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Review

Combination therapy for postoperative nausea and vomiting — a more effective prophylaxis?

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Abstract

The problem of postoperative nausea and vomiting (PONV) remains far from being resolved. Despite the introduction of new classes of antiemetics and a vast amount of published research, there is a general impression that there has been little progress in this area. The multifactorial etiology of PONV might be better addressed using a combination of drugs acting at different receptor sites. This approach of balanced antiemesis may be the answer towards achieving a significant improvement in the management of PONV. This article will cover the different strategies used to prevent PONV with particular emphasis on combination antiemetics. A review of the currently available methods to manage PONV as well as the physiological and pharmacological basis of combination therapy is presented.

Keywords: Antiemetics; Combination therapy; Nausea; Vomiting

The last decade has seen a dramatic increase in day-case surgery. Up to 80% of patients in the US are currently admitted on the day of surgery [1]. Adequate control of postoperative pain, postoperative nausea and vomiting (PONV), and early return to normal activity are important anesthetic goals in the context of ambulatory surgery. Major advances have been achieved in the field of acute pain and in the availability of short acting anesthetic agents. However, despite the availability of new antiemetic agents, the incidence of PONV has remained largely unchanged, although its severity has decreased [2]. Presently, the overall incidence of PONV for all surgeries and patient populations is estimated to be 25–30% [3]. Furthermore, it is estimated that approximately 0.18% of all patients may experience intractable PONV, leading to a delay in postanesthesia care unit (PACU) recovery room discharge and/or unanticipated hospital admission, thereby increasing medical costs [4]. Chung and colleagues [8] recently reported that PONV were responsible for increasing the duration of postoperative stay by 25 and 79% in patients undergoing ambulatory surgery, who received general anesthesia (GA) and monitored anesthesia care (MAC) respectively [5].

Nausea and vomiting are among the most unpleasant experiences associated with surgery and one of the most common reasons for poor patient satisfaction rating in the postoperative period [6]. Macario et al. [7] quantified patients' preferences for postoperative outcomes before surgery. Postoperative nausea and vomiting were among the ten most undesirable outcomes following surgery. Indeed, patients allocated the highest amount (about $30) to avoid PONV out of a total of $100 they were allowed to spend to avoid all complications. In a recent study, Gan and colleagues demonstrated that surgical patients were willing to pay up to $100 to avoid PONV (8). PONV may also be associated with serious complications, such as wound dehiscence, pulmonary aspiration of gastric contents, hematoma formation beneath skin flaps, dehydration, electrolyte disturbances, Mallory Weis tear and esophageal rupture [9–11].

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1. Who should get prophylaxis?

Since, overall, only 25–30% of the surgical patient population will experience PONV, not all patients will require antiemetic prophylaxis [12]. Systematic reviews suggest that prophylaxis might have limited efficacy, be associated with adverse drug reactions and treatment may be more cost effective than prophylaxis [13].

Patient-, anesthesia- and surgery related risk factors should be evaluated to identify patients who may benefit from prophylactic antiemetics. Anesthetic related risk factors include the type of intravenous and volatile anesthetic agents, the use of nitrous oxide in certain patient populations, the use of higher doses of neostigmine for the reversal of neuromuscular blockade, the use of opioids and experience of the anesthesiologist. Female gender, obesity, history of PONV or motion sickness and high levels of anxiety are also associated with a higher risk of PONV. Long surgical procedures and certain types of surgery carry a greater risk of PONV [14]. In adults, high incidences of PONV are found in intra-abdominal surgery (70%), major gynecological surgery (58%), laparoscopic surgery (40–77%), breast surgery (50–65%), eye and ENT surgery (71%). Pediatric operations at high risk for PONV include strabismus (up to 85%), tonsillectomy and middle ear procedures [15]. Various PONV risk scores corresponding to the above mentioned risk factors have been devised. Recently, Apfel et al. [16] developed a simplified risk score consisting of four predictors: female gender, history of motion sickness or PONV, nonsmoker and the use of postoperative opioids. If none, one, two, three, or four of these risk factors were present, the incidences of PONV were 10, 21, 39, 61 and 79% respectively. Prophylactic use of antiemetics is therefore only warranted in high-risk patients and should be part of a multimodal approach to the management of PONV.

2. Multimodal strategies for the management of PONV

As PONV are multifactorial, a multimodal strategy should be adopted to successfully reduce the incidence. Evidence suggests that the use of anxiolytic premedication [17], avoidance of intra- and post- operative opioids [3], use of a NG tube in GI surgery, oro- or naso-gastric suction prior to extubation [18], adequate intravenous hydration [19], avoidance of hypotension [20], ensuring good pain relief [21], gentle handling of patients, smooth ambulation, and avoiding overuse of oral airways and oro–pharyngeal suction [3], can affect the incidence of PONV. There is evidence from systematic reviews of randomized controlled trials, that certain interventions may help keep the baseline risk of PONV low: the use of propofol for induction and maintenance of anesthesia, omitting the use of nitrous oxide and avoiding reversal of neuromuscular blockade [13].

The use of prophylactic antiemetics should be reserved for the high-risk patient and is best achieved using a combination of drugs (balanced antiemesis). Prophylactic antiemetic therapy is cost–effective for operations with a high frequency of emesis, whereas treatment of established symptoms is more cost–effective when the frequency is lower [22]. Recently, Hill and colleagues [23] reported that the use of prophylactic antiemetic therapy in high-risk ambulatory surgical patients (women with previous history of PONV or motion sickness undergoing emetogenic procedures) was more effective in preventing PONV and achieved greater patient satisfaction at a lower cost compared with placebo.

Most published studies show that the combination of antiemetics acting at different receptors provide significantly better efficacy in preventing PONV than a single antiemetic acting at one receptor site. Knowledge of the physiology of the vomiting reflex and an understanding of the different neurotransmitters and receptors involved as well as the pharmacology and site of action of individual antiemetics are important when using combination therapy.

3. Physiology

The complex act of vomiting involves coordination of the respiratory, gastrointestinal and abdominal musculature. It is controlled by the vomiting center, which is located in the lateral reticular formation of the medulla oblongata in close proximity to the nucleus of the solitary tract in the brain stem and has access to the motor pathways that are responsible for the visceral and somatic output involved in vomiting [24]. The vomiting reflex has two main detectors of the need to vomit: the gastrointestinal tract (GIT) and the chemoreceptor trigger zone (CTZ) in the area postrema [25]. The vagus is the major nerve involved in the detection of emetic stimuli from the GIT and has two types of afferent fibers involved in the emetic response: mechanoreceptors, located in the muscular wall of the gut, that are activated by contraction and distension of the gut as well as chemoreceptors, located in the mucosa of the upper gut, that are sensitive to noxious chemicals [26,27]. Stimulation of the vagal afferents leads to activation of the CTZ in the area postrema. The latter is a U-shaped structure a few millimeters long located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle. It is one of the circumventricular organs of the brain and is outside the blood–brain barrier and the cerebrospinal fluid barrier, and thus can be activated by chemical stimuli received through the blood as well as the cere-

brospinal fluid [28]. Several other stimuli can affect the vomiting center including afferents from the oropharynx, mediastinum, peritoneum and genitalia as well as afferents from the CNS (cerebral cortex, labyrinthine, visual, vestibular apparatus) [24].

Different types of receptors are involved in the transmission of impulses to the vomiting center. Cholinergic receptors are found in the vomiting center and vestibular nuclei. The area postrema is rich in dopamine (D2), opioid and serotonin (5HT3) receptors [29,30]. The nucleus tractus solitarius is rich in enkephalins and in histaminergic (H1), muscarinic cholinergic and NK-1 receptors, the latter are also found in the dorsal motor nucleus of the vagus nerve [31–33]. Antiemetics may act at the dopaminergic (D2), cholinergic, histaminergic (H1), 5HT-3 and NK1 receptors and, when deciding upon a combination, it is logical to choose drugs acting at different receptors.

