent review[52] revealed that in 24 of 27 studies involving N_2O there was an increased incidence of emesis in patients who received N_2O compared with alternative anaesthetic regimens without N_2O.

3.3.3 Intravenous Anaesthetic Agents

Intravenous anaesthetic agents that have a slow onset and smooth recovery (i.e. thiopental, propofol) have a lower incidence of PONV compared with medications with a more rapid recovery (i.e. methohexital, propanidid) or a higher incidence of excitatory effects during or after anaesthesia (i.e. etomidate, ketamine).[21,39,41]

3.3.4 Reversal of Muscle Relaxation

While use of a muscle relaxant alone is not believed to increase the incidence of PONV, reversal of muscle relaxation with an anticholinesterase medication alone (i.e. neostigmine) may contribute to an increase in PONV compared with not using reversal agents.[53] This minor PONV-related effect is decreased when an anticholinergic medication (i.e. atropine) was used in combination with neostigmine (due to the antiemetic effect of atropine).[54]

3.3.5 Preoperative Fasting

Aspiration of gastric contents during the induction of anaesthesia is an important anaesthesia-related concern.[55] Ingestion of solid food before surgery increases risk for PONV by distending the gut and release of GI hormones that can sensitise the vomiting reflex.[21] As the normal gastric emptying time for solid food is approximately 6 to 8 hours for the average healthy adult patient, a 6- to 8-hour preoperative fasting period has been common practice. The need for a prolonged clear liquid fasting period (at least 6 hours) prior to anaesthesia for elective surgery is controversial, as clear liquids have a shorter gastric emptying time than solid food, and a recent summary of fasting recommendations (to reduce pulmonary aspiration risk) has suggested the allowance of clear liquid up to 2 hours, and a light meal (toast and clear liquids) up to 6 hours, prior to surgery.[56]

3.3.6 Nasogastric Suctioning

Nasogastric suctioning is a useful method to remove air, secretions and blood from the stomach. Surgeries on the nose, mouth and/or oropharynx frequently involve the swallowing of blood. Blood in the stomach is one of the strongest peripheral

acting emetogenic stimuli and is difficult to treat by antiemetic medication alone. Often, removal of this blood by gastric suction or emesis by the patient is necessary to obtain complete relief.[57,58]

Gastric suctioning appears to have no effect on the incidence of PONV except in cases where PONV is related to gastric distention (i.e. GI obstruction, ileus).[59,60] Gastric suctioning may reduce PONV following GI surgery or after air inflation into the stomach, which often occurs during difficult and vigorous mask ventilation.[61] However, pharyngeal suctioning and/or the continued presence of a nasogastric tube or oral airway in the postoperative period may stimulate the gag reflex, increase gagging and retching (by stimulating the glossopharyngeal nerve) and contribute to PONV.

3.3.7 Long Operations

Long operations (>3 hours) allow longer exposure to lipid soluble, potentially emetic intravenous and inhalation gas anaesthetics. This longer anaesthetic exposure time can cause an increase in PONV.[16,21,24]

3.3.8 Regional Anaesthesia

Nausea and vomiting are adverse effects of regional anaesthesia (spinal and epidural), with an incidence of approximately 10 to 20%.[16] The nausea and vomiting that occurs during regional anaesthesia is common when the sympathetic block is above the tenth thoracic dermatome level. The resulting nausea and vomiting is due to (i) decreased cerebral blood flow secondary to systemic hypotension (from vasodilation); (ii) increased GI atony and peristalsis (secondary to preganglionic sympathetic blockade); and (iii) vagal stimulation that occurs during intra-abdominal GI manipulation (i.e. Caesarian section, hysterectomy, colon operations).[62,63] Blood pressure (BP) can be maintained with crystalloid preparations and ephedrine.

3.3.9 Postoperative Pain

Postoperative pain is a major cause of PONV, especially when the pain is pelvic or visceral in origin.[27] Intravenously administered opiates have been shown to relieve both pain and nausea in patients who have pain with nausea. This pain and PONV correlation is supported by data indicating reversal of opioid effect by naloxone causes a return of pain with nausea. Vestibular disturbances (i.e. patient movement, early ambulation) contribute to an increased incidence of PONV in the PACU (by stimulating the vestibular nerve).

3.3.10 Orthostatic Hypotension

Orthostatic hypotension secondary to dehydration[64] (preoperative bowel preparation or inadequate intravenous fluid replacement), and psychological and visual stimuli may further contribute to PONV in PACU recovery phases 1 and 2. Perioperative intravenous hydration of 20 ml/kg is recommended for patients undergoing general anaesthesia for short ambulatory surgical procedures of less than 2 hours in duration, to prevent postoperative drowsiness, dizziness and nausea.[64] If the preexisting fluid and electrolyte abnormalities have been corrected before the operation, fluid administration should maintain the urine volume between 0.5 to 1.0 ml/kg/hour.[65]

3.4 Factors Related to Surgery

There appears to be a direct relationship between the incidence of PONV and the operative site with a higher incidence of PONV after eye, oral, plastic, ear, nose and throat (ENT), head and neck, gynaecological, obstetric, laparoscopic and abdominal procedures than with other procedures.[18-24]

Other factors contributing to PONV include management of the airway and respiration in regard to (i) mask ventilation (air entry into the stomach); (ii) the degree of hypoxia, hypercarbia, intravenous hydration, hypotensive episodes (especially orthostatic); and (iii) airway instrumentation of the oropharynx (inducing the gag reflex).

Specific attention to the above postoperative concerns, such as (i) pain relief; (ii) adequate intravenous fluid hydration (do not force oral fluids); (iii) ensuring good ventilation, oxygenation, normocarbia; and (iv) maintenance of the patient's normal BP, will help prevent PONV in the PACU.

4. Management and Treatment Strategies

4.1 Prophylaxis

A complete pre-anaesthesia history and physical evaluation allows the formation of a specific PONV antiemetic management plan.[25] Because, overall, only 25 to 30% of the surgical patient population will experience PONV, not all patients require antiemetic prophylaxis.[2,66] Patient-, anaesthesia- and surgery-related risk factors for PONV should be evaluated to identify patients who may benefit from prophylactic antiemetics. Prophylactic antiemetics are recommended for any patients in whom PONV would compromise their surgery, delay their recovery or cause a hospital admission. Various PONV scores corresponding to the above mentioned risk factors have been devised.[25,26,67]

Apfel and colleagues[68] recently developed a simplified risk scoring system that appears to be predictive for PONV. The score consisted of 4 predictors: (i) female gender; (ii) history of motion sickness and/or PONV; (iii) nonsmoking; and (iv) use of postoperative opioids. When 0, 1, 2, 3 or 4 of these risk factors were present, the incidence of PONV was 10, 21, 39, 61 and 79%, respectively.

4.2 Traditional Antiemetic Therapy

The development of antiemetic medications to treat motion sickness, and nausea and vomiting secondary to chemotherapy and radiation therapy have initiated the investigation of many of the currently available antiemetic medications for use in PONV.

The different classes of antiemetic agents commonly used for PONV include anticholinergics, antihistamines, phenothiazines, sedatives/anxiolytics, butyrophenones, dopamine antagonists, serotonin receptor antagonists, corticosteroids, and combinations of these. It is often difficult to decide which antiemetic to use. Drugs that may be effective prophylactic antiemetic medications for PONV may be ineffective for the treatment of active vomiting. The various antiemetic medications currently available exhibit different binding affinities for and act at different emetic neuroreceptors located in the area postrema, CTZ, nucleus of the solitary tract and the vomiting centre. As the causes of PONV are multifactorial, and there are multiple emetic neuroreceptors, no single antiemetic medication has been 100% effective for all patients and all types of anaesthesia and surgery. This suggests that a combination antiemetic management approach using antiemetics that block different antiemetic neuroreceptors may be necessary to treat the patient with difficult to treat, severe or persistent PONV. Administration and dosage details for antiemetic agents are listed in table III.

