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Prevention of Postoperative Nausea and Vomiting

With Special Reference to Supplemental Oxygen, Different Antiemetics and Anesthesia Regimens

Doctoral dissertation

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ABSTRACT

Postoperative nausea and vomiting (PONV) continues to be one of the most common and unpleasant complications after surgery. In addition to causing patient discomfort, it has also economical impact. In this study, the efficacy and adverse effects of different antiemetic interventions in the prophylaxis of PONV were evaluated in 590 patients during the first 24 hours after surgery under general anesthesia.

Two antiemetics, tropisetron and droperidol, were compared with placebo after gynecologic incontinence surgery. Further, the antiemetic efficacy and costs of three anesthetic regimens (propofol-air/O_2 anesthesia, isoflurane-nitrous oxide anesthesia with and without ondansetron) were evaluated in women undergoing gynecologic laparoscopy. Perioperative supplemental 80 % oxygen was compared with 30 % oxygen after gynecologic laparoscopy and breast surgery using intravenous ondansetron 4 mg as the active control. In addition, the efficacy of 50 % oxygen was compared with 30 % oxygen after breast surgery.

In high risk patients receiving isoflurane-nitrous oxide anesthesia without other forms of prophylaxis for PONV, tropisetron 5 mg IV decreased the incidence of PONV from 80 % to 69 % compared with placebo ($P < 0.05$), whereas droperidol alone 1.25 mg IV had no antiemetic effect. Drowsiness, anxiety, and dissatisfaction were more common after droperidol compared with tropisetron and placebo during the first 6 h after surgery. The incidence of PONV after isoflurane-nitrous oxide anesthesia with oral ondansetron 8 mg (33%) was similar to that after propofol-air/O_2 anesthesia (38 %) but lower than that found after isoflurane-nitrous oxide anesthesia alone (59 %) ($P < 0.05$). The median costs of anesthetic drugs to prevent PONV in one additional patient were $US65 after propofol-air/$O_2$ anesthesia and $US68 after isoflurane-nitrous oxide anesthesia with ondansetron. The incidences of PONV after supplemental oxygen (incidence 55–89%) did not differ from those after 30 % oxygen (incidence 62–89 %). Ondansetron 4 mg IV combined with 30 % oxygen significantly ($P < 0.05$) decreased the incidence of PONV (incidence 57 %) compared with 30 % oxygen alone (incidence 89 %).

In conclusion, tropisetron, ondansetron and propofol-air/O_2 anesthesia decrease the incidence of PONV after gynecologic and breast surgery, although their antiemetic efficacies are limited. Perioperative supplemental oxygen and droperidol alone fail to attenuate PONV in patients who are at a high risk for PONV, and in addition, droperidol seems to evoke adverse effects.

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Medical Subject Headings: postoperative nausea and vomiting/prevention & control; oxygen; antiemetics; tropisetron; ondansetron; droperidol; anesthesia; propofol; anesthetics

To Ilkka, Hanna, Mirkka and Ville

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Sinikka Purhonen

ABBREVIATIONS

$5\text{-}HT_3$	5-hydroxytryptamine-subtype 3
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
BIS	bispectral index
BMI	body mass index
bpm	beat(s) per minute
CNS	central nervous system
CO_2	carbon dioxide
CTZ	chemoreceptor trigger zone
CYP	cytochrome P450
D_2	dopamine-2
ECG	electrocardiography
ET	end-tidal
FDA	United States Food and Drug Administration
FiO_2	fraction of inspired oxygen
GABA	gamma-aminobutyric acid
GI	gastrointestinal
H_1	histamine-1
IM	intramuscular
IV	intravenous
MAC	minimum alveolar concentration
NA	not applicable
ND	not detected
NK1	neurokinin-1
NNH	number needed to harm
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
P	probability
P_6	Pericardium
PACU	post anesthesia care unit
PCA	patient controlled analgesia
PEEP	positive end-expiratory pressure
PO	peroral
PONV	postoperative nausea and vomiting
POV	postoperative vomiting
QT_c	corrected QT interval
SD	standard deviation
SpO_2	oxygen saturation
TIVA	total intravenous anesthesia

LIST OF THE ORIGINAL ARTICLES

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Purhonen S, Kauko M, Koski EMJ, Nuutinen L. Comparison of tropisetron, droperidol, and saline in the prevention of postoperative nausea and vomiting after gynecologic surgery. Anesth Analg 1997;84:662-7.

II Purhonen S, Koski EMJ, Niskanen M, Hynynen M. Efficacy and costs of three anesthetic regimens in the prevention of postoperative nausea and vomiting. J Clin Anesth, accepted for publication.

III Purhonen S, Turunen M, Ruohoaho UM, Niskanen M, Hynynen M. Supplemental oxygen does not reduce the incidence of postoperative nausea and vomiting after ambulatory gynecologic laparoscopy. Anesth Analg 2003;96:91-6.

IV Purhonen S, Niskanen M, Wüstefeld M, Mustonen P, Hynynen M. Supplemental oxygen for prevention of nausea and vomiting after breast surgery. Br J Anaesth 2003;91:284-7.

V Purhonen S, Niskanen M, Wüstefeld M, Hirvonen E, Hynynen M. Supplemental 80 % oxygen does not attenuate postoperative nausea and vomiting after breast surgery. Acta Anaesthesiol Scand, in press.
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In addition, unpublished data are presented.

CONTENTS

INTRODUCTION

Postoperative nausea and vomiting (PONV) is still one of the most common adverse events following anesthesia and surgery. Its overall incidence is 25–30 % in all patients undergoing surgery, and it has remained rather constant over the past four decades despite the development of anesthetics and antiemetics, and a great amount of published research (Bellville 1961, Kovac 2000). In patients at high risk for PONV, the incidence can increase up to 80 % (Apfel et al. 1999), in fact up to the same level as in the "ether era" (Knapp and Beecher 1956).

Although PONV is seldom life-threatening, patients experience it as very distressing and have reported that avoidance of PONV is more important than avoidance of pain (Macario et al. 1999). When the patients were asked how much they would pay for a hypothetical new drug that would eliminate PONV, they were willing to pay as much as $US100 for a totally effective antiemetic (Gan et al. 2001). Not only is PONV detrimental to a patient, it can also increase medical costs, especially in ambulatory surgery where it can prolong the stay in the post-anesthesia care unit (PACU), or cause unanticipated hospital re-admission after surgery (Fortier et al. 1998).