4. Currently used antiemetics

4.1. Older generation antiemetics

4.1.1. Phenothiazines

The antiemetic effect of phenothiazines has been attributed to blockade of D2 receptors in the CTZ. They also have moderate antihistaminergic and anticholinergic actions. The phenothiazines have an aliphatic or heterocyclic ring attached to the tenth position of a tricyclic nucleus. The aliphatic phenothiazines (promethazine, chlorpromazine) have less antiemetic potency and more sedative effects than the heterocyclic phenothiazines (perphenazine, prochlorperazine) [34,35]. They have been used for many years in the prevention and treatment of postoperative emesis, particularly if opioids have been administered. However, they are usually ineffective against motion sickness and have no effect on gastric emptying [36]. Phenothiazines can produce significant sedation (e.g. promethazine) and some have been shown to prolong recovery from anesthesia and delay discharge. Other side effects include extrapyramidal symptoms (particularly with the heterocyclic phenothiazines), hypotension, restlessness, anticholinergic side effects and the neuroleptic malignant syndrome (NMS) [15].

4.1.2. Butyrophenones

The neuroleptic drugs haloperidol and droperidol have significant antiemetic effects. They are strong D2 receptor antagonists that act at the CTZ and area postrema. Droperidol is the only drug in this class that has been extensively used in anesthesia. It has a long duration of action (as long as 24 h following administration) probably due to its strong binding affinity to the emetic receptors [3], even though its half-life is relatively short (3 h) [37]. In a recently published meta analysis, Henzi et al. [38], reported that the anti-nausea efficacy of Droperidol was superior to its anti-vomiting efficacy. However the anti- nausea effect was short lived and not dose-dependent; the number-needed-to-treat (NNT) to prevent early nausea was five with 0.25–0.30 mg. For both early and late anti-vomiting efficacy there appeared to be dose–responsiveness; the best efficacy was with 1.5–2.5 mg (NNT 7). In children there was also a dose–response relationship, with best efficacy at 75 mcg/kg (NNT 4). Sedation and drowsiness are important side effects of droperidol and are dose dependent. Studies using low doses of droperidol (0.25–1.25) did not find any increased sedation associated with its use. Extrapyramidal reactions are recognized side effects of Droperidol, but these are rare in the doses used to treat PONV and are more likely to occur in children. Anxiety and restlessness developing after discharge have been reported, suggesting that droperidol may not be an appropriate antiemetic for ambulatory anesthesia [39]. Other side effects may include hypotension due to alpha-receptor blockade, NMS, visual disturbances, nightmares and urinary retention [40,41].

4.1.3. Antihistamines

Antihistamines (dimenhydrinate, diphenhydramine, cyclizine, hydroxyzine) act by blocking acetylcholine receptors in the vestibular apparatus and histamine H1 receptors in the nucleus of the solitary tract [3]. They are effective for the prophylaxis and treatment of motion sickness and for the control of emesis following middle ear surgery. The piperazine derivative cyclizine has been used extensively for PONV. It has similar effectiveness to promethazine in preventing and treating PONV. Side effects include sedation and a dry mouth [15].

4.1.4. Anticholinergics

Anticholinergics are a first generation class of antiemetics. They block muscarinic and cholinergic CNS emetic receptors in the cerebral cortex and pons [42]. Atropine and scopolamine are tertiary amines that cross the blood–brain barrier and have efficacy against motion sickness and PONV [43,44]. The addition of these anticholinergic agents to opioid premedication decreases emesis [45]. Transdermal scopolamine is effective in controlling motion sickness and PONV following outpatient laparoscopy [46]. Side effects include sedation, dry mouth, blurred vision, mydriasis, urinary retention, hallucinations, central cholinergic syndrome, confusion and disorientation [36,47].

4.1.5. Benzamides

Metoclopramide is the most commonly used antiemetic in this group. It is a prokinetic agent that blocks D2 receptors in the GI tract and centrally at the

CTZ and area postrema. It also increases lower esophageal sphincter tone and enhances gastric motility, which may prevent the delayed gastric emptying caused by opioids [48]. At high concentrations, it has been shown to have weak serotonin receptor antagonistic effect [49]. However, the efficacy of metoclopramide in preventing PONV is uncertain, with approximately 50% of studies showing it to be no more effective than placebo [15]. In a systematic review of randomized placebo-controlled studies involving metoclopramide, Henzi et al. [50] reported that there was no significant anti nausea effect. The numbers needed to treat to prevent early (0–6 h) and late (within 48 h) vomiting were 9.1 and 10, respectively. In children the NNT to prevent early vomiting was 5.8. There was no evidence of dose–responsiveness, the best-documented dose for adults and children being 10 mg IV and 0.25mg/kg IV respectively. Metoclopramide has a short duration of action (1-2 h) and should be administered at the end of surgery or after admission to the PACU to have a reliable antiemetic effect in the early postoperative period [9]. Side effects include sedation, restlessness and extrapyramidal symptoms. Rapid intravenous administration may also be associated with cardiovascular side effects (hypotension, bradycardia or tachycardia). However the incidence of adverse events is relatively low in the doses used for the management of PONV [15].

Domperidone is a benzimidazole derivative pharmacologically similar to metoclopramide. However, it appears to be more effective than metoclopramide for the treatment of active PONV and is associated with a lower incidence of extrapyramidal symptoms [51]. It is only available as an oral or rectal preparation. The parenteral formulation was withdrawn following several reports of serious cardiac arrhythmias after intravenous administration [52–54].

4.2. Newer generation antiemetics

4.2.1. Serotonin receptor antagonists

The serotonin 5-HT3 receptor is highly specific and selective for nausea and vomiting. Members of this group exert their effects by binding to the serotonin 5-HT3 receptor in the CTZ and at vagal afferents in the gastrointestinal tract. Serotonin receptor antagonists were first used in the management of radiotherapy and chemotherapy induced nausea and vomiting. They proved to be superior to other antiemetics in this respect and were then investigated for the treatment of PONV.

Ondansetron was the first member of this group to be evaluated and approved for PONV. The optimal effective dose was found to be 4 mg intravenously at induction or 8 mg orally 1–2 h before anesthesia [55,56]. For children the optimal effective dose was found to be 0.1 mg/kg [57]. In a quantitative systematic review of randomized placebo controlled trials involving Ondansetron, Tramer reported that the best NNT to prevent PONV with the best-documented regimes was between 5 and 6. This was achieved with an intravenous dose of 8 mg and an oral dose of 16 mg. In all published studies, the antiemesis efficacy of Ondansetron was consistently better than antinausea efficacy [58]. In 1997 Sun et al. suggested that the efficacy of Ondansetron may be improved by administration at the end of the surgical procedure compared with at induction of anesthesia. This was confirmed in another study by Tang and colleagues, [59,60].

Three other serotonin receptor antagonists (Tropisetron, Granisetron and Dolasetron) have been studied for the prevention and treatment of PONV. Dolasetron is available in intravenous and oral forms. The recommended intravenous dose for prophylaxis and treatment of PONV is 12.5 mg. The prophylactic dose should be given 15–30 min before the end of anesthesia, as the active compound is hydro-dolasetron, a metabolite of the parent drug. The oral prophylactic dose is 100 mg [3]. In a multicenter trial it was demonstrated that 2 mg tropisetron intravenously had similar efficacy and side effect profiles to those of 4 Ondansetron mg [61]. The longer half-life of Tropisetron (7–30 h) compared with Ondansetron (3.5 h) did not result in a clinically beneficial effect in clinical studies. The recommended prophylactic dose is 5 mg given at induction of anesthesia [62]. The optimum effective dose of intravenous Granisetron was found to be 1mg and 40 mcg/kg in different studies [63,64].