4.2.1 Anticholinergics

Anticholinergic agents are among the oldest first-generation class of antiemetics. Anticholinergics are potent inhibitors of muscarinic and cholinergic CNS emetic receptors in the cerebral cortex and pons.[73] Compounds with selective muscarinic M_3 and M_5 receptor antagonism possess activity against motion sickness. As tertiary amines, atropine and scopolamine cross the blood-brain barrier and have efficacy against motion sickness and PONV.[39,74] Scopolamine is an effective preoperative antiemetic, especially when sedation is required. Atropine has weaker antiemetic properties than scopolamine. Both appear to be more effective against motion-induced vomiting than motion-induced nausea. Prophylactic transdermal scopolamine is more effective for the prevention of motion sickness than PONV.[74-76]

Although these medications are more effective in treating motion sickness than PONV, they are useful as premedication combined with opioids to reduce PONV. Scopolamine blocks impulses from vestibular nuclei to higher areas in the CNS, reticular activating formation and vomiting centre. Scopolamine helps to correct the CNS imbalance of acetylcholine and noradrenaline (norepinephrine) that occurs in patients who have motion sickness.[73,77] Adding an anticholinergic medication to an opioid for use as premedication has been shown to decrease emesis.[40] Transdermal scopolamine is effective in preventing the PONV caused by opioids (i.e. epidural morphine).[77,78] However, as the emetogenic properties of opioids such as morphine

Table III. Administration and dosage details of antiemetic medications[69-72]

Class	Drug	Route	Initial average dose	Frequency/timing	Adverse effects
Anticholinergics	Scopolamine	IM, IV	Adult: 0.2-0.65mg	q6-8h	Sedation, dry mouth, restlessness, central cholinergic syndrome
		TD patch	Adult: 1.5mg	q72h (apply 4h before exposure)	
Phenothiazines	Chlorpromazine	IM, IV	Adult: 25-50mg Child: 0.5-1.0 mg/kg/dose Max.: 5-12y (22.7-45.5kg): 75 mg/day Max.: <5y (22.7kg): 40 mg/day	q4-6h q6-8h	Sedation, EPS, hypotension, restlessness, anticholinergic syndrome
		PO	Adult: 10-25mg	q4-6h	
			Child: 0.5-1.0 mg/kg/dose	q4-6h	
	Promethazine	IM, IV, PO	Adult: 12.5-25mg	q4-8h	Sedation, EPS, hypotension, restlessness, anticholinergic syndrome
			Child: (<12y) 0.25-0.5 mg/kg	q6-8h	
	Perphenazine	IM	Adult: 2.5-5mg	q6h	Sedation, EPS, hypotension, restlessness
		IV	Adult: 1mg	q1-2min (max. 5mg)	
		PO	Adult: 2-4mg	q4-6h	
	Prochlorperazine	IV	Adult: 2.5-10mg (max. 40 mg/day)		Sedation, EPS, hypotension, restlessness
		IM, PO	Adult: 5-10mg	q3-4h	
		IM	Child: 0.1-0.15 mg/kg/dose	q4-6h	
		PO	Child: (<10kg): 0.5 mg/kg/24h in 3-4 divided doses		
Antihistamines	Cyclizine	IM, IV, PO	Adult: 25-50mg	q4-6h	Sedation, dry mouth, restlessness
	Hydroxyzine	PO	Adult: 25-50mg	q6h	Sedation, dry mouth, restlessness
		IM	Adult: 25-100mg	At start of anaesthesia	Do not give IV or SC (significant anticholinergic effects)
	Diphenhydramine	IM, IV	Adult: 10-50mg (max. 300 mg/day)	q2-4h	Sedation, dry mouth, restlessness
		PO	Adult: 25-50mg	q6-8h	
Butyrophenones	Droperidol	IM, IV	Adult: 0.625-2.5mg (prevention)	At start of anaesthesia	Sedation, hypotension, EPS, restlessness, neurolyptic malignant syndrome
			Adult: 0.625-1.25mg (treatment)		
	Haloperidol	IV	Adult: 7 μg/kg (prevention)	At start of anaesthesia	
		IM	Adult: 0.5-4mg (prevention)	15 min before anaesthesia	
			Adult: 1.0mg (treatment)		
Benzamides	Metoclopramide	IV, IM	Adult: 10-20mg (prevention)	At end of surgery	Sedation, restlessness, EPS
			Adult: 10-20mg (treatment)		
	Domperidone	IV, IM	Adult: 4-10mg (treatment)		Sedation, restlessness, EPS
	Benzquinamide	IM	Adult: 25-50mg (0.5-0.75 mg/kg)	15 min before end of anaesthesia	Do not give IV (tachycardia, hypertension, cardiac arrhythmias)
		PO	Adult: 100mg	q6-8h	
Corticosteroids	Betamethasone	IM	Adult: 12mg (prevention)	At start of anaesthesia	Adrenal suppression, wound healing

Table III. Contd

Class	Drug	Route	Initial average dose	Frequency/timing	Adverse effects
	Dexamethasone	IV	Adult: 8mg (prevention)	At start of anaesthesia	
5-HT_3 receptor antagonists	Ondansetron	PO	Adult: 8-16mg	1-2h before anaesthesia	Headache, dizziness
		IV	Adult: 4mg (prevention)	At start of anaesthesia	
			Adult: 4mg (treatment)		
			Child: 0.1 mg/kg (max. 4mg) [prevention and treatment]		
	Granisetron	IV	Adult: 1mg (prevention)	At start of anaesthesia	Headache, dizziness
		PO	Adult: 1mg (treatment)		
	Tropisetron	IV	Adult: 5mg (prevention)	At start of anaesthesia	Headache, dizziness
		IV	Adult: 2mg (treatment)		
	Dolasetron	PO	Adult: 100mg (prevention)	1-2h before anaesthesia	Headache, dizziness
		IV	Adult: 12.5mg (prevention)	15-30 min before end of anaesthesia	
		IV	Adult: 12.5mg (treatment)		
		PO	Child: 1.2 mg/kg (max. 100mg) [prevention]	1-2h before anaesthesia	
		IV	Child: 0.35 mg/kg (max. 12.5mg) [prevention and treatment]	15-30 min before end of anaesthesia (prevention)	

5-HT = serotonin (5-hydroxytryptamine); **EPS** = extrapyramidal symptoms; **IM** = intramuscular; **IV** = intravenous; **Max** = maximum dosage; **PO** = orally; **q*x*h** = every *x* hours; **SC** = subcutaneous; **TD** = transdermal.

have a longer duration than the antiemetic properties of scopolamine, delayed PONV may occur when opioids and anticholinergics are used concurrently.

The main disadvantages of the use of anticholinergics include anticholinergic adverse effects, which are sedation, blurred vision, mydriasis, dry mouth, memory loss, urinary retention, hallucinations, confusion and disorientation.[79,80]

4.2.2 Dopamine Receptor Antagonists

The phenothiazines (promethazine, prochlorperazine), benzamides (metaclopramide) and butyrophenones (droperidol) are strong D_2 antagonists.

Phenothiazines

Phenothiazines (promethazine, chlorpromazine, prochlorperazine, perphenazine, thiethylperazine) are among the most widely used antiemetic medications worldwide. The phenothiazines have a common tricyclic nucleus. The attached chemical radical group on the tenth position of the tricyclic nucleus appears to determine antiemetic efficacy. This side chain radical group may be either aliphatic (promethazine, chlorpromazine) or heterocyclic (prochlorperazine, perphenazine, thiethylperazine). The aliphatic phenothiazines have less antiemetic potency and more sedative effects than the heterocyclic phenothiazines.[81,82]

The phenothiazines exert a direct D_2 receptor blocking effect in the CTZ with moderate antihistaminergic and anticholinergic actions. These medications are used as sedatives and major tranquillisers, and are especially effective in countering the effect of certain drugs (i.e. opioids) on the CTZ. Although they are effective for the prevention and treatment of PONV, they are less effective against motion sickness and have no effect on gastric emptying.[80-82]

Chlorpromazine has PONV antiemetic effectiveness, with adverse effects of sedation and hypotension, but it is not effective for the prevention of motion sickness. Promethazine is an effective prophylactic antiemetic with more sedation and a more prolonged recovery period from anaesthesia than the heterocyclic phenothiazines (i.e. prochlorperazine). Promethazine is the most effective of the phenothiazines for prevention of motion sickness. The long duration of action of promethazine makes it preferable to scopolamine.[83]

Heterocyclic phenothiazines (perphenazine, prochlorperazine) have a piperazine ring substituted at position number 10 of the tricyclic nucleus. Perphenazine and prochlorperazine are the 2 heterocyclic phenothiazines most commonly used as antiemetics. Perphenazine is useful for the prevention and treatment of PONV caused by opioids.[84] As a prophylactic PONV antiemetic in paediatric patients, intravenous perphenazine 70 μg/kg decreased emesis after tonsillectomy.[85] This prophylactic dose (70 μg/kg) of perphenazine also was more effective than dexamethasone 150 μg/kg[86] and equally as effective as ondansetron 150 μg/kg[87] in preventing PONV in children after tonsillectomy operations. Prophylactic intramuscular prochlorperazine 0.2 mg/kg and intravenous ondansetron 0.06 mg/kg had similar and better efficacy than intravenous prochlorperazine 0.01 mg/kg in preventing PONV following tympanoplasty.[88] Intramuscular prochlorperazine has an onset time of 30 to 60 minutes and lasts up to 4 hours. Prochlorperazine and perphenazine have similar antiemetic effectiveness, but perphenazine causes more sedation. Similarly, prochlorperazine and promethazine were also determined to be equally as effective for PONV prevention, but promethazine had more postoperative sedation.[81-83]

Although the heterocyclic phenothiazines are more effective antiemetic medications than the aliphatic phenothiazines, they have a higher incidence of extrapyramidal symptoms (EPS). These include (i) akathesia (motor restlessness); (ii) acute dystonia (spasmodic contractures producing trismis, torticollis, opisthotonos and oculogyric crisis); (iii) pseudo-parkinsonism; and (iv) tardive dyskinesia. Treatment of these EPS is accomplished by (i) discontinuing the heterocyclic phenothiazine causing the problem; (ii) administering another phenothiazine that does not have the heterocyclic ring (i.e. aliphatic, promethazine); (iii) switching to a different class of antiemetics; or (iv) administering diphenhydramine. EPS are less common when the heterocyclic phenothiazines are administered in combination with opiates.[81,82,84]

The neuroleptic malignant syndrome (hypyrexia, muscle rigidity, autonomic instability, altered mental status) has been reported with the phenothiazines, droperidol and metoclopramide. Anticholinergic adverse effects of the phenothiazines include dry mouth, urinary retention, tachycardia and drowsiness. The hypotensive adverse effects can be treated with intravenous fluid hydration and phenylephrine.