PONV has a multifactorial etiology (Kovac 2000). The risk factors for PONV have often been categorized into three groups, the patient-, anesthesia-, or surgery-related factors. Patient related risk factors are female gender, history of previous PONV, or motion sickness and non-smoking status. For example, the incidence of PONV in women is two to three times higher than that of men (Koivuranta et al. 1997, Apfel et al. 1999). In the prevention of PONV, patient and surgery related risk factors cannot be influenced, but the anesthesia related risk can be decreased by choosing less emetic drugs for anesthesia and pain relief (Tramer 2001a, Gan et al. 2003). Anesthesia with propofol for both induction and maintenance has been shown to result in the reduction of PONV compared with inhalation anesthesia (Tramer 1997a, Apfel et al. 2004b).

The efficacy of the currently available antiemetic drugs against PONV is rather poor. In general, they decrease PONV only by about 30 % (Apfel et al. 2004b). In addition, they can cause adverse effects, such as sedation, anxiety, hypotension, dry mouth, or headache (Kovac 2000). Furthermore, the costs of newer antiemetics, for example 5-HT_3 (5-hydroxytryptamine-subtype 3) receptor antagonists, are high (Hill et al. 2000). Therefore, antiemetic prophylaxis needs to be focused on those patients who will most benefit from it, i.e. the patients at moderate or high risk for PONV (Gan et al. 2003).

The aim of the present study was to evaluate the efficacy of different antiemetic interventions against PONV in women undergoing general anesthesia. First, tropisetron (a 5-HT_3 receptor antagonist) and droperidol were compared with placebo, taking into account also adverse effects. Second, the antiemetic efficacy and costs of three different anesthetic regimens were evaluated. Third, the antiemetic efficacy of perioperative supplemental oxygen was studied.

REVIEW OF THE LITERATURE

1 Incidence and consequences of postoperative nausea and vomiting

In spite of improved anesthetic agents and surgical techniques the incidence of postoperative nausea and vomiting has remained largely unchanged over the past 40 decades (Bellville 1961, Kovac 2000). The overall incidence of PONV is estimated to be 25 to 30 % of all patients undergoing surgery (Kovac 2000). In patients at considerable risk for PONV, the incidence can climb to as high as 70 to 80 % (Apfel et al. 1999, Gan et al. 2003). Ambulatory patients seem to suffer less PONV compared with inpatients (Visser et al. 2001). This has been suggested to be related to underrecognition of postdischarge nausea and vomiting (Gan 2002a). However, in the study of Visser et al. (2001), the differences between the incidences of PONV in inpatients and outpatients may well have been attributable also to other factors such as the longer duration of anesthesia in the inpatient group. In the study of Carroll et al. (1995), the incidence of the postdischarge nausea and vomiting was 35 %, and it is noteworthy that many of the patients in this study had not experienced nausea and vomiting in the recovery room.

The importance of PONV is generally underestimated because it is self-limiting and almost never fatal. However, PONV is among the most unpleasant experiences associated with surgery and it can have a major negative impact on patient satisfaction (Myles et al. 2000). Patients have reported that the avoidance of PONV is of even greater concern than the avoidance of pain (Macario et al. 1999, Eberhart et al. 2002a). In addition, they would be willing to pay as much as US$100 for a completely effective antiemetic (Gan et al. 2001).

Morbidity associated with PONV is infrequent. Pulmonary aspiration of gastric contents can be associated with vomiting in the immediate postoperative period because protective reflexes have been depressed by anesthetics. In addition, dehydration and electrolyte disturbances might be consequences of prolonged vomiting (Andrews 1992). PONV does not usually cause life-threatening complications but occasionally subcutaneous emphysema with sudden airway compromise (Schumann and Polaner 1999) and esophageal ruptures (Barik 2000, Atallah et al. 2004) have been described.

Vomiting and retching can sometimes deteriorate surgical outcome by increasing the incidence of postoperative wound hematoma, dehiscence and intraocular bleeding (Andrews 1992, Eberhart et al. 2004). Skin flaps and transplants after plastic surgery in the upper body can be destroyed by venous stasis and bleeding secondary to retching and vomiting (Stein 1982). However, it is difficult to evaluate the association between surgical complications and emesis, and thus, the frequency is unknown.

In addition to the discomfort and complications for the patient her/himself, PONV can increase medical costs in many ways. It is a limiting factor in the early discharge of ambulatory surgery patients and an important cause of unanticipated hospital re-admission (Gold et al. 1989, Fortier et al. 1998, Gan 2002a). However, the numbers of unanticipated hospital admission attributable to PONV vary greatly (0.002–2 %) between surveys because of the different study designs (Tramer 2001a). In addition, PONV can lead to increased recovery room time and expanded nursing care (Chung and

Mezei 1999, Gan 2002a). Drugs and equipment needed for the treatment of established PONV also increase costs (Watcha 2000).

2 Physiology of postoperative nausea and vomiting

Vomiting is the forceful expulsion of gastric contents involving the rhythmic contraction of respiratory muscles including the diaphragm and abdominal muscles. In retching, no expulsion takes place but the same muscle groups are activated as in vomiting (Watcha 2002). Both vomiting and retching are objective symptoms (Kovac 2000). Nausea is a subjective unpleasant sensation in the throat and epigastrium associated with the urge to vomit. Nausea is often associated with vomiting but the two symptoms do not necessarily occur together (Andrews 1992).

Initially, nausea and vomiting have developed for important defense mechanisms against the ingestion of toxins (Andrews 1992). The exact mechanism of PONV has not been completely resolved (Andrews 1999, Apfel and Roewer 2004). Several animal models have been established to investigate mechanisms and treatment of chemotherapy or radiation-induced sickness. However, there is no animal model for human PONV (Andrews 1992).

Nausea and vomiting are mediated through very complex neural pathways (Leslie et al. 1990) (Figure 1). The neuroanatomical site coordinating vomiting is found in an ill-defined area in the lateral reticular formation situated in the brainstem (Figure 2). This area is called the vomiting center and it innervates the motor pathways that are responsible for the visceral and somatic output involved in vomiting (Andrews 1992). The vomiting center receives input from several afferents: higher cortical centers, cerebellum, the optic, olfactory, vagal, glossopharyngeal, and trigeminal nerves, and somatic structures such as the gastrointestinal tract, mediastinum, renal pelvis, testis, pharynx, and heart (Watcha 2002). The vomiting center also communicates with the surrounding nucleus tractus solitarius and the chemoreceptor trigger zone (CTZ). The latter area is situated in the floor of the IV ventricle, in the area postrema. It is a highly vascularized area in which the blood-brain barrier is not effective (Cameron and Gan 2003). The CTZ can be activated by direct chemical stimulation through the cerebrospinal fluid or blood, but not by direct electrical stimulation (Watcha 2002). The areas in the central nervous system associated with balance, vasomotor activity, salivation, respiration and bulbar control are located in the vicinity and have an innervation to the vomiting centre. The close proximity of these areas to the vomiting centre corresponds to the physiological reaction often seen with PONV such as salivation, increased swallowing, dizziness, sweating, pallor, tachypnea, tachycardia, and cardiac dysrythmias (Kovac 2000).