The reported side effects of serotonin receptor antagonists include headache (3:100), dizziness, flushing and elevated liver enzymes (3:100) [58].

4.2.2. NK-1 receptor antagonists

NK-1 receptor antagonists demonstrated broad spectrum antiemetic activity in animals and have recently been found to be effective in the treatment of established PONV and superior to ondansetron for the prophylaxis of PONV in females undergoing major gynecological surgery under general anesthesia [65,66].

4.3. Non-traditional antiemetics

4.3.1. Steroids

The mechanism of the antiemetic action of corticosteroids is not well understood. An anti-inflammatory and/or membrane stabilizing effect may play a role [3]. The release of endorphins resulting in mood elevation, a sense of well-being and appetite stimulation may also underlie the antiemetic properties of corticosteroids [67]. Following the successful use of dexamethasone in the prevention and treatment of chemotherapy induced nausea and vomiting, this agent has been evaluated for

the management of PONV. A single prophylactic dose of Dexamethasone was found to be superior to placebo [68,69]. The most commonly used dose regimen is 8–10 mg in adults and 1–1.5 mg/kg in children. A dose–response relationship for dexamethasone could not be established. In a meta-analysis, Henzi and colleagues reported that dexamethasone is particularly effective against late PONV. The NNT in children to prevent early (0–6 h) and late (0–24 h) vomiting was 7.1 and 3.8 respectively. In adults the NNT to prevent late nausea was 4.3. The combination of dexamethasone with 5-HT3 receptor antagonists further increases its efficacy. There are no reports on dexamethasone related adverse effects in the doses used for the management of PONV [70].

4.3.2. Propofol

The possible antiemetic effects of propofol have been the focus of much interest. Propofol-based anesthetics were associated with a lower incidence of PONV compared with enflurane [71], isoflurane [72] or desflurane anesthesia [73]. The findings from these studies show a low incidence of PONV only when propofol was used throughout the procedure. Intraoperative propofol anesthetics have been shown to be as efficacious in the reduction of postoperative nausea as ondansetron 4 mg [74]. The beneficial effect on PONV, however, is likely to be of short duration after surgery. The protective effect of propofol against PONV was not evident when it was used as an induction drug only [75]. More recently, continuous subhypnotic propofol infusion has been shown to be effective in the prophylactic treatment of PONV [76]. The use of patient-controlled antiemesis (PCAE) with propofol has also been investigated. Patients self-administered 20 mg (2 ml) of propofol with a lockout interval of 5 min. This technique was found to be effective in the treatment of PONV and associated with great degree of patient satisfaction, oversedation did not appear to be a problem in this dose range [77].

The effective plasma concentrations of propofol for the 50% reduction in nausea scores has been found to be 343 ng/ml [78]. This is much lower than the range required for sedation (900–1300 ng/ml) and anesthesia (3000–10 000 ng/ml).

The mechanism of the antiemetic action of propofol is not known. It is not due to the intralipid emulsion in the formulation and propofol appears to have direct antiemetic property [79]. It has been postulated that propofol may act via an antidopaminergic pathway [80]. However, two recent studies have not substantiated this claim [81,82]. Several other mechanisms have been postulated including a depressant effect on the CTZ, the vagal nuclei and a decreased concentration of serotonin in the area postrema following prolonged infusion of propofol [78].

4.3.3. Other therapies

Two studies have shown that intramuscular ephedrine was superior to placebo and had similar antiemetic effectiveness to droperidol and propofol following outpatient gynecological laparoscopy [83,84]. Recently, Grief and colleagues [85] have shown that, after colonic resection, supplemental oxygen reduced the incidence of PONV nearly twofold. A number of studies have shown a reduction in PONV associated with the use of benzodiazepines [86,87]. They do not appear to show true antiemetic receptor binding affinity, but decrease the production of catecholamines, thereby decreasing anxiety.

4.4. Nonpharmacologic techniques

Nonpharmacologic techniques that have been used to prevent PONV include acupuncture, electroacupuncture, laser stimulation of the P6 point, transcutaneous electrical nerve stimulation, acupoint stimulation and acupressure. Acupuncture has been used as a medical modality for over 3000 years in China. In 1996, the FDA reclassified acupuncture needles from class III (experimental) medical devices to class II (nonexperimental, but regulated) [88]. Several investigators have shown a useful effect of these nonpharmacological methods in the management of PONV. A few studies, however, failed to demonstrate a beneficial effect. Lee and Done in 1999 performed a meta-analysis to assess the efficacy of nonpharmacologic techniques in the prevention of PONV. Their main findings were that there was a significant reduction in early PONV in adults using nonpharmacologic methods compared with placebo and that antiemetics (metoclopramide, cyclizine, droperidol, prochlorperazine) versus nonpharmacologic techniques were comparable in preventing early or late PONV in adults. In children, however, no benefit was found. There were no studies comparing nonpharmacologic techniques with 5-HT3 receptor antagonists [89].

4.5. Combination antiemetics

None of the available antiemetics is entirely effective for preventing PONV, especially in high-risk patients, probably because most of them act through blockade of mainly one receptor. The etiology of PONV is multifactorial and a better prophylaxis might be achieved using a combination approach. The concept of combination therapy was introduced by Parikh in chemotherapy induced vomiting [90]. The use of a combination of antiemetics from different pharmacological classes might provide enhanced antiemetic efficacy with a reduced side-effect profile. A number of combinations have been studied.

A summary of the published papers comparing combination therapy versus monotherapy is shown in Tables 1–3.

4.5.1. Ondansetron and droperidol

This was the most commonly studied combination. This combination is theoretically attractive for several reasons. Both agents proved to be superior to placebo for the prevention and treatment of PONV while acting at different receptor sites. Droperidol has greater antinausea efficacy, whereas ondansetron has better effect on preventing vomiting [38]. The protective effect of droperidol against postoperative headache combined with an increased risk of headache with 5-HT3 receptor

Table 1
Efficacies of combination of 5-HT3 receptor antagonists and droperidol versus single agent studies[a,b]

Reference	Surgery	Regimen	Complete response (%)[c]	No ponv 24h	Result
Pueyo et al. [92]	Abdominal	P		28	O+D>O=D>P
		D2.5mg+D1.25mg		60*	
		O4mg		56*	
		O4mg+D2.5mg+D1.25mg		92	
Bugendo et al. [93]	Gyn&bilary	P		77	O+D>D>P
		D2.5mg		83	O+D=O>P
		O4mg		91	
		O4mg+D2.5mg		95*	
Wu et al. [94]	Gyn laparoscopy	O4mg+D1.2		77*	O+D>O=D>P
		O4mg		54*	
		D1.25mg		39*	
		P		29	
McKenzie et al. [95]	Tubal banding	D1.25mg+O4mg	91.6*		O+D>D
		D1.25mg	78.3		
Riley et al. [96]	Major Gyn	D1.25mg+O4mg	45		O+D=D
		D1.25mg	38		
Peixoto et al. [97]	Major Gyn	D1.25mg		67	O+D=O=D
		O4mg		60	
		O4mg+D1.25mg		57	
Wrench et al. [98]	Major Gyn	O4mg+8mg/60ml/PCA		65	O+D=O=D
		D1.25mg+3mg/60ml/PCA		85	
		O+D		80	
Warrick et al. [99]	Gyn laparoscopy	D1.25mg then P		59	O+D=D
		D1.25mg then D1.25mg		48	
		D1.25mg+O4mg then P		65	
		D1.25mg+O4mg then P		69	
		D1.25mg+O4mg then D1.25mg+O4mg			
Klockgether-Radke et al. [100]	Strabismus	D75mcg/kg		73.5*	O+D=O=D>P
		O0.1mg/kg		60*	
		D75mcg/kg+O0.1mg/kg		55*	
		P		5	
Fujii et al. [106]	Laparoscopic cholecystectomy	G3mg	86		G+D>G,D
		D1.25mg	64		
		G3mg+D1.25mg	98*		
Fujii et al. [107]	Breast surgery	G3mg	82		G+D>G,D
		D1.25mg	62		
		G3mg+D1.25mg	96*		
Fujii et al. [108]	Tonsillectomy	G40mcg/kg	83*		G+D>G>D
		D50mcg/kg	55		
		G40mcg/kg+D50mcg/kg	97*		
Fujii et al. [109]	Strabismus	G40mcg/kg	78*		G+D>G>D
		D50mcg/kg	38		
		G40mcg/kg+D50mcg/kg	98*		