Butyrophenones

The butyrophenones (haloperidol, droperidol) have a similar pharmacological and antiemetic effectiveness profile as the phenothiazines. They are α-blockers, with adverse effects of sedation and EPS. They are also strong D_2 receptor antagonists that act at the CTZ and area postrema. Both haloperidol and droperidol are effective antiemetic medications for the prevention and treatment of PONV. However, droperidol is more commonly used in anaesthesia than haloperidol. Intramuscular haloperidol has an onset of action of approximately 30 minutes and a duration of approximately 12 hours.[89] Haloperidol 7 μg/kg intravenously,[90] and 0.5 to 4.0mg intramuscularly[91] for prevention and 1mg intramuscularly[92] for treatment, has been shown to be effective in PONV, with little sedative effect. Haloperidol causes less sedation than prochlorperazine.[93]

Droperidol is similar to haloperidol and the phenothiazines in regard to effectiveness for PONV prevention and treatment. Intramuscular droperidol 5mg has equivalent antiemetic effectiveness to intramuscular haloperidol 2mg. The onset of antiemetic action for droperidol is slower than that of haloperidol or prochlorperazine. The effect of dro-

peridol is longer (as long as 24 hours following administration), even though it has a shorter half-life than haloperidol.[93,94] Whereas haloperidol appears to act at the D_2 receptors in the CTZ and area postrema vomiting centres more rapidly than droperidol, droperidol appears to have a stronger binding affinity for these emetic receptors and is retained at the receptor sites for a longer period of time.

When administered immediately before the end of anaesthesia, intravenous droperidol 1.25mg was determined to be superior to intravenous metoclopramide 10mg, intravenous domperidone 5mg and an intravenous saline placebo for the prevention of PONV after a balanced (N_2O/O_2/opioid) general anaesthesia in day-stay gynaecological[95] and major gynaecological[96] surgery. Droperidol 1.25mg intravenously administered before the end of general anaesthesia was also determined to be significantly superior to intravenous metoclopromide 10mg and a saline placebo in the prevention of PONV in female patients undergoing elective orthopaedic surgery.[97] Droperidol 5 μg/kg intravenously administered 1 hour before the end of anaesthesia was effective in preventing PONV in children 11 to 15 years old.[98] Intravenous droperidol 0.625mg was found to be as effective as intravenous droperidol 1.25mg for PONV prevention when these doses were administered immediately following intubation.[99] At these doses, droperidol was judged to have few adverse effects (i.e. dystonic reactions, EPS, sedation).

With repeated and high doses, both haloperidol and droperidol may cause EPS, anxiety, restlessness, hypotension and postoperative sedation, especially in young adults and the elderly.[91,100-103] These adverse effects appear to be more severe (especially the EPS) than those observed with the phenothiazines. These drugs should be used cautiously in outpatient surgery because these adverse effects may delay discharge from outpatient surgery.[102] As haloperidol has a more rapid onset but shorter duration compared with droperidol, a combination of haloperidol and droperidol may be more effective by providing antiemetic action of more rapid onset and longer duration than either alone.[93] However, the additive adverse effects (sedation, EPS, dystonias) of both drugs would be a disadvantage.[100,102] A better approach appears to be the administration of intravenous droperidol 0.625 to 2.5mg immediately after induction of anaesthesia, or 0.625 to 1.25mg 15 to 30 minutes before the end of surgery.[95-97,99,104,105]

Benzamides

Metoclopramide and domperidone are specific dopamine D_2 antagonists, unrelated to the phenothiazines and without antihistamine properties. Metoclopramide is a procainamide derivative and a benzamide prokinetic agent with dual sites of action, blocking D_2 receptors in the periphery (GI tract) and centrally (CTZ and area postrema vomiting centres). Metoclopramide increases lower oesophageal sphincter tone and promotes gastric motility, which may prevent the delayed gastric emptying caused by opioid analgesics.[106]

The antiemetic efficacy of metoclopramide has been controversial and varied due to the use of different doses, timing of administration, types of surgery and anaesthetic techniques. Because of its short duration of action (1 to 2 hours), metoclopramide does not appear to be as effective for PONV prevention when administered before anaesthesia.[107] To allow an adequate plasma concentration for antiemetic effectiveness, metoclopramide appears to be best administered either at the end of surgery or after initial entry to the PACU. Metoclopramide appears to have better antiemetic efficacy in the immediate postoperative period when administered to patients receiving opioids for postoperative pain.[107,108] In this way, the prokinetic effects of metoclopramide improve motility of the stomach and small bowel, and counteract the delayed stomach emptying effect of opioids. Preoperative metoclopramide 10 and 20mg intramuscularly abolished the pre-anaesthetic emetic effects of pethidine. An additional 10 to 20mg of metoclopramide intramuscularly administered at the end of the operation reduced the emetic effects of pethidine, but had less effect when morphine was given.[107] Metoclopramide 10mg intravenously has been

shown to be as effective as intravenous droperidol 1.25mg and more effective than intravenous propofol 10mg for the treatment of PONV.[109] In addition, metoclopramide 15mg[110] and 0.15 mg/kg[111] administered intravenously (immediately after the umbilical cord was clamped) has been shown to effectively reduce the incidence of nausea and vomiting during epidural anaesthesia (lidocaine, morphine) for elective Caesarean section.

Metoclopramide has relatively few adverse effects when used in low doses and does not affect perioperative haemodynamic stability or anaesthetic recovery time. As with droperidol and haloperidol, EPS have occurred following metoclopramide use.[106,111]

Domperidone is a benzimidazole medication pharmacologically similar (but with a different chemical structure) to metaclopramide. Domperidone is a D_2 antagonist acting at the CTZ. Domperidone has a lower incidence of EPS than metoclopramide. Similar to metaclopramide, domperidone has prokinetic properties that increase gastric emptying in combination with lower oesophageal sphincter tone.[112] While domperidone appears to have similar effectiveness to metaclopramide for the prevention of PONV,[113] it appears to be more effective than metoclopramide for the treatment[114] of active PONV. Domperidone 4 and 10mg intravenously has been shown to be superior to intravenous metaclopramide 10mg when used for the treatment of PONV.[114]

Benzquinamide is a short-acting benzquinalone derivative that has antiemetic efficacy secondary to its antihistamine, anticholinergic and antiserotonin properties. The antiemetic action of benzquinamide occurs via blockade of emetic receptors in the CTZ.[115] Sedation is a common adverse effect. Intramuscular benzquinamide has been found to be effective for the prevention[116] and treatment[117,118] of PONV. Benzquinamide should not be administered intravenously because of its tendency to cause tachycardia, hypertension and ventricular arrhythmias.[119]

4.2.3 Antihistamines

Antihistamines (dimenhydrinate, diphenhydramine, cyclizine, hydroxyzine) act by blocking (i) acetylcholine in the vestibular apparatus; and (ii) histamine H_1 receptors in the nucleus of the solitary tract. Antihistamines are effective for the treatment of vertigo and motion sickness. Their main site of action is the vomiting centre and vestibular pathways, with little action at the CTZ. They are the drugs of choice to control PONV following operations on the middle ear, which involve components of the vestibular nerve. Their major disadvantages are sedation, dry mouth, blurred vision, urinary retention, and prolonged anaesthesia and PACU recovery times.[84,120,121]

Cyclizine has similar effectiveness to promethazine in preventing and treating PONV (caused by opioids) and motion sickness. While the overall incidence of adverse effects is less frequent with cyclizine compared with the phenothiazine antiemetics, excess sedation is the most frequent adverse effect of cyclizine.[84,120]

Hydroxyzine is an anxiolytic antiemetic medication with antihistamine, anticholinergic and bronchodilatory effects that is useful in treating vertigo, motion sickness and PONV. Hydroxyzine has a duration of action of 4 to 6 hours with minimal circulatory and/or respiratory depression. The sedation and antisialogogue antiemetic effects of hydroxyzine make it a good premedication when given in combination with opioids to supplement their analgesic effect. As hydroxyzine potentiates the CNS depressant action of opioids and barbiturates, the dosage of these medications should be reduced by 50% (or more) when administered concurrently with hydroxyzine. Intramuscular hydroxyzine 100mg administered after induction of anaesthesia (in non-premedicated patients) was shown to decrease the incidence of PONV more effectively than intramuscular droperidol 2.5mg.[121]

4.2.4 Benzodiazepines

Benzodiazepines (diazepam, midazolam, lorazepam) have sedative, anxiolytic and amnestic properties. They decrease the anxiety and restlessness associated with anaesthesia and surgery, thereby

decreasing PONV.[122,123] For children, premedication with benzodiazepines appears to have an antiemetic effect. Midazolam 75 μg/kg administered intravenously after induction of anaesthesia has been found to be effective for the prevention of vomiting after tonsillectomy operations in children.[124] Intravenous lorazepam 10 μg/kg was compared with intravenous droperidol 75 μg/kg in children and administered prophylactically after an inhalation induction, but before the start of strabismus surgery. Lorazepam produced similar antiemetic effectiveness but less postoperative agitation compared with droperidol.[125] The benzodiazepines do not appear to show true antiemetic receptor binding affinity, but decrease the production of catecholamines, thereby decreasing anxiety. Their amnesia-producing effects are helpful to prevent memory of any existing PONV.