Immunohistochemical studies have shown that the central structures involved in the vomiting response are rich in dopamine$_2$, histamine$_1$, serotonin (5-hydroxytryptamine; 5-HT), muscarinic, opioid, and neurokinin-1 (NK_1) receptors (Diemunsch and Grelot 2000, Kovac 2000, Cameron and Gan 2003). Blockage of these receptors may be the

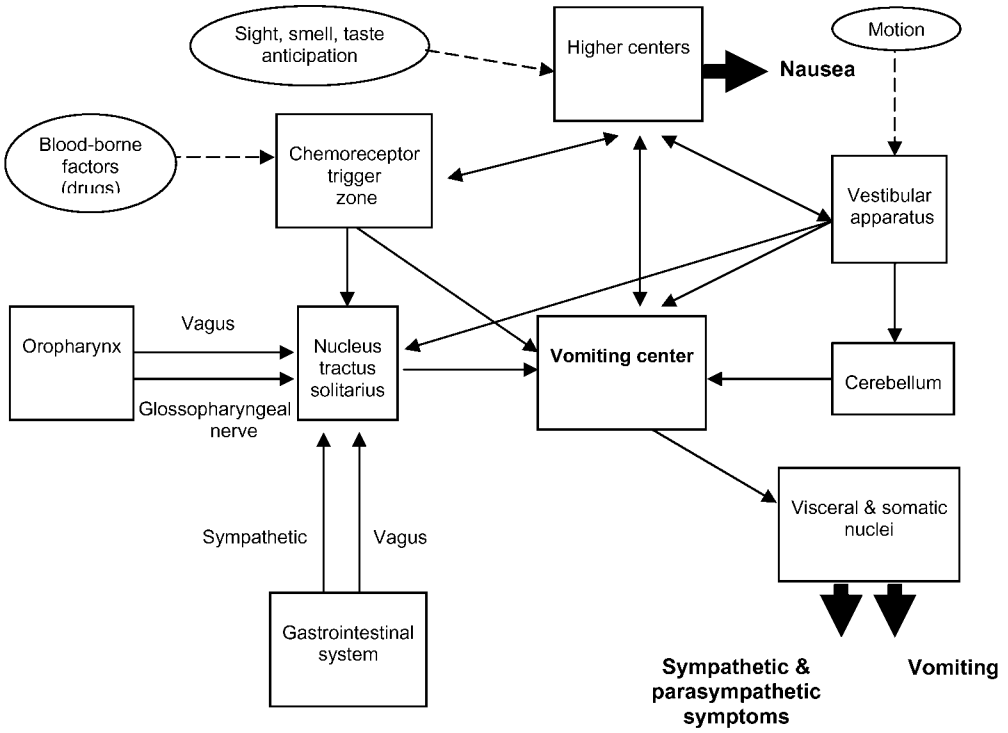

Figure 1. Mechanism of nausea and vomiting.

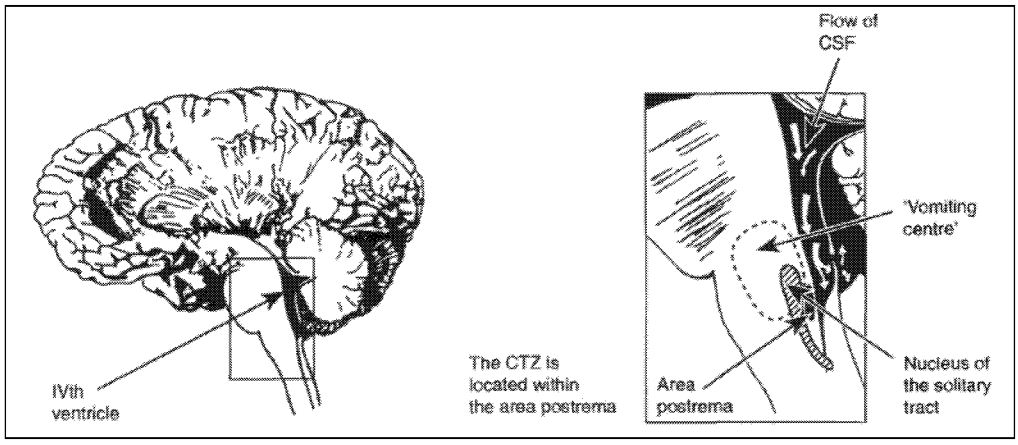

Figure 2. The anatomical location of the area postrema and the region of the vomiting center (Naylor and Inall 1994). Published with permission from Blackwell Publishing.

mechanism of the antiemetic action of many drugs (Kovac 2000). To date, no universal antiemetic agent has been found (Heffernan and Rowbotham 2000), and it is generally accepted that for the control of PONV, block of all the recognized receptors is needed (Rose and Watcha 1999).

3 Risk factors for postoperative nausea and vomiting

Postoperative nausea and vomiting has a complex and multifactorial etiology (Kovac 2000) (Table 1). Numerous studies have attempted to identify the factors associated with PONV in order to predict which patients are at the highest risk of suffering this complication. Identification of those high risk patients allows targeting antiemetic prophylaxis to those who will benefit from it most (Gan et al. 2003). Risk factors are often categorized into those related to patients, anesthesia, or surgical procedures.

Table 1. Risk factors for PONV, categorized according to evidence and significance

Level of evidence	Risk factor	
Good evidence and clinical effect very impressive	+++	Female sex
	++	Non-smoking status
	++	History of PONV/motion sickness
	+++	General anesthesia
	++	Volatile anesthetics
	++	Duration of anesthesia/surgery
	++	Postoperative opioids
Good evidence but clinical effect less impressive	+	Nitrous oxide
Controversial		Type of surgery
		Young age (adults)
		Experience of anesthesiologist
		Nasogastric tube
Insufficient evidence		Pain
		Movement
		Anxiety
		Neostigmine
No evidence		Obesity
		Menstruation cycle

Significance: + moderate; ++ strong; +++ very strong.
(modified from Apfel and Roewer 2004a).