[a] P, placebo; D, droperidol; O, ondansetron; G, granisetron
[b] = indicates no difference; > indicates significantly ($P<0.05$) more effective; * indicates $P<0.05$ versus other group or placebo.
[c] Complete response = no PONV and no rescue.

Table 2
Efficacies of combination of 5-HT3 receptor antagonists and dexamethasone versus single agent studies[a,b]

Reference	Surgery	Regimen	Complete response (%)[c]	No PONV 24 h (%)	Result
Fujii	Major Gyn	D1.25mg	49		G+Dex>G>D=D+Dex=M=M+Dex
et al. [68]		D1.25mg+Dex8mg	60		
		M10mg	51		
		M10mg+Dex8mg	62		
		G40mcg/kg	80*		
		G40mcg/kg+Dex8mg	96*		
Rajeeva	Gyn	O4mg+Dex8mg		92*	
et al. [101]	laparoscopy	O4mg		65	O+Dex>Dex
McKenzie	Major Gyn	O4mg	37.5		O+Dex=O
et al. [102]		O4mg+Dex20mg	52.5		
Lopez-Orlando	Major Gyn	P		20	O+Dex>O=Dex>P
et al. [103]		O4mg		52	
		Dex8mg		60	
		O4mg+Dex8mg		84*	
McKenzie	Major Gyn	O4mg	38		O+Dex>O
et al. [105]		O4mg+Dex8mg	52*		
Splinter	Strabismus	O150mcg/kg		72	O+Dex>O
et al. [104]		O50mcg/kg +Dex150mcg/kg		91*	
Fujii	Major Gyn	P		77	G+D>G=Dex=P
et al. [110]		G20mcg/kg		77	
		Dex8mg		77	
		G20mcg/kg+Dex8mg		95*	
Fujii	Breast	P	56		G+Dex>G>P
et al. [111]		G40mcg/kg	84		
		G40mcg/kg+Dex8mg	98*		
Fujii	Middle ear	G3mg	80*		G+Dex>G>Dex
et al. [112]		Dex8mg	55		
		G3mg+Dex8mg	98*		
Fujii	Laparoscopic	G40mcg/kg	83		G+Dex>G
et al. [113]	cholecystectomy	G40mcg/kg+Dex8mg	98*		
Fujii	Thyroidectomy	G40mcg/kg	86		G+Dex>G
et al. [114]		G40mcg/kg+Dex8mg	98*		
Fujii	Cesarean section	G3mg	85		G+Dex>G
et al. [115]		G3mg+Dex8mg	98*		
Janknegt	Abdominal/Gyn	D1.25mg		58	G+Dex=G>D>P
et al. [116]	Breast/ENT	G1mg		78*	
		G1mg+Dex5mg		82*	
		P		5	
Holt	Tonsillectomy	T0.1mg/kg		39	T+Dex>T
et al. [127]		T0.1mg/kg +Dex0.5mg/kg		61*	

[a] O, ondansetron; Dex, dexamethasone; P, placebo; G, granisetron; D, droperidol; T, tropisetron.
[b] = indicates no difference; > indicates significantly ($P<0.05$) more effective; * indicates $P<0.05$ versus other group or placebo.
[c] Complete response = no PONV and no rescue.

antagonists provides another reason for this combination [58,91]. Pueyo et al. [92] studied the intravenous combination of 4 mg ondansetron and 2.5 mg droperidol at induction of anesthesia followed by 1.25 mg droperidol 12 h later for the prevention of PONV in elective abdominal surgery. The combination was more effective than each individual drug or placebo with a complete response (no PONV in 48 h) of 92% compared with 28, 60 and 56% in the placebo, droperidol and ondansetron groups respectively. However sedation was greater in patients receiving droperidol.

The combination of 4 mg ondansetron and 2.5 mg droperidol was also studied by Bugedo et al. [93] in patients undergoing biliary or gynecological surgery. The combination was better than placebo and droperidol but not ondansetron. Sedation scores were also higher in patients receiving droperidol or the combination. These studies suggest that droperidol in doses above 1.25 mg should be avoided. In another study, a combination of 4 mg ondansetron and 1.25 mg droperidol was found to be superior to each drug alone especially in the first 3.5 postoperative hours following

outpatient gynecological laparoscopy. Drowsiness was more severe in the group receiving droperidol alone, but not in the combination group [94]. The same doses were used by Mckenzie et al. in two studies comparing the combination with droperidol in females undergoing laparoscopic tubal banding and abdominal hysterectomy. The combination was significantly superior to droperidol in achieving a complete response (no emesis, no rescue) and in reducing the incidence and severity of nausea in the tubal banding study, but not in the hysterectomy study. However, in both studies the combination was significantly better that droperidol in reducing the time to and the number of emetic episodes [95,96]. Similar doses were used by Peixoto and colleagues in females undergoing major gynecological surgery. The combination was significantly better than either drug alone in the first 2 h, the incidence of PONV was, however similar in all groups over the 24 h period [97].

This combination was also studied during patient-controlled analgesia (PCA) using morphine. Ondansetron (4 mg bolus) followed by 0.13 mg/ml mixed in the morphine solution was compared to droperidol (1.25 mg bolus) and 0.05 mg/ml in the morphine solution and with the combination of ondansetron and droperidol. The combination provided better control of nausea in the first 12 h postoperatively, however there was no difference in vomiting or in nausea beyond 12 h. There was no increased sedation in patients receiving droperidol [98].

These results were not confirmed by Warrick et al. who compared a single dose of 1.25 mg droperidol with and without 4 mg ondansetron and two doses of 1.25 mg droperidol with and without 4 mg ondansetron. The first dose of droperidol was given at induction followed by a second dose 4 h later. Although the combination regimen did not show greater efficacy in reducing the incidence of PONV, a reduction in the severity of nausea was noted up to 24 h postoperatively in the

Table 3
Efficacies of other combination antiemetic studies for PONV prophylaxis[a]