4.3 Nontraditional Antiemetic Therapy

4.3.1 Ephedrine

In a prospective intramuscular PONV prevention study for outpatient gynaecological laparoscopy comparing ephedrine 0.5 mg/kg with droperidol 0.04 mg/kg or saline placebo, ephedrine was determined to have similar antiemetic effectiveness to droperidol and significantly better effectiveness than placebo without sedative adverse effects or effect on BP.[126] Another study[127] investigated the effect of ephedrine 0.5 mg/kg intramuscularly compared with intravenous propofol 0.25 mg/kg for preventing PONV after laparoscopic surgery. Both the ephedrine and propofol groups were more effective, with no haemodynamic changes, than placebo. Intramuscular ephedrine appears to be an effective alternative antiemetic for PONV, especially when the PONV may be related to fluid dehydration and orthostatic hypotension.

4.3.2 Propofol

Since the introduction of propofol as a hypnotic induction agent for outpatient anaesthesia, patients administered propofol have appeared to have less PONV.[128,129] The exact mechanism of the antiemetic effect of propofol is not known. A recent study determined that the antiemetic properties of subhypnotic doses of propofol (1 mg/kg/hour) were not related to any antidopaminergic properties.[130]

Intraoperative intravenous propofol was found to be equally as effective as intravenous ondansetron 4mg in preventing PONV during the first 6 hours postoperatively.[131] Subhypnotic intravenous doses of thiopentone versus propofol have been compared for antiemetic effectiveness at the end of outpatient middle ear surgery. Intravenous propofol administered at a subhypnotic dose of 0.5 mg/kg provided significantly better PONV prophylaxis against retching and vomiting for the first 6 hours after middle ear surgery than thiopentone 1.0 mg/kg.[132]

A subhypnotic dose of propofol 0.5 mg/kg intravenously was more effective in preventing PONV after sevoflurane anaesthesia than desflurane anaesthesia for outpatient laparoscopic cholecystectomy.[133] Another study[134] comparing a 20-hour postoperative 0.1 ml/kg/hour infusion of either propofol or 10% Intralipid (placebo control) determined that the overall occurrence of PONV was less with propofol.

A plasma propofol concentration of 343 ng/L achieved with a 10mg intravenous bolus followed by an infusion of 10 μg/kg/min was determined to be necessary to obtain a 50% reduction in postoperative nausea.[135] However, in another study,[136] an intravenous bolus of propofol 0.1 mg/kg followed by a constant infusion of 1 mg/kg/hour had no effect on PONV. It was hypothesised that this dose was below the PONV efficacy threshold for propofol.

4.3.3 Corticosteroids

Corticosteroids have been evaluated for their usefulness in preventing PONV after they were found to be effective in preventing chemotherapy-induced nausea and vomiting. An anti-inflammatory and/or membrane stabilising effect may play a role in the antiemetic action of corticosteroids. Asboe et al.[137] concluded that intramuscular betamethasone 12mg, when given before general anaesthesia for ambulatory foot or haemorrhoid operations, produced less PONV and postoperative pain in the first 24 hours following surgery. Intravenous dexamethasone 1 mg/kg significantly decreased the

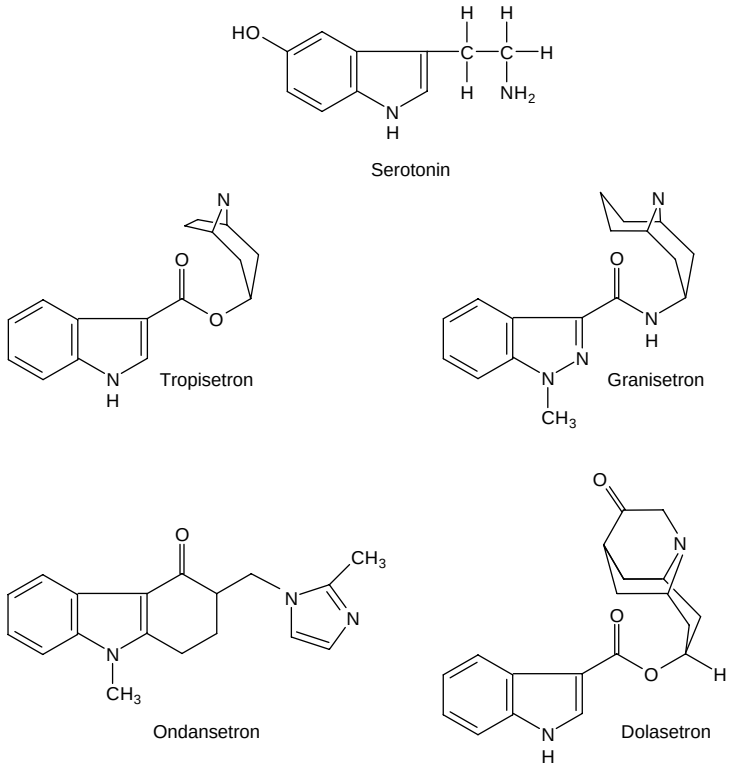

Fig. 2. Chemical structure of serotonin (5-hydroxytryptamine; 5-HT) and 5-HT_3 receptor antagonists.

incidence of PONV in children (age 2 to 12 years) undergoing tonsillectomy when administered after a mask inhalation induction and before the start of surgery compared with a saline placebo.[138]

4.4 Serotonin Receptor Antagonists

The serotonin 5-HT_3 receptor is highly specific and selective for nausea and vomiting. The 5-HT_3 receptor antagonists (fig. 2) have been determined to be effective for chemotherapy- and radiation therapy–induced nausea and vomiting. These positive results initiated investigations for their use in PONV.

4.4.1 Ondansetron

Ondansetron was the first 5-HT_3 receptor antagonist evaluated and approved for PONV by both oral and intravenous administration in adults and children. Several studies have been conducted in adults to determine dosage regimens for ondansetron. The optimal effective dose was found to be 8mg orally administered 1 to 2 hours before anaesthesia or 4mg intravenously at the start of anaesthesia.[139-143] In children older than 2 years, 0.1 mg/kg orally for prevention[144] and 0.1 mg/kg (<40 kg) and 4mg (≥40 kg) intravenously for treatment[145] were determined to be the optimal ondansetron doses for PONV (table III).

In these PONV prevention studies,[139-143] intravenous ondansetron was administered before the start of anaesthesia, however, 2 studies[146,147] have investigated the efficacy of ondansetron administered at the end of surgery. Both studies determined that the efficacy of intravenous ondansetron 4mg was significantly better when administered at the end of surgery rather than before induction of anaesthesia. This improved efficacy of intravenous ondansetron given at the end of surgery was believed

to be related to the length of surgery (with longer operations having decreased ondansetron effectiveness than when administered at the start of surgery).

Because of the increased cost of the 5-HT_3 receptor antagonists compared with traditional antiemetics, Kovac and colleagues[148] conducted a multicentre study to compare repeat intravenous administration of ondansetron 4mg with placebo for the treatment of PONV in patients for whom prophylactic preoperative intravenous ondansetron 4mg was inadequate. They determined that, in patients for whom preoperative prophylaxis with intravenous ondansetron 4mg is not successful, a repeat dose of intravenous ondansetron 4mg in the PACU does not appear to offer additional control of PONV. However, the administration of an additional dose of ondansetron 4mg postoperatively did not result in an increased incidence of adverse events.

4.4.2 Ondansetron and Opioids

Intravenous ondansetron has been evaluated for the treatment of PONV secondary to postoperative opioid administration following regional anaesthesia.[149] Patients were administered intravenous ondansetron 0.1, 4 or 16mg or placebo if they had nausea and/or emesis after the start of postoperative opioid administration for pain control. More patients who received ondansetron 4 and 16mg had no emetic episodes and received no rescue antiemetic medications than those who received placebo. Ondansetron 4mg was determined to be the optimally effective dose for the treatment of opioid-induced PONV.