3.1 Patient related risk factors

Female gender is the best established predictor for PONV. In female patients, there is a 2 to 3-fold increase in the incidence of PONV compared with males (Koivuranta et al. 1997, Apfel et al. 1999, Sinclair et al. 1999). This finding has been attributed to fluctuations in female sex hormone concentrations that occur during the menstrual cycle (Belville 1961, Watcha and White 1992). However, results of studies investigating the relationship of PONV to the phase of the menstrual cycle have been inconsistent (Honkavaara et al. 1991, Beattie et al. 1993, Gratz et al. 1996). In the systematic review of Eberhart et al. (2000a), the results based on 2625 patients suggested that the phase of the menstrual cycle had no impact on the occurrence of PONV.

The patients who do not smoke have a considerably increased risk for PONV (Apfel et al. 1999, Sinclair et al. 1999, Stadler et al. 2003). The exact antiemetic mechanism of cigarette smoking is unclear, although several possible theories have been presented. For instance, it has been suggested that tobacco smoke might contain an antiemetic substance (Chimbira and Sweeney 2000) but to date, however, no such substance has been found. Another mechanism by which nicotine could reduce PONV is that it might decrease dopamine receptor density by the blocking gamma-aminobutyric acid (GABA) ergic system (Sershen et al. 1995, Apfel and Roewer 2004a). Further, it has been postulated that liver enzyme induction might be one of the most likely reasons for the antiemetic effect in smokers (Chimbira and Sweeney 2000). Polycyclic hydrocarbons and nicotine present in cigarette smoke are known to induce the cytochrome P450 enzyme system which is responsible for the degradation of a number of anesthetic agents (Chimbira and Sweeney 2000, Sweeney 2002). This liver enzyme induction could explain some differences in the recovery rate from anesthesia and manifestation of PONV between smoking and non-smoking patients.

Alcohol intake, although underestimated, is probably as important as smoking in determining the risk of PONV (Sweeney 2002). The antiemetic effect of alcohol could also arise by the above mentioned enzyme induction.

A history of PONV or motion sickness can increase the incidence of PONV by up to 2 to 3 times (Palazzo and Evans 1993, Koivuranta et al. 1997). The impact of motion on the activation of the vomiting reflex is well known (Pusch et al. 2000). In the study by Koivuranta et al. (1997), of those patients who experienced nausea on the ward, 38 % associated it with movement. However, the neural connection from the labyrinth to the medullary vomiting center still remains unclear (Pusch et al. 2000).

Increasing age has decreased the incidence of PONV in some studies (Apfel et al. 1998, Sinclair et al. 1999). However, this effect of age on PONV could not be confirmed in other studies (Koivuranta et al.1997, Apfel et al. 1999, Stadler et al. 2003). Thus, the effect of age on PONV has remained unclear.

Contrary to previous impressions, Kranke et al. (2001) demonstrated in a meta-analysis that increased body mass index is not a risk factor for PONV. Also preoperative anxiety has been suggested to be predictive for PONV (Lermann 1992, Watcha and White 1992) but until recently, data supporting this hypothesis have been lacking. However, a recent study of 1389 inpatients indicated that high levels of preoperative anxiety were associated with PONV, however, the association was weak (van den Bosch et al. 2005).

3.2 Anesthesia related risk factors

General anesthesia is a strong risk factor of PONV (Sinclair et al. 1999, Stadler et al. 2003). In the large study of Sinclair et al. (1999) which enrolled 17.638 ambulatory patients, the incidence of PONV after general anesthesia was approximately 11 times greater than that after regional anesthesia. In addition, each 30-min increase in duration of surgery/anesthesia increased the likelihood of PONV by 59 %. Also in a study of inpatients (Stadler et al. 2003), general anesthesia was a risk factor for PONV compared with locoregional anesthesia. However, Stadler et al. (2003) could not find any direct association between the duration of anesthesia and the incidence of PONV.

Inhalation anesthesia increases the incidence of PONV compared with anesthesia maintained with propofol (Sneyd et al. 1998, Hofer et al. 2003). Apfel et al. (2002a) demonstrated in their study enrolling 1180 high risk patients that volatile anesthetics were a leading cause of early postoperative vomiting (up to 2 h after surgery), and that a dose-response relationship was present. The emetic effect of volatile anesthetics was apparent irrespective of whether halothane, enflurane, isoflurane, sevoflurane or desflurane were used (Watcha and White 1992, Apfel et al. 2002a, Gupta et al. 2003). The emetic effect of volatile anesthetics was confirmed in a recent multicenter study where avoidance of volatile anesthetics reduced the incidence of PONV by 19 % (Apfel et al. 2004b).

Early studies reported conflicting results about the possible association of nitrous oxide and PONV (Rose and Watcha 1999). Finally, three meta-analyses showed that the omission of nitrous oxide could reduce the risk for postoperative nausea and vomiting in adults undergoing procedures known to be associated with a high risk for PONV, but not in those at low risk for this complication (Divatia et al. 1996, Hartung 1996, Tramer et al. 1996). In the study of Tramer et al. (1996), the avoidance of nitrous oxide reduced early (up to 6 h after surgery) and late (up to 48 h after surgery) vomiting with NNT (number needed to treat) of 13, but in the high-risk group NNT for early and late vomiting was 5 and 6, respectively. In a recent large multicentre study, omitting nitrous oxide reduced the incidence of PONV only by 12 % (Apfel et al. 2004b), a reduction which cannot be regarded clinically significant. Nitrous oxide has been shown to activate several receptor systems associated with PONV. These include activation of the medullary dopaminergic system (Murakawa et al. 1994), and the opioid receptors in the brain (Finck et al. 1995). In addition, diffusion of nitrous oxide into the middle ear and bowel, resulting in stimulation of the vestibular apparatus and bowel distension, also may contribute to PONV (Nader et al. 2004, Acka et al. 2004).

The association of pain and opioids with PONV is complex. Pain itself has been demonstrated to cause nausea (Andersen and Krohg 1976). On the other hand, the opioids used for the abolishment of pain increase nausea and vomiting (Wheeler et al. 2002). In the survey of Koivuranta et al. (1997), 540 of 1107 patients experienced nausea after surgery on the ward. Ten percent of those patients associated nausea with pain medication, and only a few patients with the pain itself. At high doses, opioids have been shown to possess an antiemetic effect, probably by stimulation of central opioid receptors (Andrews 1992, Bates et al. 2004). In contrast to this antiemetic effect of high-dose opioids, the routine intra- and postoperative administrations of opioids most often are a risk for PONV (Sukhani et al. 1996, Koivuranta et al. 1997, Apfel et al.