Reference	Surgery	Regimen	No PONV 24h (%)	Result
Michaloudis et al. [117]	Laparoscopy	D0.5mg + M5mg + H0.1mg	53	D + M + H = D
		D1.25mg	37	
Kymer et al. [118]	Strabismus	D300mcg/kg	73*	D + M = D > M,P
		M0.15mg/kg	38	
		D300mcg/kg + M0.15mg/kg	78*	
		P	44	
Pendeville et al. [119]	Strabismus	P		D + M = D = M = P
		D10mcg/kg		
		M0.1mg/kg		
		D10mcg/kg + M0.1mg/kg		
Kathirvel et al. [120]	Strabismus	P	28	O + M = O > M,P
		M250mcg/kg	40	
		O150mcg/kg	60*	
		O100mcg/kg + M150mcg/kg	56*	
Steinbrook et al. [121]	Laparoscopic cholecystectomy	O4mg	55.2	D + M > O(nausea)
		D0.625mg + M10mg	75.6*	
Eberhart et al. [122]	Nasal	P	62.9	Di + D > D,Di,P
		Di1mg/kg	77.1	
		D15mcg/kg	82.9	
		Di1mg/kg + D15mcg/kg	94.3*	
Khalil et al. [123]	Middle ear	O4mg	52	O + PR = PR > O,P
		PR25mg	61*	
		O2mg + PR12.5mg	71*	
		P	26	
Eberhart et al. [124]	Endonasal	P	62.5	Di + M > P(not Di, M)
		M0.3mg/kg	72.5	
		Di1mg/kg	75	
		M + Di0.3mg/kg + 1mg/kg	85*	
Barst et al. [125]	Tonsillectomy	O0.1mg/kg + PRO120–140mcg/kg/min	93.3*	O + PRO + > PRO
		P + Pro120-140mcg/kg/min	77.8	
Ahmed et al. [126]	Gyn laparoscopy	O4mg	15	O + C > O > P
		O4mg + C50mg	27*	
		P	2	

[a] D, droperidol, M, metoclopramide; H, hyoscine; P, placebo; O, ondansetron; Di, dimenhydrinate; PR, promethazine; PRO, propofol; = indicates no difference; > indicates significantly ($P < 0.05$) more effective; * indicates $P < 0.05$ versus other group or placebo.

combination groups versus the droperidol groups [99]. However, in children undergoing surgery for strabismus, ondansetron and droperidol combination did not provide any advantage over either agent alone [100].

4.5.2. Ondansetron and dexamethasone

Rajeeva et al. [101] reported better control of delayed vomiting using a combination of 4 mg ondansetron and 8 mg dexamethasone when compared with ondansetron alone, in females having a diagnostic laparoscopy. Patients in the combination group also had significantly lower nausea scores. Similar results were obtained by McKenzie and colleagues [102] in women undergoing major gynecologic procedures using the same dosage. Lopez and colleagues [103] used similar doses and reported that the combination was more effective than ondansetron for nausea and vomiting, and better than dexamethasone for vomiting but not for nausea in females undergoing major gynecologic surgery. The incidence of vomiting was also significantly lower in the combination group compared with ondansetron alone in children undergoing strabismus surgery [104].

A study by McKenzie et al. [105] however, did not find a reduction in PONV when 20 mg dexamethasone was added to 4 mg ondansetron in patients undergoing major gynecologic surgery. Patients in this study had a low incidence of vomiting (17.5 and 12.5% in the ondansetron and combination groups, respectively). The use of droperidol with the first complaint of nausea in about 50% of patients may have contributed to this reduction in vomiting and the lack of a difference between the groups. These studies did not report any difference in adverse events when using a combination or each agent alone, headache being the most commonly reported side effect.

4.5.3. Granisetron and droperidol

Fujii et al. compared a combination of 3 mg granisetron plus 1.25 mg droperidol with each agent alone in patients undergoing laparoscopic cholecystectomy and breast surgery.

In both studies, the combination was found to be superior to each agent alone in achieving a complete response (no PONV and no rescue antiemetic during the 24 h study period) and better than droperidol when nausea and vomiting are analyzed separately [106,107]. The same group found similar results in children undergoing tonsillectomy and strabismus surgery [108,109]. Excessive sedation was not observed in these studies and there was no difference in adverse events between the groups.

4.5.4. Granisetron and dexamethasone

This combination was studied extensively by one group from Japan. Fujii et al. published six papers comparing the combination with either agent alone. The doses of granisetron were 20 mcg/kg in one study, 40 mcg/kg in three studies and 3 mg in two studies. Eight milligrams of dexamethasone were used in all studies. They included patients undergoing breast surgery, thyroidectomy, middle ear surgery, laparoscopic cholecystectomy, cesarean section and major gynecological procedures. In all these studies they reported that the combination was superior to each agent alone with a complete response (no PONV and no rescue for 24 h) of 98% compared with 50% in the dexamethasone group and 83–86% in the granisetron group. They postulated that dexamethasone enhances the efficacy of granisetron by inhibiting stimulation of 5-HT3 receptors where granisetron exerts its effects. There was no difference in adverse events between the combination and either agent alone [110–115].

Janknegt et al. also compared the combination of 1 mg granisetron plus 5 mg dexamethasone with 1 mg granisetron and 1.25 mg droperidol in patients undergoing gynecological, breast, abdominal and ENT surgery. Both granisetron and the granisetron/dexamethasone combination performed better than droperidol alone in reducing the incidence of vomiting and combined nausea and vomiting. The combination was also more effective than the other groups against nausea [116].

4.5.5. Combinations involving metoclopramide

Three studies involving a combination of metoclopramide with droperidol did not show an improved outcome over droperidol alone [117–119]. The combination of metoclopramide with ondansetron was also not superior to ondansetron alone in children undergoing surgery for strabismus [120], however a combination of droperidol and metoclopramide was found to be more effective than ondansetron in preventing postoperative nausea in patients undergoing laparoscopic cholecystectomy [121]. Eberhart et al., found that the incidence of patients free from PONV, in males undergoing endonasal surgery, was significantly higher compared with placebo using a combination of dimenhydrinate and metoclopramide but not with each agent alone [122].

4.5.6. Other combinations

In a study comparing the ondansetron plus promethazine combination versus each agent alone in adult patients undergoing middle ear surgery, Khalil et al. reported that the combination and promethazine alone, but not ondansetron reduced the incidence of PONV compared with placebo; the combination was also superior to individual antiemetic groups in reducing the severity of vomiting [123]. In male patients undergoing nasal surgery, Eberhart et al. found that a complete response (no PONV for 24 h) was significantly greater (94%) using a combination of droperidol

and dimenhydrinate, compared with each agent alone and with placebo [124]. A combination of ondansetron and propofol infusion was also superior to propofol alone in reducing the incidence of emesis in children following tonsillectomy [125]. Recently, Ahmed and colleagues have shown that a combination of ondansetron and cyclizine was significantly better than ondansetron alone in reducing the incidence of vomiting, the incidence and severity of nausea as well as the need for rescue [126]. Holt and colleagues have also found that a combination of tropisetron and dexamethasone was more effective than tropisetron alone in reducing the incidence of PONV following pediatric tonsillectomy [127]. More recently, a combination of Ondansetron and the NK-1 receptor antagonist [CP-122,721] was shown to significantly prolong the time of the first administration of the first rescue antiemetic, compared with either drug alone, and almost completely prevented the occurrence of emesis (2% of patients vomited) when used as a prophylaxis in patients undergoing abdominal hysterectomy [66].

4.6. Multiple antiemetic combination

Scuderi et al., investigated a multimodal approach to the management of PONV in female patients undergoing outpatient laparoscopy. Their multimodal clinical care algorithm consisted of total intravenous anesthesia (propofol and remifentanil), no nitrous oxide, no neuromuscular blockade, aggressive intravenous hydration (25 ml/kg), triple prophylactic antiemetics (ondansetron 1 mg, droperidol 0.625 mg and dexamethasone 10 mg), and 30 mg ketorolac. Control groups included standard balanced outpatient anesthetic with or without 4 mg ondansetron prophylaxis. Multimodal management demonstrated superior efficacy in preventing symptomatic PONV compared to routine monotherapy prophylaxis; no patients in the multimodal group vomited prior to discharge and time to readiness for discharge was significantly shorter in this group compared to the other groups [128].

Recently, a triple antiemetic combination with ondansetron and droperidol in the presence of propofol maintained anesthetic was also associated with a lower incidence of PONV and greater patient satisfaction compared with similar antiemetic combination without propofol [129].