4.4.3 Granisetron

The effectiveness of intravenous granisetron for prevention of PONV has been determined.[150-152] Dose-ranging studies comparing intravenous granisetron 0.1, 1 and 3mg in adults, determined that granisetron 1mg was the optimum effective prophylactic dose when administered immediately before the start of anaesthesia[150] or for treatment of PONV.[153] However, in other studies on PONV prevention, intravenous granisetron 40 μg/kg was determined to be the optimal dose for adults[151] and children.[152]

4.4.4 Tropisetron

Tropisetron has been studied for prevention[154,155] and treatment[156,157] of PONV in adults and has an elimination half-life of 8 to 12 hours. Tropisetron 5mg intravenously before the start of anaesthesia has been found effective for prevention of PONV after breast[154] and gynaecological surgery.[155,156] Alon and colleagues[157] determined that intravenous tropisetron 2mg was the optimal effective dose for the treatment of PONV following a variety of abdominal and non-abdominal surgeries.

4.4.5 Dolasetron

The parent compound, dolasetron, is converted to the active metabolite, hydrodolasetron, by the plasma enzyme carbonyl reductase. Dolasetron has an elimination half-life of 9 minutes and is undetectable in the serum 2 to 4 hours after intravenous administration. Hydrodolasetron has a mean half-life of approximately 7.1 and 8.3 hours for the oral and intravenous forms, respectively, and is responsible for the majority (87%) of the antiemetic effect.[158]

In adults, intravenous dolasetron has been evaluated for PONV prevention[159] and treatment,[160,161] and the oral formulation for PONV prevention.[162,163] The recommended intravenous dose of dolasetron for prophylaxis and treatment of PONV in adults is 12.5mg. The prophylactic dose should be given 15 to 30 minutes before the end of anaesthesia (table III). Dolasetron pharmacokinetic data in children[164] indicate that oral doses administered 1 to 2 hours before anaesthesia were similar to intravenous doses administered at induction of anaesthesia. Dolasetron was determined to have an increased clearance and a shorter half-life in children compared with young healthy adult volunteers. The recommended oral dolasetron dose for prevention of PONV, and the intravenous dose for prevention and treatment in paediatric patients (2 to 16 years old) are shown in table III.[165]

Following a model used for chemotherapy-induced nausea and vomiting, Kovac et al.[166] studied the utilisation of hospital resources in adult

patients treated for PONV with intravenous dolasetron. Treatment with dolasetron was found to significantly decrease the utilisation of emesis supplies and other hospital resources, including staff/emesis supplies and patient/bed linens. In addition, patients receiving dolasetron used fewer healthcare resources in time spent by hospital personnel than patients who were not treated with dolasetron.

4.4.6 Comparative Studies

Studies have compared the antiemetic efficacy of the 5-HT_3 receptor antagonists with the older, traditional antiemetics (i.e. droperidol, metoclopramide) and with other 5-HT_3 receptor antagonists (table IV).

Various studies[168-172] have compared droperidol with ondansetron. Alon and Himmelseher[168] evaluated the antiemetic efficacy of ondansetron with metoclopramide and droperidol and concluded that fewer patients treated with intravenous ondansetron 8mg prior to anaesthesia had emesis than with intravenous metoclopramide 10mg or droperidol 0.625mg.

One study[169] determined that an intravenous dose of droperidol 0.625mg administered at the start of anaesthesia was as effective in preventing PONV following outpatient gynaecological operations as intravenous droperidol 1.25mg or ondansetron 4mg. Droperidol caused no increase in sedation or other adverse effects. Similar antiemetic effectiveness between intravenous ondansetron 4mg and droperidol 20 μg/kg was shown when they were administered prior to anaesthesia for outpatient gynaecological laparoscopy.[170] There was no difference found in sedation between the droperidol and ondansetron groups. Fortney and co-workers[171] reached similar conclusions. They conducted a multicentre, comparative study of intravenous ondansetron 4mg, droperidol 0.625mg or droperidol 1.25mg versus placebo administered prior to induction of anaesthesia with a barbiturate for PONV prevention. Droperidol 0.625mg and 1.25mg had similar antiemetic effectiveness to ondansetron 4mg. All antiemetics evaluated were more effective than placebo. Furthermore, Fortney et al. found that the best antiemetic effectiveness was obtained with the droperidol 1.25mg dose, and this dose caused no increase in sedation or other adverse effects.

There were more patients who received intravenous droperidol 2.5mg and had no emesis than patients receiving intravenous ondansetron 8mg in a PONV prophylaxis study in women undergoing inpatient minor gynaecological surgery.[172] However, use of the intravenous droperidol 2.5mg dose was associated with more adverse effects (i.e. sedation, dizziness) than that seen in other studies[169-171] using a droperidol dose less than 2.5mg.

Polati and colleagues[181] found that intravenous ondansetron 4mg had better efficacy than intravenous metoclopramide 10mg or placebo for the treatment of PONV following gynaecological laparoscopy. Other researchers[182] have reached a similar conclusion that intravenous ondansetron 4mg has increased antiemetic effectiveness compared with metoclopramide 10mg for the treatment of PONV.

A comparative PONV treatment study between ondansetron and dolasetron was conducted by Roberson et al.[183] in 92 patients after ambulatory surgery. Intravenous dolasetron 12.5mg was determined to have significantly better antiemetic efficacy in the PACU than intravenous ondansetron 4mg on the basis of a lower requirement for rescue drugs in the PACU and greater patient satisfaction.

An intravenous PONV prevention study[173] in children undergoing adenotonsillectomy determined that intravenous ondansetron 0.1 mg/kg was more effective in preventing vomiting than dimenhydrimate 0.5 mg/kg or placebo. However, special note was made by the authors of this study that use of antiemetics (to prevent vomiting) may mask the presence of blood in the stomach (from bleeding at the surgical site) and should be appreciated when adenotonsillectomy is performed on an outpatient basis.

Desilva et al.[174] compared the prophylactic antiemetic efficacy of intravenous ondansetron 4mg, perphenazine 5mg, metoclopramide 10mg, droperidol 1.25mg and placebo administered prior to induction of anaesthesia in inpatients undergoing total abdominal hysterectomy. Ondansetron,

Table IV. Comparison of postoperative nausea and vomiting (PONV) antiemetics with serotonin (5-hydroxytryptamine) 5-HT_3 receptor antagonists summarised data from randomised double-blind studies. Doses administered at start of anaesthesia unless indicated[167]

Reference	Type of surgery (no. patients treated and gender)	Regimen (IV dosage)	Complete response (%)[a]	Comments
Prophylaxis:				
Comparisons with odansetron (OND)				
Alon & Himmelseher[168]	Minor GYN (66 F)	OND 8mg METO 10mg DROP 0.625mg	87* 46 55	OND > METO = DROP
Tang et al.[169]	Minor GYN (161 F)	OND 4mg DROP 0.625mg DROP 1.25mg P	70* 63* 80* 35	OND = DROP 0.625 = DROP 1.25 > P
Sniadach and Alberts[170]	Minor laparoscopic GYN (158 F)	OND 4mg DROP 20 μg/kg	NR	OND = DROP
Fortney et al.[171]	Adult surgical outpatients [2061 (1817 F)]	OND 4mg DROP 0.625mg DROP 1.25mg P	53* 48* 56* 36	OND = DROP 1.25 > DROP 0.65 > P (no difference in sedation between groups)
Grond et al.[172]	Major GYN (80 F)	OND 8mg DROP 2.5mg	68 88*	DROP > OND, but more sedation with DROP
Hamid et al.[173]	Adenotonsillectomy in children (2-10 years) [71 (39 F)]	OND 0.1 mg/kg Dimenhydrimate 0.5 mg/kg P	58* 21 18	OND > Dimenhydrimate = P
Desilva et al.[174]	Major GYN, inpatients (360 F)	OND 4mg DROP 1.25mg Perphenazine 5mg METO 10mg P	63* 76* 70* 50 43	OND = DROP = Perphenazine > METO = P
Korttila et al.[175]	GYN or laparoscopy or thyroidectomy [514 (483 F)]	OND 4mg DOL 50mg DOL 25mg P	54* 60* 43 36	DOL 50 = OND 4 > DOL 25 = P
Naguib et al.[176]	Laparoscopic cholecystectomy [132 (108F)]	OND 4mg GRAN 3mg TROP 5mg METO 10mg P	65.5* 52.0* 48.0* 29.2 27.6	OND = GRAN = TROP > METO = P (doses given 20 min before induction of anaesthesia)
Comparisons with tropisetron (TROP)				
Purhonen et al.[177]	GYN, inpatients (150 F)	TROP 5mg DROP 1.25mg P	81* 55 43	TROP > DROP = P (all doses at end of surgery)
Comparisons with granisetron (GRAN)				
Fujii et al.[178]	Major GYN (90 F)	GRAN 2.5mg DROP 1.25mg METO 10mg	80* 43 40	GRAN > DROP = METO = P (patients with history of PONV)
Fujii et al.[179]	Major GYN (120 F)	GRAN 2.5mg DROP 1.25mg METO 10mg P	77* 50 43 30	GRAN > DROP = METO = P (patients with history of motion sickness
Fujii et al.[180]	Major GYN (120 F)	GRAN 40 μg/kg DROP 25 μg/kg METO 0.2 mg/kg	70* 45 38	GRAN > DROP = METO (patients during menstruation)

Table IV. Contd

Reference	Type of surgery (no. patients treated and gender)	Regimen (IV dosage)	Complete response (%)[a]	Comments
Treatment: Comparisons with OND				
Polati et al.[181]	GYN, laparoscopy (175 F)	OND 4mg METO 10mg P	93* 67* 35	OND > METO > P
Diemunsch et al.[182]	GYN, laparoscopy (175 F)	OND 4mg METO 10mg	59* 41	OND > METO

a A complete response is defined as no nausea, emesis or rescue medications.