1999). Bates et al. (2004) claimed that this emetic effect of opioids might be mediated by opioid receptors located in the chemoreceptor trigger zone (CTZ) outside the blood brain barrier and the cerebrospinal fluid-brain barrier. When administered in equi-analgesic doses, all opioids are capable of eliciting PONV (Rose and Watcha 1999). However, there is inter-individual variation in the emetic effect of opioids, thus it is possible to reduce PONV by selecting a different opioid (Rose and Watcha 1999). The proposed mechanisms by which opioids can cause PONV include in addition to the above mentioned stimulation of opioid receptors in the CTZ (Bates et al. 2004), sensitization of the vestibular organ to movement-induced emesis, and decreased gastrointestinal motility (Andrews 1992, Bates et al. 2004). In addition, opioids can enhance the release of 5-HT from the small intestine (Racke and Schworer 1991).

Previously, antagonism of residual neuromuscular block with a mixture of neostigmine and atropine at the end of surgery was believed to increase PONV, even though atropine was thought to possess some antiemetic efficacy (Rabey and Smith 1992). Later, results from randomized controlled trials have been contradictory. Tramer and Fuchs-Buder (1999a) stated in their systematic review of 1134 patients that omitting neostigmine may have a clinically relevant antiemetic effect only when high doses (> 2.5 mg) would be used. In that review and subsequently later (Fuchs-Buder and Mencke 2001), the authors have recommended that it is advisable to antagonize neuromuscular blockade in order to avoid any possible residual paralysis. The latest meta-analysis by Cheng et al. (2005) claimed that neostigmine did not increase the risk of postoperative vomiting and that there is insufficient evidence to conclude that neostigmine would increase the risk of PONV.

PONV has also been associated with hemodynamic variations (Pusch et al. 2002a, Pusch et al. 2002b). Pusch et al. (2002a) noticed that a decrease of systolic blood pressure (> 35 %) from preanesthetic baseline during the anesthetic induction in gynecologic patients was associated with more PONV. It was not clear whether the blood pressure decrease triggered PONV or the PONV symptoms evoked the hemodynamic changes. Furthermore, the same group found a strong association between orthostatic dysregulation and PONV (Pusch et al. 2002b). The underlying mechanism of this finding remains unsolved. The association of hypotension and PONV is still unclear.

3.3 Surgery related risk factors

It has been believed that there is a direct relationship between the incidence of PONV and the type of surgery, with a higher incidence following some operations such as eye, oral, ear-nose-throat, head and neck, plastic, gynecologic, laparoscopic and abdominal procedures than occurs with other operations (Kovac 2000). In agreement with this proposal, a large study of 18,000 ambulatory patients revealed an increased risk for PONV among patients undergoing breast augmentation, dental surgery, orthopedic shoulder procedures, gynecologic laparoscopy (for sterilization), varicose vein stripping, and strabismus repair (Sinclair et al. 1999). On the contrary, in a study of 1566 inpatients, Apfel et al. (1999) found that the type of surgery was not an independent risk factor for PONV. The authors stated that although there was an association between the type of surgery and PONV, the causal effect on PONV

attributable to the type of surgery remained questionable because a high incidence of PONV after certain operation might have been caused by other risk factors, such as the type of anesthetic used, the duration of operation, and the use of postoperative opioids. In addition, in the recent large multicenter study with over 5000 patients, Apfel et al. (2004c) could not find any interactions between the antiemetic interventions and the type of surgery. Thus, it has remained unclear whether or not the type of surgery is a risk factor for PONV (Gan et al. 2003).

3.4 Risk scores

Prophylaxis of PONV is not appropriate for every patient. Targeting of antiemetic prophylaxis to those patients at a high risk of PONV has economical implications and will also help to decrease the probability of adverse drug reactions (Tramer 2004). In order to identify those patients who are in high risk for PONV and may benefit from antiemetic medication, several predictive models and scores have been formulated. Many studies have attempted to rank the relative importance of different risk factors of PONV using logistical regression analysis (Palazzo and Evans 1993, Koivuranta et al. 1997, Apfel et al.1998, Sinclair et al. 1999, Apfel et al. 1999, Stadler et al. 2003). The most common risk factors in these risk scores are female gender, nonsmoking status, and previous PONV or motion sickness. Apfel et al. (1999) created a simplified risk score identifying four primary risk factors for PONV in patients receiving balanced inhaled anesthesia: female sex, nonsmoking status, history of PONV or motion sickness, and the use of postoperative opioids. The incidence of PONV with the presence of none, one, two, three, or all four risk factors was 10 %, 21 %, 39 %, 61 %, and 79 %, respectively. This risk score has been validated in a 428 in-patient study by Pierre et al. (2002). The simplification is an important characteristic for this score, since it is feasible for use in daily practice. Stadler et al. (2003) found different risk factors for nausea and vomiting. Female gender, nonsmoking status, and general anesthesia were predictive of both nausea and vomiting, while a history of migraine and type of surgery were mainly responsible for nausea but not for vomiting.

The use of scoring systems can provide a rational basis for choosing an antiemetic strategy (Apfel et al. 2002b). In addition, validated scores predicting PONV have been recommended for use in demographic tables for group comparisons in randomized controlled trials (Apfel et al. 2002c). However, also criticism has been raised against the use of risk scores. None of the risk score models is able to predict with certainty which individual will actually suffer from PONV (Apfel et al. 2002b). In addition, agreement between the different scoring systems is poor (Thomas et al. 2002). In a recent study of 1388 inpatients, van den Bosch et al. (2005) tested the applicability of two of the scoring systems (Koivuranta et al. 1997 and Apfel et al. 1999) for predicting the risk of PONV within 24 h after surgery. The predictive accuracy of the scores in the validation dataset was substantially lower than in the datasets that were used to develop the scoring systems. Therefore, the investigators have cautioned the clinicians not to trust blindly to existing scoring systems that may not be ideal for one's own patient population.

4 Prevention of postoperative nausea and vomiting

In the consensus guidelines for managing PONV (Gan et al. 2003), the panel stated that prophylaxis should be reserved for those patients at moderate to high risk for PONV because patients at low risk are unlikely to benefit from prophylaxis and would be put at unnecessary risks of suffering potential side effects of antiemetics. The health care professionals who use the guidelines should themselves determine the level of risk according to their own local and institutional norms (Gan et al.2003). In general, in patients undergoing general anesthesia, prophylaxis of PONV is composed of reduction of baseline risk factors, use of antiemetics and their combinations, and possible nonpharmacological therapies.