5. Conclusion

There is a strong evidence from published work that a much better prophylaxis against PONV may be achieved by using a combination of antiemetic agents acting at different receptor sites. Such prophylaxis should be considered for patients at high risk for PONV. There is, however, a striking lack of data on the efficacy of combination therapy for the treatment of established PONV. Further work is required to identify the optimal combination of antiemetic drugs that is most efficacious, least likely to be associated with adverse effects and cost–effective. Minimal effective doses of these combinations need to be established. More studies are needed to explore the potential of additional benefit of combining more than two antiemetics.

References

[1] White PF. Ambulatory anesthesia and surgery: past, present and future. In: White PW, editor. Ambulatory Anesthesia and Surgery. Philadelphia: WB Saunders, 1997.
[2] Scholz J, Steinfath M, Tonner P. Postoperative nausea and vomiting. Curr Opinion Anesthesiol 1999;12:657–61.
[3] Kovac AL. Prevention and treatment of postoperative nausea and vomiting. Drugs 2000;59(2):213–43.
[4] Gold BS, Kitz DS, Lecky JH, et al. Unanticipated admission to the hospital following ambulatory surgery. J Am Med Assoc 1989;262:3003–40.
[5] Chung F, Mezei G. Factors contributing to a prolonged stay after ambulatory surgery. Anesth Analg 1999;89:1352–9.
[6] Mytes PS, Williams DL, Hendrata M, et al. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10811 patients. Br J Anaesth 2000;84:6–10.
[7] Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid?, The prespective of patients. Anesth Analg 1999;89:652–8.
[8] Gan TJ, Sloan F, Dear GD, et al. How much patients are willing to pay to avoid postoperative nausea and vomiting? Anesth Analg 2001;92(2):393–400.
[9] Watcha M, White P. Postoperative nausea and vomiting: its etiology, treatment and prevention. Anesthesiology 1992;77:162–84.
[10] Wilder-Smith OH, Martin NC, Morabia A. Postoperative nausea and vomiting: a comparative survey of attitudes, perceptions and practice of Swiss anesthesiologists and surgeons. Anesth Analg 1997;84(4):826–31.
[11] Kapur PA. The big little problem. Anesth Analg 1991;73:243–5.
[12] Adriani J, Summers FW, Antony SO. Is the prophylactic use of antiemetics in surgical patients justified? J Am Med Assoc 1961;175(8):666–71.
[13] Tramer MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part II. Recommendations for prevention and treatment, and research agenda. Acta Anesthesiol Scand 2001;45:14–9.
[14] Kenny GNC. Risk factors for postoperative nausea and vomiting. Anaesthesia 1994;49(Suppl.):6–10.
[15] Rowbotham DJ. Current management of postoperative nausea and vomiting. Br J Anaesth 1992;69(Suppl. 1):46S–59.
[16] Apfel C, Laara E, Koivuranta M, et al. A simplified risk score for predicting postanesthetic nausea and vomiting. Anesthesiology 1999;91:693–700.
[17] Philip BK. Etiologies of postoperative nausea and vomiting. Pharmacy Ther 1997;22(Suppl. 7):18–25.
[18] McCarroll SM, Mori S, Bras P, et al. The effect of gastric intubation and removal of gastric contents on the incidence of postoperative nausea and vomiting (abstract). Anesth Analg 1990;70:S262.

[19] Suntheralingham Y, Buvanendran A, Cheng DCH, et al. A prospective randomized double-blinded study of the effect of intravenous fluid therapy on adverse outcomes on outpatient surgery. Anesth Analg 1995;80:682–6.
[20] Palazzo MGA, Strunin L. Anaesthesia and emesis. I: etiology. Can Anaesth Soc J 1984;31:178–87.
[21] Anderson R, Krohg K. Pain as a major cause of postoperative nausea. Can Anaesth Soc J 1976;23:366–9.
[22] Watcha MF, Smith I. Cost-effectiveness analysis of antiemetic therapy for ambulatory surgery. J Clin Anesth 1994;6(5):370–7.
[23] Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology 2000;92(4):958–67.
[24] Andrews PLR. Physiology of nausea and vomiting. Br J Anaesth 1992;69(Suppl. 1):S2–S19.
[25] Wang SC, Borison HE. A new concept in the organisation of the central emetic mechanisms: recent studies on the site of action of apomorphine, copper sulphate and cardiac glycosides. Gastroenterol 1952;22:1–12.
[26] Andrews PLR. Vagal afferent innervation of the gastrointestinal tract. In: Cervero F, Morrison JFB, editors. Progress in brain research, vol. 67. London: Elsevier Science Publishers, 1986:65–86.
[27] Grundy DG, Scratcherd T. Sensory afferents from the gastrointestinal tract. In: Wood JD, editor. Handbook of physiology. Bethesda, Maryland: American Physiological Society, 1989:593–620.
[28] Leslie RA. Comparative aspects of the area postrema: fine structural considerations help to determine its function. Cell Mol Neurobiol 1986;6:95–120.
[29] Stefani E, Clement-Cormier Y. Detection of receptors in the area postrema. Eur J Pharmacol 1981;74:257–60.
[30] Waeber C, Dixon K, Hoyer D. Localisation by autoradiography of neuronal 5-HT3 receptors in the mouse. Eur J Pharmacol 1988;151:351–2.
[31] Palacios JM, Wamsley JK, Kuhar MJ. The distribution oh histamine H1-receptors in the rat brain: an autoradiographic study. Neuroscience 1981;6:15–7.
[32] Wamsley JK, Lewis MS. Autoradiographic localization of muscarinic cholinergic receptors in rat brainstem. J Neurosci 1981;1:176–91.
[33] Maubach KA, Jones RSG, Stratton SC, Gale JD. Autoradiographic distribution of substance P binding sites in the brainstem of rat and ferret. Br J Pharmacol 1995;116:249P.
[34] Howat DDC. Antiemetic drugs in anaesthesia. Anaesthesia 1960;15(3):289–97.
[35] Dundee JW, Moore J, Love WJ, et al. Studies of drugs given before anaesthesia. VI: the phenothiazine derivatives. Br J Anaesth 1965;37:332–52.
[36] Wood C. Antimotion sickness and antiemetic drugs. Drugs 1979;17:471–9.
[37] Fischer M, Bonnet F, Trang H, et al. The pharmacokinetics of droperidol in anesthetized patients. Anesthesiology 1986;64:486–9.
[38] Henzi I, Sonderegger J, Tramer MR. Efficacy, dose-response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting. Can J Anesth 2000;47(6):537–51.
[39] Melnick B, Sawyer R. Delayed side effects of droperidol after ambulatory anesthesia. Anesth Analg 1989;69:748–51.
[40] Fortney JT, Gan TJ, Graczyk, et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. Anesth Analg 1998;86:731–8.
[41] Koivuranta M, Laara E, Ranta P, et al. Comparison of ondansetron and droperidol in the prevention of postoperative nausea and vomiting after laparoscopic surgery in women. A randomised, double-blind, placebo-controlled trial. Acta Anaesthesiol Scand 1997;41:1273–9.
[42] McCarthy BG, Peroutka SJ. Differentiation of the muscarinic cholinergic receptor subtypes in human cortex and pons: implications for anti-motion sickness therapy. Aviat Space Environ Med 1988;49:63–6.
[43] Golding JF, Scott JR. Comparison of the effects of a selective muscarinic receptor antagonist and hyoscine (scopolamine) on motion sickness, skin conductance and heart rate. Br J Clin Pharmacol 1997;43:633–7.
[44] Clarke RSJ. Nausea and vomiting. Br J Anaesth 1984;56:19–27.
[45] Bailey PL, Streisand JB, Pace NL, et al. Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. Anesthesiology 1990;72:977–80.
[46] Loper KA, Ready LB, Dorman BH. Prophylactic transdermal scopolamine patches reduce nausea in postoperative patients receiving epidural morphine. Anesth Analg 1989;68:144–6.
[47] Clissold SP, Heel RC. Transdermal hyoscine (scopolamine): a preliminary review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1985;29:189–207.
[48] Harrington RA, Hamilton CW, Brogden RM, et al. Metoclopramide: an updated review of its pharmacological properties and clinical use. Drugs 1983;25:451–94.
[49] Fozard JR. Neuronal 5-HT receptors in the periphery. Neuropharmaclol 1984;23:1473–86.
[50] Henzi I, Walder B, Tramer MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review or randomized, placebo controlled studies. Br J Anaesth 1999;83(5):761–71.
[51] Boghaert A, Carron D, Gallant J, et al. Postoperative vomiting treated with domperidone: a double-blind comparison with metoclopramide and placebo. Acta Anesthesiol Belg 1980;31(2):129–37.
[52] Cameron HA, Reyntjens AJ, Lake-Bakaar G. Cardiac arrest after treatment with intravenous domperidone. Br Med J 1985;290:160.
[53] Osborne RJ, Slemn ML, Hunter RW, Hamer J. Cardiotoxicity of intravenous domperidone. Lancet 1985; ii: 385.
[54] Roussak JB, Carey P. Cardiac arrest after treatment with intravenous domperidone. Br Med J 1984;289:1579.
[55] Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT3 receptor antagonist. Anesth Analg 1991;72:751–5.
[56] Kenny GNC, Oates JDL, Lesser J, et al. Efficacy of orally administered ondansetron in the prevention of postoperative nausea and vomiting: a dose ranging study. Br J Anaesth 1992;68:466–70.
[57] Khalil S, Rodarte A, Weldon BC, et al. Intravenous ondansetron in established postoperative emesis in children. Anesthesiology 1996;85(2):270–6.
[58] Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997;87(6):1277–89.
[59] Sun R, Klein KW, White PF. The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesth Analg 1997;84:331–6.
[60] Tang J, Wang B, White PF, et al. The effect of timing of ondansetron administration on its efficacy, cost–effectiveness, and cost-benefit as a prophylactic antiemetic in the ambulatory setting. Anesth Analg 1998;86:274–82.
[61] Scholz J, Hennes HJ, Steinfath M, et al. Tropisetron or ondansetron compared with placebo for prevention of postoperative nausea and vomiting. Eur J Anaesthesiol 1998;15:676–85.
[62] Alon E, Kocian R, Nett PC, et al. Tropisetron for the prevention of postoperative nausea and vomiting in women undergoing gynecologic surgery. Anaesth Analg 1996;82:338–41.