DOL = dolasetron; **DROP** = droperidol; **F** = female; **GYN** = gynaecological; **IV** = intravenous; **METO** = metoclopramide; **NR** = not reported; **P** = placebo; **=** indicates the regimens were equivalent; **>** indicates significantly ($p < 0.05$) more effective; ***** $p < 0.05$ *vs* placebo (or other groups).

droperidol and perphenazine were determined to have similar antiemetic effectiveness, and all 3 were found to be significantly better than metoclopramide or placebo.

A PONV prevention comparison study by Purhonen et al.[177] evaluated intravenous tropisetron 5mg, droperidol 1.25mg and placebo given at the end of gynaecological surgery. These researchers determined that tropisetron 5mg effectively prevented vomiting, but not nausea and retching. Droperidol 1.25mg failed to prevent any PONV symptoms and resulted in an increase in anxiety and drowsiness.

In an intravenous PONV prevention study, Korttila et al.[175] found that dolasetron 50mg and ondansetron 4mg administered prior to anaesthesia induction had similar antiemetic effectiveness and were significantly more effective than dolasetron 25mg or placebo. The protocol design of this study differed from another intravenous dolasetron PONV prevention study by Gracyzk et al.,[159] in which intravenous dolasetron 12.5mg was found to be effective when administered 15 to 30 minutes before the end of surgery. The administration timing schedule change was made to conform with the approved administration schedule of the comparator drug (i.e. ondansetron).

Zarate et al.[184] compared the cost effectiveness of dolasetron (12.5 or 25mg) and ondansetron (4 or 8mg) for prophylaxis of PONV after ambulatory surgery. Total costs were calculated using the perspective of a surgical centre. The total costs were lowest in the dolasetron 12.5mg group. Excluding nursing labour costs did not change this finding.

A study by Naguib and co-workers[176] gives insight into comparisons among the 5-HT_3 receptor antagonists. For a PONV prevention study, these researchers compared intravenous ondansetron 4mg with granisetron 3mg, tropisetron 5mg, metoclopramide 10mg or placebo. All doses were administered before the start of anaesthesia. The 5-HT_3 receptor antagonists (ondansetron, tropisetron, granisetron) had significantly greater antiemetic effectiveness than metoclopramide or placebo. There was no statistical difference in efficacy between the ondansetron, tropisetron and granisetron groups.

When administered immediately prior to anaesthesia, intravenous granisetron 2.5mg was determined to be more effective than droperidol 1.25mg or metoclopramide 10mg in preventing PONV after major gynaecological surgery in female patients with a history of postoperative emesis[178] and motion sickness.[179] Similarly, a third study by Fujii et al.,[180] concluded that granisetron 40 μg/kg administered immediately prior to anaesthesia induction was more effective than droperidol 25 μg/kg or metoclopramide 0.2 mg/kg for prevention of PONV after major gynaecological surgery in women during menstruation.

In summary, regarding intravenous PONV prevention, numerous studies[169-171,174] have determined that droperidol has similar antiemetic effectiveness to ondansetron. Ondansetron, granisetron,

tropisetron and droperidol had significantly better PONV effectiveness than metoclopramide when administered before anaesthesia.[168,174,176,178-180] Regarding intravenous treatment for PONV, 2 studies[181,182] determined that ondansetron had significantly better antiemetic effectiveness than metoclopramide, while another study[183] determined less effectiveness than dolasetron.

4.5 Combination Antiemetic Regimens

The many emetogenic neuroreceptors and neurochemicals in the midbrain (table I) suggests the effectiveness of antiemetics will be increased by combining them, especially in the patient with severe and/or intractable PONV. Combination antiemetic therapy was a disadvantage with the older traditional antiemetics (i.e. antihistamines, phenothiazines, butyrophenones, etc.) because of the possibility of additive toxic CNS effects (i.e. hypotension, sedation, dry mouth, EPS, etc.). Recent studies[185-193] have evaluated and supported the effectiveness of the 5-HT_3 receptor antagonists when used in combination with other antiemetics (table V).

McKenzie et al.[185-187] conducted 3 combination antiemetic studies. An initial study[185] combined intravenous ondansetron 4mg with intravenous dexamethasone 8mg and concluded that the prevention of PONV was significantly greater in the combined ondansetron plus dexamethasone group compared with patients receiving ondansetron alone. In a follow-up study,[186] the effectiveness of intravenous ondansetron 4mg in combination with propofol for anaesthesia induction for preventing PONV after major gynaecological surgery was not increased with the addition of intravenous dexamethasone 8mg. A third study[187] by this research group found that the antiemetic effectiveness for tubal banding operations of a prophylactic PONV combination of intravenous ondansetron 4mg plus droperidol 1.25mg given immediately prior to anaesthesia was more effective than either ondansetron or droperidol alone.

Fujii, Tanaka and Toyooka[188-190] combined granisetron with droperidol or dexamethasone and determined that antiemetic effectiveness was improved over each antiemetic alone. The combination of intravenous granisetron 2.5mg plus droperidol 1.25mg given immediately prior to induction of anaesthesia for prevention of PONV was found to be more effective than either granisetron or droperidol alone.[188] In another combination study[189] by these researchers on female patients receiving intravenous antiemetics for prevention of PONV, the number of patients who had nausea or emesis or who required antiemetic medication was significantly less when intravenous dexamethasone 8mg was combined with intravenous granisetron 20 μg/kg, compared with patients who received dexamethasone or granisetron alone.[189] Similarly, a prevention combination PONV study[190] was conducted by these researchers with either intravenous droperidol 1.25mg, metoclopramide 10mg, or granisetron 40 μg/kg alone or with each antiemetic combined with dexamethasone 8mg in female patients undergoing major gynaecological surgery. Dexamethasone improved the antiemetic efficacy of granisetron but did not improve the antiemetic effectiveness of the other medications.

The effect of combination antiemetic therapy also was studied during morphine patient-controlled analgesia (PCA). The PCA solution (ondansetron 4mg intravenous bolus plus a 0.13 mg/ml ondansetron infusion combined with droperidol 1.25mg intravenous bolus plus a 0.05 mg/ml droperidol infusion) was compared with intravenous ondansetron 4mg or droperidol 1.25mg after major gynaecological surgery. Improved antiemetic efficacy was attained with the ondansetron plus droperidol combination compared with either antiemetic alone.[191]

Koivuranta and co-workers[192] concluded that better prophylactic antiemetic efficacy with a lower degree of sedation occurred with the combination of intravenous ondansetron 8mg plus droperidol 0.75mg compared with ondansetron 8mg plus droperidol 1.25mg given before anaesthesia.

Pueyo et al.[193] studied the intravenous combination of ondansetron 4mg and droperidol 2.5mg at the time of anaesthesia induction (plus intravenous droperidol 1.25mg 12 hours later) for the prevention of PONV in elective abdominal surgery.

Table V. Combination antiemetic studies for postoperative nausea and vomiting prevention summarised data from randomised double-blind studies (doses administered at start of anaesthesia unless indicated) [167]

Reference	Type of surgery (no. patients, gender)	Regimen (IV dosage)	Complete response (%)[a]	Comments
McKenzie et al.[185]	Major GYN (180 F)	OND 4mg + DEX 8mg OND 4mg	52* 38	OND + DEX > OND (doses given during operation)
McKenzie et al.[186]	Major GYN (80 F)	OND 4mg + DEX 20mg + PROP OND 4mg	52.5* 37.5	OND + DEX > OND
McKenzie et al.[187]	Minor GYN, outpatients (80 F)	DROP 1.25mg DROP 1.25mg + OND 4mg	78.3 91.6*	OND + DROP > DROP
Fujii et al.[188]	Major GYN (150 F)	GRAN 2.5mg DROP 1.25mg GRAN 2.5mg + DROP 1.25mg	84 54 96*	GRAN + DROP > GRAN = DROP
Fujii et al.[189]	Major GYN (150 F)	GRAN 20 μg/kg + DEX 8mg GRAN 20 μg/kg DEX 8mg P	95* 77 77 77	GRAN + DEX > GRAN = DEX = P
Fujii et al.[190]	Major GYN (270 F)	GRAN 40 μg/kg DROP 1.25mg METO 10mg GRAN 40μg/kg + DEX 8mg DROP 1.25mg + DEX 8mg METO 10mg + DEX 8mg	80* 49 51 96* 60 62	GRAN + DEX = GRAN > DROP + DEX = METO + DEX = METO = DROP
Koivuranta et al.[192]	Laparoscopic (94 F)	OND 8mg + DROP 0.75mg OND 8mg + DROP 1.25mg	84 86	OND + DROP 0.75 = OND + DROP 1.25 (less sedation with DROP 0.75)
Pueyo et al.[193]	Abdominal (100 F)	P DROP 2.5 (+1.25)mg OND 4mg OND 4mg + DROP 2.5 (+1.25)mg	28 60 56 92*	OND + DROP > OND = DROP > P (second dose DROP 1.25 administered 12h post first dose)
Steinbrook et al.[194]	Laparoscopic cholecystectomy [200 (172 F)]	OND 4mg DROP 0.625mg + METO 10mg	56 76*	DROP + METO > OND
Lopez-Olaondo et al.[195]	Major GYN (100 F)	OND 4mg DEX 8mg OND 4mg + DEX 8mg P	52 60 84* 20	OND + DEX > OND = DEX > P

a A complete response is defined as no nausea, emesis or rescue medications.