4.1 Antiemetic drugs

Antiemetic drugs are often categorized according to the receptors sites through which they have their main activities. These sites are dopamine (D_2), muscarinic cholinergic, histamine (H_1), serotonin (5-HT_3) and neurokinin-1 (NK_1) receptors (Table 2, Table 3).

4.1.1 Anticholinergics

Anticholinergics are among the oldest antiemetics. Since they can cross the blood-brain barrier, scopolamine and atropine can antagonize muscarinic cholinergic receptors in the cerebral cortex and pons (Golding and Stott 1997). Peripherally, they reduce the excitability of the labyrinth receptors and depress conduction in the vestibular cerebellar pathway (Sung 1996). Both atropine and scopolamine have efficacy against motion sickness and PONV (Salmenperä et al. 1992, Honkavaara et al. 1994). However, atropine has weaker antiemetic properties than scopolamine (Kovac 2000). The meta-analysis of Kranke et al. (2002a) showed that transdermal scopolamine was an effective antiemetic but its use was associated with adverse effects, the two most common being visual disturbances [NNH (number needed to harm) 6] and dry mouth (NNH 13).

4.1.2 Antihistamines

Antihistamines are traditional antiemetics, which produce their pharmacological effect by blocking the H_1 receptors in the nucleus of the solitary tract (Kovac 2000). They also block cholinergic muscarinic receptors in the vestibular apparatus (Habib and Gan 2003b) and thus have been suggested for controlling emesis resulting from vestibular stimulation, as occurs in patients with motion sickness, after middle ear surgery, or after opioid administration (Rose and Watcha 1999). Recently, the relatively inexpensive antihistamines have actively been studied as alternative drugs to droperidol and newer more expensive antiemetics in the prevention of PONV (Cholwill et al. 1999, Kranke et al. 2002b, Turner et al. 2004).

Cyclizine has been shown to be as effective as ondansetron in the prevention of PONV in day-case gynecologic laparoscopy (Cholwill et al. 1999). In addition, a

combination of cyclizine and ondansetron decreased PONV more effectively than ondansetron alone (Ahmed et al. 2000).

In the meta-analysis of Kranke et al. (2002b), dimenhydrinate (a salt of diphenhydramine) prevented PONV as well as the newer antiemetics such as serotonin receptor antagonists, droperidol and dexamethasone. Reporting of side effects in the studies including to this meta-analysis was inconsistent and sparse. In a recent study in gynecologic outpatients undergoing laparoscopy, an oral dose of long-acting dimenhydrinate with intravenous droperidol significantly reduced vomiting, with no difference in sedation when compared with droperidol alone (Turner et al. 2004).

4.1.3 Dopamine receptor antagonists

Phenothiazines are traditionally claimed to be antiemetics but this property is poorly documented (Tramer 2001b). In the prevention of PONV, the low cost of phenothiazines is attractive but side effects can complicate postoperative care resulting in prolonged hospitalization (Rose and Watcha 1999).

Butyrophenones such as haloperidol and droperidol, have significant antiemetic effects (Henzi et al. 2000b, Buttner et al. 2004). In the recent meta-analysis based on 1994 patients, parenteral haloperidol 1–2 mg prevented postoperative nausea and vomiting compared with placebo without any evidence of dose dependence (Buttner et al. 2004).

4.1.3.1 Droperidol

Droperidol has been used for the management of PONV for approximately 4 decades (Henzi et al. 2000b). It has a long duration of action probably because of its strong binding affinity to the emetic receptor, even though its plasma half-life is relatively short (127 min) (Lehman et al. 1988). In the prevention of PONV, droperidol is most often used at low doses 0.625–1.25 mg IV (Apfel and Roewer 2004a). Henzi et al. (2000b) found in their meta-analysis of 5351 patients that doses as low as 0.3 mg IV possessed anti-nausea efficacy (NNT 5). This effect was short-lived and the researchers suggested that low doses should be given repeatedly to achieve the best anti-nausea protection. The anti-vomiting effect was less pronounced (NNT 7), and showed some evidence of dose-responsiveness. Additionally, droperidol was most effective when it was administered at the end of surgery. In a recent large multifactorial trial of six interventions for the prevention of PONV, droperidol, ondansetron and dexamethasone reduced the risk of PONV with similar efficacies of about 26 % (Apfel et al. 2004b). Droperidol is also effective when given concomitantly with patient-controlled analgesia (PCA) devices that deliver morphine (Tramer and Walder 1999b). In a dose-finding study the optimal dose of droperidol, when added to the morphine PCA, was between 15–50 μg/mg of morphine (Culebras et al. 2003). The larger doses were suggested to have a better antivomiting effect but at a possible risk of causing increased sedation.

Table 2. Antiemetic drugs and their receptor sites.

Pharmacological group and drug	Dopamine (D_2)	Muscarinic cholinergic	Histamine (H_1)	Serotonin ($5\text{-}HT_3$)	Gluco-corticoid	Neurokinin-1 (NK_1)
Anticholinergics • Atropine • Scopolamine	+	+++	+	-	-	-
Antihistamines • Cyclizine • Diphenhydramine • Hydroxyzine	+	+	+++	-	-	-
Butyrophenones • Droperidol • Haloperidol • Domperidone	+++		+	+	-	-
Phenothiazines • Chlorpromazine • Fluphenazine • Promazine • Perphenazine • Prochlorperazine • Thiethylperazine • Dixyrazine	+++	+	+	+	-	-
Benzamides • Metoclopramide	++	-	+	+	-	-
Serotonin$_3$ (5-hydro-xytryptamine$_3$) antagonists • Ondansetron • Tropisetron • Granisetron • Dolasetron • Ramosetron • Palonosetron	-	-	-	+++	-	-
Corticosteroids • Betamethasone • Dexamethasone	-	-	-	-	+(?)	-
Propofol	-	-	-	+ (?)	-	-
Neurokinin-1 (NK_1) antagonists	-	-	-	-	-	+++

+++ main activity of the pharmacologic group.
+ + moderate activity of some or all drugs in this pharmacological group.
+ mild activity of some or all drugs in this pharmacological group.
+ (?) insufficient evidence.

Table 3. Pharmacological groups of antiemetics, the mechanism of their antiemetic effect, adverse effects, and examples of number needed to treat (NNT) for preventing PONV.