[63] Wilson AJ, Diemunsch P, Lindeque BG, et al. Single-dose iv granisetron in the prevention of postoperative nausea and vomiting. Br J Anaesth 1996;76:515–8.
[64] Fujii Y, Tanaka H, Toyooka H. Optimal antiemetic dose of tropisetron for preventing postoperative nausea and vomiting. Can J Anaesth 1994;51:794–7.
[65] Diemunsch P, Schoeffler P, Bryssine B, et al. Anti-emetic activity of the NK-1 receptor antagonist GR 205171 in the treatment of established PONV following major gynecological surgery. Br J Anaesth 1999;82:274–6.
[66] Gesztesi Z, Scuderi P, White PF, et al. Substance P (Neurokinin-1) antagonist prevents postoperative vomiting after abdominal hysterectomy procedures. Anesthesiology 2000;93(4):931–7.
[67] Harris AL. Cytotoxic-therapy-induced vomiting is mediated via enkephalin pathways. Lancet 1982;1:714–6.
[68] Fujii Y, Tanaka H, Toyooka H. The effects of dexamethasone on antiemetics in female patients undergoing gynecologic surgery. Anesth Analg 1997;85:913–7.
[69] Liu K, Hsu CC, Chia YY. Effect of dexamethasone on postoperative emesis and pain. Br J Anaesth 1998;80:85–6.
[70] Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000;90:186–94.
[71] Price ML, Walmsley A, Ponte J. Comparison of a total intravenous anaesthetic technique using a propofol infusion, with an inhalational technique using enflurane for day case surgery. Anaesthesia 1988;43(Suppl):84–7.
[72] Doze VA, Shafer A, White PF. Propofol-nitrous oxide versus thiopental-Isoflurane-nitrous oxide for general anesthesia. Anesthesiology 1988;69:63–71.
[73] Lebenbom-Mansour MH, Pandit SK, Kothary SP, et al. Desflurane versus propofol anesthesia: A comparative analysis in outpatients. Anesth Analg 1993;76:936–41.
[74] Gan TJ, Ginsberg B, Grant AP, Glass PS. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology 1996;85(5):1036–42.
[75] Tramer M, Moore A, MaQuay H. Propofol anesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. Br J Anaesth 1997;78:247–55.
[76] Kim SI, Han TH, Kil HY, et al. Prevention of postoperative nausea and vomiting by continuous infusion of subhypnotic propofol in female patients receiving intravenous patient-controlled analgesia. Br J Anaesth 2000;85(6):888–90.
[77] Gan TJ, El-Molem H, Ray J, Glass PSA. Patient-controlled antiemesis — a randomized, double-blind comparison of two doses of propofol versus placebo. Anesthesiology 1999;90(6):1564–70.
[78] Gan TJ, Glass PSA, Howell ST, et al. Determination of plasma concentrations of propofol associated with a 50% reduction in postoperative nausea. Anesthesiology 1997;87(4):779–84.
[79] Ostman PL, Faure E, Glosten B, et al. Is the antiemetic effect of the emulsion formulation of propofol due to the lipid emulsion? Anesth Analg 1990;71:536–40.
[80] DiFlorio T. Is propofol a dopamine antagonist? Anesth Analg 1993;77:200–1.
[81] Appadu BL, Strange PG, Lambert DG. Does propofol interact with D2 dopamine receptors? Anesth Analg 1994;79:1191–2.
[82] Hvarfner A, Hammas B, Thorn SE, Wattwil. The influence of propofol on vomiting induced by apomorphine. Anesth Analg 1995;80:967–9.
[83] Rothenberg DM, Parnass SM, Litwack K, et al. Efficacy of ephedrine in the prevention of postoperative nausea and vomiting. Anesth Analg 1991;72:58–61.
[84] Naguib K, Osman HA, Al-Khayat, et al. Prevention of postoperative nausea and vomiting following laparoscopic surgery: ephedrine vs propofol. Middle East J Anesthesiol 1998;14(4):219–30.
[85] Greif R, Laciny S, Rapf B, et al. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology 1999;91:1246–52.
[86] Splinter WM, MacNeil HB, Menard EA. Midazolam reduces vomiting after tonsillectomy in children. Can J Anaesth 1995;42:201–3.
[87] Khalil SN, Berry JM, Howard G, et al. The antiemetic effect of lorazepam after outpatient strabismus surgery in children. Anesthesiology 1992;77:915–9.
[88] Mayer DJ. Acupuncture: an evidence-based review of the clinical literature. Annu Rev Med 2000;51:49–63.
[89] Lee A, Done M. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth Analg 1999;88(6):1362–9.
[90] Parikh PM, Charak BS, Banavali SD, et al. A prospective randomized double-blind trial comparing metoclopramide alone with metoclopramide plus dexamethasone in preventing emesis induced by high-dose cisplatin. Cancer 1988;66:2263–4.
[91] Melnick B, Sawyer R. Delayed side effects of droperidol after ambulatory anesthesia. Anesth Analg 1989;69:748–51.
[92] Pueyo FJ, Carrascosa F, Lopez L, et al. Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. Anesth Analg 1996;83:117–22.
[93] Bugedo G, Gonzalez J, Asenjo C, et al. Ondansetron and droperidol in the prevention of postoperative nausea and vomiting. Br J Anaesth 1999;83(5):813–4.
[94] Wu O, Belo S, Koutsoukos G. Additive anti-emetic efficacy of prophylactic ondansetron with droperidol in out-patient gynecological laparoscopy. Can J Anesth 2000;47(6):529–36.
[95] McKenzie R, Lim UN, Riley T, Hamilton D. Droperidol/Ondansetron combination controls nausea and vomiting after tubal banding. Anesth Analg 1996;83:1218–22.
[96] Riley TJ, McKenzie R, Tantisira BR, Hamilton DL. Droperidol-ondansetron combination versus droperidol alone for postoperative control of emesis after total abdominal hysterectomy. J Clin Anesth 1998;10:6–12.
[97] Peixoto AJ, Peixoto Filho AJ, Leaes LF, et al. Efficacy of prophylactic droperidol, ondansetron or both in the prevention of postoperative nausea and vomiting in major gynecological surgery. A prospective, randomized, double-blind clinical trial. Eur J Anesthesiol 2000;17:611–5.
[98] Wrench IJ, Ward JEH, Walder AD, Hobbs GJ. The prevention of postoperative nausea and vomiting using a combination of ondansetron and droperidol. Anaesthesia 1996;51:776–8.
[99] Warrick PD, Belo SE. Treating rebound emesis following outpatient gynecologic laparoscopy: The efficacy of a two-dose regimen of droperidol and ondansetron. J Clin Anesth 1999;11:119–25.
[100] Klockgether-Radke A, Neumann S, Braun U, Muhlendyck H. Ondansetron, droperidol and their combination for the prevention of post-operative vomiting in children. Eur J Anaesiol 1997;14:362–7.
[101] Rajeeva V, Bhardwaj N, Batra YK, Dhaliwal LK. Comparison of ondansetron with ondansetron and dexamethasone in prevention of PONV in diagnostic laparoscopy. Can J Anaesth 1999;46(1):40–4.
[102] McKenzie R, Tantisira B, Karambelkar D, et al. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth Analg 1994;79:961–4.
[103] Lopez-Olaondo L, Carrascosa F, Pueyo FJ, et al. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996;76:835–40.