DEX = dexamethasone; **DROP** = droperidol; **F** = females; **GRAN** = granisetron; **IV** = intravenous; **METO** = metoclopramide; **OND** = ondansetron; **P** = placebo; **PROP** = propofol; **=** indicates the regimens were equivalent; **>** indicates significantly ($p < 0.05$) more effective; ***** $p < 0.05$ *vs* P (or other group).

The combination of ondansetron plus droperidol was more effective than each antiemetic alone or placebo.

The combination of intravenous droperidol 0.625mg plus metoclopramide 10mg was more effective than intravenous ondansetron 4mg for prevention of PONV following laparoscopic cholecystectomy in a study by Steinbrook and co-workers.[194]

An intravenous combination prevention study[195] compared either (i) ondansetron 4mg; (ii) dexamethasone 8mg; (iii) ondansetron 4mg plus dexamethasone 8mg; or (iv) placebo during major gynaecological surgery. The antiemetic effect of ondansetron plus dexamethasone was more than in the other study groups. No difference was found between

ondansetron and dexamethasone when they were administered alone. Dexamethasone, however, appeared to be more effective in preventing nausea than emesis.

Overall, a majority of studies show that the combination of antiemetic medications acting at different emetogenic receptor sites had significantly better effectiveness in preventing PONV than a single antiemetic acting at 1 receptor site alone.

The multimodal management of PONV is an important concept that has been previously proposed and recently tested. Scuderi et al.[196] investigated a predefined multimodal clinical care algorithm for the prevention of PONV following outpatient laparoscopy. Their multimodal management consisted of total intravenous anaesthesia (propofol and remifentanil), no N_2O, no neuromuscular blockade, aggressive intravenous hydration (25 ml/kg), triple antiemetic combination (ondansetron, droperidol, dexamethasone) and ketorolac. Multimodal management was determined to have superior efficacy in preventing symptomatic PONV compared with routine monotherapy prophylaxis.

4.6 Nonpharmacological Therapy for PONV – P6 Acupressure

As a nonpharmacological method, acupressure has been utilised for the prevention of nausea related to pregnancy, cancer chemotherapy and PONV. An elastic wrist pressure band in combination with spherical beads is applied bilaterally at the P6 (Nei-Guan) pressure point located between the flexor tendons 3 fingerbreadths below the hand-wrist crease (fig. 3).

Dundee et al.[197] investigated the effect of P6 acupressure and invasive P6 acupuncture (manual and 10Hz of electrical stimulus, respectively) applied for 5 minutes at the time of surgical premedication and determined that PONV incidence decreased in the first 6 hours postoperatively compared with untreated controls. P6 acupressure was shown to be as effective as invasive P6 acupuncture over the early postoperative (0- to 1-hour) period but less effective than invasive P6 acupuncture over the later 1- to 6-hour postoperative period. Acupressure at P6 was as effective as intravenous cyclizine 50mg or intravenous metoclopramide 10mg.

When P6 acupressure was compared with prochlorperazine, the incidence of postoperative nausea (but not vomiting) was significantly reduced on days 1 and 2 postoperatively compared with placebo controls and prochlorperazine-treated patients.[198] The use of P6 acupressure has been investigated for the prevention of PONV following major gynaecological surgery of 6 to 8 hours duration. A small metal bullet was fastened to the P6 point preoperatively by means of an elastic bandage and kept in place for 24 hours postoperatively. The P6 acupressure group had a significant reduction in nausea (23%) up to the sixth postoperative hour compared with the placebo group.[199] Several other studies[200,201] have also investigated the use of acupressure at the P6 point for the prevention of PONV.

Acupressure at the P6 point is believed to be an alternative to conventional antiemetic treatment. While use of P6 acupressure appears promising for prevention of PONV, its effectiveness is far from complete or long-lasting. Transcutaneous acupoint electrical stimulation (TAES, also called Relief-Band) is a battery-powered electrical device which can continuously stimulate the P6 point for 6- to 12-hour periods and has had promising results for

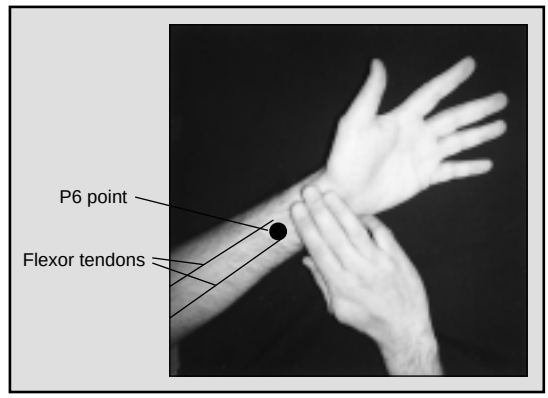

Fig. 3. Location of the P6 (Nei-Kuan) point. The P6 point is located between the flexor tendons 3 fingerbreadths below the hand-wrist crease.

the prevention of chemotherapy-induced nausea and vomiting, and PONV. A study by Zarate et al.[202] assessed the antiemetic efficacy of TAES, a variant of transcutaneous electrical nerve stimulation (TENS), in preventing PONV after laparoscopic cholecystectomy. These researchers found that the Relief-Band significantly reduced PONV compared with: (i) placebo; and (ii) inactivated Relief-Bands applied to the P6 acupoint. More research must be conducted to determine its role in PONV management.

5. Tolerability and Safety Profiles

Depending on the frequency of administration and the total dose administered, traditional antiemetic therapy may have adverse effects. The butyrophenones (e.g. droperidol) and phenothiazines (e.g. promethazine) may cause sedation, hypotension and/or EPS. The anticholinergics (e.g. scopolamine) and antihistamines (e.g. diphenhydramine) may cause drowsiness, sedation, dry mouth and/or restlessness. The substituted benzamides (e.g. metoclopramide) may cause EPS. The adverse effects of the currently available antiemetics are listed in table VI.

The 5-HT_3 receptor antagonists as a class have been found to be clinically well tolerated. At the doses used for PONV, they cause no dose-related trend in sedation or EPS, and do not affect vital signs (heart rate, BP, respiratory rate) or liver function tests.[197] The most common adverse effects are headache and lightheadedness, but they are usually of short duration. As a class, the 5-HT_3 receptor antagonists can block sodium and/or potassium channels and cause mild ECG effects. Ondansetron appears to predominantly affect ventricular repolarisation and dolasetron mainly affects ventricular depolarisation. However, at the doses commonly used for PONV, and compared with placebo, these ECG effects are believed to be minor, asymptomatic, transient and with no clinical significance.[203]

There are no drug-drug interactions between the 5-HT_3 receptor antagonists and other commonly used anaesthesia perioperative medications. These include hypnotics, barbiturates, antibiotics, anxiolytics, corticosteroids, opioids, muscle relaxants, anticholinesterases, the traditional antiemetics and other 5-HT receptor agonists and antagonists. The 5-HT_3 receptor antagonists do not prolong anaesthesia or PACU discharge times. They have little or no affinity for other receptor sites, including α- or β-adrenergic, benzodiazepine, γ-aminobutyric acid, D_2, histamine or other 5-HT receptors.