Antiemetics	**Mechanism of antiemetic effect**	**Adverse effects**	**NNT**
Anticholinergics	Antagonism of muscarinic cholinergic receptors in CNS: cortex and pons peripherally in the vestibular system	Sedation, amnesia, fatigue, dizziness, hallucinations, confusion, restlessness, disorientation, visual disturbances, dry mouth, urinary retention	Transdermal scopomorphine NNT for PONV 4 (Kranke et al. 2002a)
Antihistamines	Antagonism of histamine (H_1) receptors in the nucleus tractus solitarius Antagonism of muscarinic cholinergic receptors in the vestibular apparatus	Sedation, dry mouth, visual disturbances, urinary retention	Dimenhydrinate NNT for PONV 5 (Kranke et al. 2002b)
Butyrophenones Phenthiazines	Antagonism of dopamine (D_2) receptors in CTZ	Sedation, extrapyramidal symptoms, QT_c prolongation	Parenteral haloperidol 1-2 mg NNT for nausea 3-4 NNT for vomiting 4-5 (Buttner et al. 2004)
Benzamides	Antagonism of dopamine (D_2) receptors in CTZ Increasing of GI-motility Antagonism of 5-HT_3 receptors at high doses	Sedation, extrapyramidal symptoms	Metoclopramide 10 mg IV NNT for vomiting 9-10 (Henzi et al. 1999)
Serotonin$_3$ (5-hydroxy-tryptamine$_3$) antagonists	Antagonism of 5-HT_3 receptors on vagal afferents in GI- tract and centrally in the area postrema and in the nucleus tractus solitarius	Headache, dizziness, liver enzyme elevation, QT_c prolongation, constipation	Ondansetron 8 mg IV NNT for nausea 6-7 NNT for vomiting 4-5 (Tramer et al.1997b)
Corticosteroids	Glucocorticoid receptors in the nucleus tractus solitarius? Antagonism of prostaglandins? Anti-inflammatory and/ or membrane stabilizing effect? Reduction of serotonin (5-hydroxytryptamine) synthesis and release	ND	Dexamethasone 8-10 mg IV NNT for PONV 4 (Henzi et al. 2000a)
Neurokinin-1 (NK_1) receptor antagonists	Antagonism of NK_1 receptors	Headache	Not available

(?) insufficient evidence. CNS = central nervous system. GI = gastrointestinal. ND = not detected. QT_c = corrected QT interval.

With repeated and high doses, droperidol may cause extrapyramidal symptoms, anxiety, restlessness, hypotension and sedation, especially in young adults and the elderly (Kovac 2000). Melnick et al. (1989) reported that in 23 % of patients given droperidol 1.25 mg IV, anxiety or restlessness developed after discharge from the ambulatory care unit. In the meta-analysis of Henzi et al. (2000b) dose-dependent sedation with droperidol (NNH 7.8 with 2.5 mg IV) was found, however, extrapyramidal symptoms were rare (NNH 408). Other side effects possibly related to droperidol were hypotension (caused by alpha-adrenoceptor blockade), visual disturbances, nightmares, and urinary retention (Henzi et al. 2000b). An unexpected finding in this meta-analysis was a protective effect of droperidol against postoperative headache (NNT 25).

In 2001, The United States Food and Drug Administration (FDA) issued a "black box" warning about droperidol (FDA 2001). The warning states that droperidol may cause death or life-threatening events associated with QT prolongation and cardiac arrhythmia, such as torsades de pointes. Consequently, the FDA cautioned that droperidol should only be used when other "first line" drugs fail. The warning is based on 273 cases reported to the FDA between November 1st, 1997, and January 2nd, 2002. Of those, 127 cases resulted in serious adverse outcomes, but there were only 10 cases in which serious adverse cardiovascular events were reported when doses of 1.25 mg or less were administered. This warning has been challenged by many anesthesiologists because there have been no case reports in which droperidol in the doses used for the management of PONV has been associated with QT_c prolongation, arrhythmias, or cardiac arrest (Gan et al. 2002b, Bailey and White 2003). Habib and Gan (2003a) evaluated all of the reports submitted to the FDA, and concluded that in none of these cases in which arrhythmias occurred after small doses of droperidol ($\leq$ 1.25 mg) was there any evidence of a cause-and-effect relationship. Zhang et al. (2004) used mathematical modeling of QT interval to evaluate the relationship between the dose of droperidol and QT_c prolongation. They demonstrated that there was no significant effect of small-dose droperidol ($\leq$ 1.25 mg) on prolonging the QT_c interval, thus it was unlikely that droperidol at these doses would produce proarrhythmogenic effects during the perioperative period. In accordance to the findings of Zhang et al. (2004), White et al. (2005b) found in a clinical study only a slight prolongation in the QT interval after droperidol 0.625 and 1.25 mg IV, in fact this change was not different from that occurring after placebo. In addition, there was no evidence of any droperidol-induced QT_c prolongation immediately after surgery. Charbit et al. (2005) demonstrated that both droperidol 0.75 mg and ondansetron 4 mg IV induced similar clinically relevant QT_c interval prolongations when used in the treatment of PONV. These investigators stated that although the risk of proarrhythmias seemed to be very low, caution needed to be taken when these drugs were administered to treat PONV. However, in his recent editorial Scuderi (2005) criticized the warning of FDA, and questioned if QT_c prolongation is really the underlying mechanism for the dysrhythmias. The issue is under active research and no doubt new data will emerge for or against the warning. At present, the use of droperidol differs between countries. It is acceptable in Finland but not for example in the United Kingdom or Germany because of the "black box warning" (Apfel and Roewer 2004a).

4.1.3.2 Metoclopramide

Metoclopramide is the most widely used antiemetic in the group of benzamides. It blocks central dopaminergic (D_2) receptors in the CTZ and area postrema (Henzi 1999, Kovac 2000). It also increases lower oesophageal sphincter tone and enhances gastric motility which may prevent the delayed gastric emptying caused by opioid analgesics (Harrington et al. 1983). In addition, metoclopramide possesses parasympathomimetic activity and at high doses it antagonizes 5-HT_3 receptors (Habib and Gan 2003b). High-dose metochlopramide 1–2 mg/kg has been used successfully in the management of chemotherapy-induced emesis (Habib and Gan 2004b). Since serious side effects can occur at these high doses, notably sedation and dystonic reactions, lower doses (0.1–0.2 mg/kg) have been employed in the prevention of PONV. In the meta-analysis of Henzi et al. (1999), there was no relevant antiemetic efficacy for a 10 mg intravenous dose of metoclopramide nor any increased risk for adverse effects (sedation, dizziness, drowsiness, extrapyramidal symptoms). These findings suggest that the doses used in the prevention of PONV may be too low (Tramer et al. 2001a). Thus, it is possible that the effect of short-lasting metoclopramide (the elimination half life 2.5–6 h) given in a low dose at the start of surgery may have been worn off by the time the patient is fully awake and in need of antiemetic prophylaxis (Quaynor and Raeder 2002). Metoclopramide at a dose of 20 mg IV has been shown to decrease PONV with a similar efficacy as ondansetron 8 mg IV given at the end of laparoscopic cholecystectomy (Quaynor and Raeder 2002). However, more studies are needed with a high dose metoclopramide (> 10 mg IV) before its efficacy and side effects in the prevention of PONV can be determined.