[104] Splinter WM, Rhine EJ. Low-dose ondansetron with dexamethasone more effectively decreases vomiting after strabismus surgery in children than does high-dose ondansetron. Anesthesiology 1999;88:72–5.
[105] McKenzie R, Riley TJ, Tantisira B, Hamilton DL. Effect of propofol induction and ondansetron with or without dexamethasone for the prevention of nausea and vomiting after major gynecologic surgery. J Clin Anesth 1997;9:15–20.
[106] Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Prophylactic antiemetic therapy with granisetron-droperidol combination in patients undergoing laparoscopic cholecystectomy. Can J Anaesth 1998;45(6):541–4.
[107] Fujii Y, Toyooka H, Tanaka H. Granisetron-droperidol combination for the prevention of postoperative nausea and vomiting in female patients undergoing breast surgery. Br J Anaesth 1998;81:387–9.
[108] Fujii Y, Toyooka H, Tanaka H. A granisetron-droperidol combination prevents postoperative vomiting in children. Anesth Analg 1998;87:761–5.
[109] Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Combination of granisetron and droperidol for the prevention of vomiting after paediatric strabismus surgery. Paed Anaesth 1999;9:329–33.
[110] Fujii Y, Tanaka H, Toyooka H. Granisetron-dexamethasone combination reduces postoperative nausea and vomiting. Can J Anaesth 1995;42(5):387–90.
[111] Fujii Y, Tanaka H, Toyooka H. Prophylactic antiemetic therapy with granisetron-dexamethasone combination in women undergoing breast surgery. Acta Anaesthesiol Scand 1998;42:1038–42.
[112] Fujii Y, Toyooka H, Tanaka H. Prophylactic antiemetic therapy with a combination of granisetron and dexamethasone in patients undergoing middle ear surgery. Br J Anaesth 1998;81:754–6.
[113] Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Eur J Anaesth 2000;17:64–8.
[114] Fujii Y, Tanaka H, Kobayashi@Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after thyroidectomy, Anaesth. Intensive Care 2000, 28: 266-269
[115] Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Granisetron/dexamethasone combination for reducing nausea and vomiting during and after spinal anesthesia for cesarean section. Anesth Analg 1999;88:1346–50.
[116] Janknegt R, Pinckaers JWM, Rohof MHC, et al. Double-blind comparative study of droperidol, granisetron and granisetron plus dexamethasone as prophylactic anti-emetic therapy in patients undergoing abdominal, gynaecological, breast or otolaryngological surgery, Anaesthesia 54:1059–1068.
[117] Michaloudis D, O'Keeffe N, O'Sullivan K, Healy TEJ. Postoperative nausea and vomiting: a comparison of anti-emetic drugs used alone or in combination. J Royal Society Med 1993;86:137–8.
[118] Kymer PJ, Brown RE, Lawhorn CD, et al. The effects of oral droperidol versus oral metoclopramide versus both oral droperidol and metoclopramide on postoperative vomiting when used as a premedicant for strabismus surgery. J Clin Anesth 1995;7:35–9.
[119] Pendeville PE, Veyckemans F, Van Boven J, Steinier JR. Open placebo controlled comparison of the antiemetic effect of droperidol, metoclopramide or a combination of both in pediatric strabismus surgery. Acta Anaesthesiol Belg 1993;44(1):3–10.
[120] Kathirvel S, Shende D, Madan R. Comparison of anti-emetic effects of ondansetron, metoclopramide or a combination of both in children undergoing surgery for strabismus. Eur J Anaesthesiol 1999;16:761–5.
[121] Steinbrook RA, Freiberger D, Gosnell JL, Brooks DC. Prophylactic antiemetics for laparoscopic cholecystectomy: ondansetron versus droperidol plus metoclopramide. Anesth Analg 1996;83:1081–3.
[122] Eberhart LHJ, Seeling W, Ulrich B, et al. Dimenhydrinate and metoclopramide alone or in combination for prophylaxis of PONV. Can J Anesth 2000;47(8):780–5.
[123] Khalil S, Philbrook L, Rabb M, et al. Ondansetron/promethazine combination or promethazine alone reduces nausea and vomiting after middle ear surgery. J. Clin. Anesth. 1999:596-600.
[124] Eberhart LHJ, Seeling W, Hartschuh T, et al. Droperidol and dimenhydrinate alone or in combination for the prevention of post-operative nausea and vomiting after nasal surgery in male patients. Eur J Anaesthesiol 1999;16:790–5.
[125] Barst SM, Leiderman JU, Markowitz A, et al. Ondansetron with propofol reduces the incidence of emesis in children following tonsillectomy. Can J Anaesth 1999;46(4):359–62.
[126] Ahmed AB, Hobbs GJ, Curran JP. Randomized, placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery. Br J Anaesth 2000;85(5):678–82.
[127] Holt R, Rask P, Coulthard KP, et al. Tropisetron plus dexamethasone is more effective than tropisetron alone for the prevention of postoperative nausea and vomiting in children undergoing tonsillectomy. Paed Anaesth 2000;10:181–8.
[128] Scuderi P, James R, Harris L, Mims GR. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. Anesth Analg 2000;91:1408–14.
[129] Gan TJ, Hill RP, Moretti E, Kucmeroski D, Pappas T, Eubanks S. Triple antiemetic prophylaxis involving propofol, droperidol and ondansetron is highly effective in preventing PONV. Anesth Analg 2000;90:S4.