6. Cost Effectiveness

The economics of using a particular medication involves both direct and indirect costs. Direct costs include (i) drug acquisition charges; (ii) pharmacy supply charges; (iii) medical and nursing time and salary costs for PONV management; and (iv) hospital costs for a prolonged PACU discharge stay or if hospital admission occurs. Indirect costs include (i) increased hospital costs as a result of an extended PACU recovery room stay (delayed discharge) or hospital admission; and (ii) lost patient income because of the patient's inability to return to work. PONV increases both direct and indirect medical care costs.[204,205]

Important correlations can be deduced from the use of antiemetics for chemotherapy-induced nausea and vomiting. Roila and colleagues[206] studied the tolerability and antiemetic effectiveness of ondansetron, granisetron, tropisetron and dolaset-

Table VI. Adverse effects of currently available antiemetics

Sedation	Phenothiazines Antihistamines Droperidol
Hypotension	Promethazine Prochlorperazine Droperidol
Extrapyramidal symptoms	Benztropine Metoclopramide Droperidol
Dry mouth	Atropine Scopolamine Hydroxyzine Antihistamines
Dysphoria	Scopolamine Droperidol
Headache/lightheadedness	Serotonin (5-hydroxytryptamine; 5-HT) receptor antagonists

ron for the treatment of chemotherapy-induced nausea and vomiting. They concluded that the 5-HT_3 receptor antagonists were nearly identical for antiemetic efficacy and safety in the prevention of cisplatin-induced emesis, but that differences, related to the administration schedule of each 5-HT_3 receptor antagonist, exist from an economic perspective. As the antiemetic efficacy and safety of the 5-HT_3 receptor antagonists for chemotherapy-induced nausea and vomiting appears to be similar, this author believes a similar conclusion may be drawn for PONV. At the present time, the main differences in 5-HT_3 receptor antagonists for PONV appear to be related to drug acquisition costs and administration schedules.

Routine prophylactic antiemetics are not needed for each patient. The decision of the most cost effective prophylactic antiemetic to use can be determined based on the expected frequency of PONV and determining which patients are at risk for PONV. When costs have been analysed in comparative PONV antiemetic studies, no cost savings have been determined using the 5-HT_3 receptor antagonists versus droperidol. This suggests that the first choice of antiemetic medications for management of PONV should be the lower-cost antiemetics.[169] However, differences in drug acquisition costs and choice in the initial management of PONV by prevention versus treatment have made conclusions of direct and indirect costs of antiemetic therapy difficult to evaluate. Further research is needed to determine the overall effects of new antiemetic medications and lower emetogenic anaesthesia techniques on cost, patient satisfaction, quality of life, and overall outcome issues.

7. Guidelines for Management of PONV

The management of PONV involves the preoperative selection of patients who are most likely to be at risk for PONV, and the choice of antiemetic medications for PONV management. Patients may be at risk for PONV based on patient-, anaesthesia- and surgical-related risk factors (section 3). For the adult patient at high risk for PONV, this includes (i) history of PONV; (ii) motion sickness; (iii) female gender; (iv) obesity; (v) long surgeries (>2 hours); (vi) high anxiety; and (vii) operations that include gynaecological, breast, testicular, abdominal, oral, ENT or eye procedures. Paediatric operations at high risk for PONV include strabismus, tonsillectomy and middle ear procedures.

7.1 Prevention of PONV

Considerations for the induction of anaesthesia, intraoperative and postoperative management of PONV are listed in table VII. Regarding the choice of anaesthesia for prevention of PONV, one should consider propofol for anaesthesia induction (1 to 2 mg/kg) and maintenance (50 to 100 μg/kg/min) if the patient is to undergo a high-risk PONV surgical procedure lasting less than 2 hours. Because of cost considerations, traditional intravenous antiemetics (i.e. droperidol, metoclopramide) are commonly considered for first-line PONV prophylaxis. Fifteen to 30 minutes before the end of surgery, intravenous droperidol 0.625mg (adults) or intravenous metoclopramide 10mg (adults) can be administered. If there are concerns about the adverse effects of traditional antiemetics, a 5-HT_3 receptor antagonist such as intravenous dolasetron 12.5mg (adults) or 0.35 mg/kg (maximum 12.5mg, paediatrics), or ondansetron 4mg (adults) or 0.1 mg/kg (maximum 4mg, paediatrics) can instead be administered 15 to 30 minutes before the end of surgery. If PONV occurs in the PACU, the use of an antiemetic medication that acts at a different emetic receptor site from the initially administered antiemetic should be considered to obtain an optimal effect.

7.2 Treatment of PONV

For the treatment of PONV in the PACU for patients who received no prophylactic antiemetic medication intraoperatively, a common cost conscious antiemetic protocol involves initial treatment with a traditional intravenous antiemetic medication such as metoclopramide 10mg, droperidol 0.625mg or promethazine 12.5mg followed (if no relief) by intravenous dolasetron 12.5mg or ondansetron 4mg. If intravenous promethazine

Table VII. Post operative nausea and vomiting (PONV) anaesthesia induction/intraoperative care and postanaesthesia care unit (PACU) management

A	Consider anxiolytics (i.e. IV midazolam 1-5mg)[21,28,29]
B	Limit opioids; no nitrous oxide[27,28,43-46]
C	Rapid sequence induction with cricoid pressure (Sellick manoeuvre), no mask ventilation or pharyngeal stimulation (to minimise air entry into the stomach)[55,61]
D	IV anaesthetic agents[21,39,41]
	1. Slow, smooth recovery – low PONV potential (diazepam, pentobarbital, propofol)
	2. Avoid agents with high PONV potential
	Rapid recovery (methohexital)
	Excitatory effects (ketamine, etomidate)
E	Prophylactic antiemetics (droperidol, metoclopramide, dexamethasone, 5-HT_3 receptor antagonists)[69-72]
F	NG tube if GI surgery[59,60]
G	Oro- or naso-gastric suction prior to extubation[60]
H	Adequate IV hydration (>20 ml/kg)[64]
I	Maintain BP, avoid hypotention (especially if regional anesthesia)[16,62,63]
J	PONV management in the PACU[20,27,38,69-72]
	1. Ensure: (a) pain control-PRN opiates, nonsteroidal anti-inflammatory drugs; (b) Adequate hydration – do not force oral fluids; (c) adequate oxygenation; (d) encourage slow, deep breaths; (e) maintain BP; (f) gentle handling of patients; and (g) easy ambulation
	2. Avoid: (a) tight-fitting oxygen masks; (b) overuse of oral airways; and (c) overuse of oral-pharyngeal suctioning
	3. Antiemetic treatment PRN

5-HT = serotonin (5-hydroxytryptamine); **BP** = blood pressure; **GI** = gastrointestinal; **IV** = intravenous; **NG** = nasogastric; **PACU** = postanaesthesia care unit; **PONV** = postoperative nausea and vomiting; **PRN** = as necessary.

12.5mg (adults) is used in a patient with difficult to control PONV, one must keep in mind the additive sedative effects that can occur with traditional antiemetics. Similar to the prevention protocol outlined in section 7.1 for the patient with difficult to control PONV, the approach for treatment of PONV is the use of antiemetics that act at different emetic receptor sites (fig. 1; table I).

Adequate intravenous hydration (as needed up to 20 ml/kg) should be achieved to avoid orthostatic BP changes in patients in the PACU. Hypotension causes a decrease in blood flow to the midbrain emetic centres, releasing emetogenic chemicals and increasing the possibility of PONV. Replacing fluid and blood loss with intravenous fluid hydration may be necessary in the PACU to prevent orthostatic hypotension secondary to perioperative fluid loss, inadequate intravenous fluid replacement and the adverse effects (i.e. hypotension with droperidol) of antiemetic medications. As postoperative pain can be an initiating cause of PONV, it should be treated with analgesics (as needed) rather than withholding pain treatment for fear of opiate-induced PONV. Patients entering the PACU should not be placed near other patients actively experiencing PONV, as this increases the chance for PONV in these patients due to psychological, auditory, olfactory and visual stimuli.

Many PONV prevention and treatment protocols list traditional, less expensive antiemetic medications as first-line therapy for PONV. The adverse effects (sedation, drowsiness, EPS) of these older more traditional antiemetics (especially with combination therapy) may delay an outpatient's PACU discharge home, thereby increasing overall medical costs. Even though the new 5-HT_3 receptor antagonists are more expensive than traditional antiemetics, they are important alternative additions to our PONV antiemetic armamentarium. The 5-HT_3 receptor antagonists may be preferred as initial therapy in the patient with a strong history of PONV, motion sickness or being more difficult-to-treat, based on the cost and benefit of their use. Optimal antiemetic efficacy may be achieved via a combination approach (using different receptor site–

acting antiemetics) to block emetic stimuli acting at different receptor sites.

8. Conclusion

The aetiologies of PONV are multifactorial and complex. Risk factors for PONV include (i) patient (gender, individual history and medical condition); (ii) anaesthesia type; and (iii) surgical procedure. Knowledge of all available antiemetic medications is necessary to successfully manage PONV. Routine use of antiemetics for prevention of PONV is not necessary for all patients. PONV is best controlled by avoiding and/or minimising preventable PONV risk factors, and by using prophylactic antiemetics for patients at high risk.

Presently, there is no single PONV antiemetic medication or technique that is 100% effective for all patients. If the first antiemetic of choice is not effective, the use of a second or third antiemetic acting at a different midbrain emetic receptor site may be necessary. A combination antiemetic therapy approach and multimodal use of anaesthetic techniques with lower emetogenic potential are methods used to manage the patient with difficult to control PONV. The choices for management of PONV are as many and varied as the number of medications, patients and practitioners. Future research may lead to the best antiemetic combination and technique for the optimal management of PONV.

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