4.1.4 5-hydroxytryptamine$_3$ receptor antagonists

The introduction of serotonin (5-hydroxytryptamine$_3$, 5-HT_3) receptor antagonists in the beginning of the 1990's was met with great enthusiasm among anesthesiologists, and there were believed by many to have solved the problem of PONV. The efficacy of these drugs in the prevention of chemotherapy-induced nausea and vomiting has been very impressive but unfortunately their effect on PONV has not been as good as was originally hoped (Heffernan and Rowbotham 2000, Gan et al. 2003).

5-HT_3 receptor antagonists are believed to induce their antiemetic effects by blocking selectively 5-HT_3 receptors mainly peripherally at vagal afferents in the gastrointestinal tract but also centrally in the area postrema and in the nucleus tractus solitarius (Gan 2005). Thus, they fail to block the emetic responses mediated via non-serotoninergic systems, such as those caused by opioids and motion (Diemunsch and Grélot 2000).

Although the efficacy and safety profiles of the 5-HT_3 receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron) are similar (Gan et al. 2003), there are differences between the agents in terms of pharmacology, pharmacokinetics and duration of action (Aapro 2004, Candiotti et al. 2005, Gan 2005). The most recently introduced compounds, ramosetron and palonosetron, with a long terminal elimination half-life have been recommended for delayed chemotherapy-induced nausea and

vomiting (Aapro 2004, Siddiqui and Scott 2004), and they might have a beneficial effect also on late PONV up to 24–48 h after surgery (Fujii et al. 2004).

4.1.4.1 Ondansetron

Ondansetron is the best documented 5-HT_3 receptor antagonist (Cameron and Gan 2003). Its bioavailability after oral dosing is approximately 60 %, with an elimination half-life of about 4 h (Gan 2005). Multiple forms of cytochrome P450 (CYP) enzymes are involved in the metabolism of ondansetron including CYP1A1, CYP1A2, CYP2D6, and the CYP3A family (Blower 2002). In addition to the binding to the 5-HT_3 receptor, ondansetron has detectable affinity to 5-HT_{1B}, 5HT_{1C}, α1-adrenergic, and μ-opioid receptor sites. However, the significance of this binding is unclear (Gregory and Ettinger 1998, Aapro 2004).

Originally the optimal effective dose of ondansetron in the prevention of PONV was considered to be 4 mg IV at induction, or an oral dose of 8 mg 1–2 h before anesthesia (Russell and Kenny 1992). However, in the meta-analysis of Tramer et al. (1997b), the optimal dose of ondansetron for the prevention of PONV was reported as 8 mg IV and 16 mg orally. With these doses, the antiemetic effect (NNT 4–5) of ondansetron was better than its antinausea effect (NNT 6–7). In disagreement with Tramer et al., Derschwitz et al. (1998) found that patients receiving 4 mg ondansetron IV required less rescue medication than those receiving lower doses (0.5 mg, 1 mg, 2 mg), but they found no benefit from increased doses (8 mg and 16 mg). Thus, the appropriate dose of ondansetron in the prophylaxis of PONV has remained somewhat controversial. Two studies have reported that an IV dose at the end of surgery results in a better efficacy compared with its administration at induction (Sun et al. 1997, Tang et al. 1998).

Compared with other antiemetics, ondansetron has been proved to be as effective as droperidol or dexamethasone but more effective than metoclopramide in the prevention of PONV (Apfel et al. 2004b, Domino et al. 1999).

In general, ondansetron has been shown to be safe with minimal significant side effects (Gan 2005). Headache (NNH 36), light-headedness, dizziness, constipation (NNH 23), and increased risk for elevated liver enzymes (NNH 31) have been described (Tramer et al. 1997b, Rose and Watcha 1999). The most serious side effects are rare hypersensitivity reactions (Rose and Watcha 1999). In addition, some case reports have been published where ondansetron has induced extrapyramidal symptoms (Sprung et al. 2003). All of the currently used 5-HT_3 receptor antagonists can block sodium channel conductance, and this may become a significant issue, particularly if large doses are used (Gan 2005). Although a single dose of the 5-HT_3 receptor antagonists for the management of PONV is unlikely to evoke cardiovascular effects in healthy patients, in patients with underlying QT prolongation, 5-HT_3 receptor antagonists including ondansetron need to be used with caution.

4.1.4.2 Tropisetron

Tropisetron is a selective antagonist of the 5-HT_3 receptor, and at therapeutic dosages, it has virtually no affinity for any other receptors, such as histamine, muscarine, dopamine, substance P receptors, and α_1-, α_2-, β_1 or β_2-adrenoceptors (de

Bruijn 1992). The bioavailability of tropisetron is dose-dependent, ranging from 52 % to 66 % (Lee et al. 1993). The cytochrome P450 enzymes, CYP2D6 mainly and CYP3A4 to a lesser extent (< 10 %), are involved in the metabolism of tropisetron (Blower 2002). CYP2D6 is an enzyme that is highly polymorphic and this leads to variable rates of drug metabolism. Thus, the half-life and metabolic clearance of tropisetron is markedly longer in poor CYP2D6 metabolizers than in extensive metabolizers (40 h versus approximately 8 h, and 0.197 L/min versus 0.964 L/min) (Blower 2002). This variability in the pharmacokinetics of tropisetron may be influenced when the agent is co-administered with enzyme inducing or inhibiting drugs. It is unclear whether a longer half-time is associated with any clinical advantage (Rose and Watcha 1999). On the other hand, there is no risk of accumulation at the recommended dose of 5 mg per day even in the elderly, or in patients with impaired liver and kidney function (Lee et al. 1993). The ratio between poor and extensive metabolizers in Caucasian populations is approximately 1:12 (Lee et al. 1993).

In a meta-analysis where 1267 patients received tropisetron, the 2–5 mg IV dose significantly reduced the incidence of PONV (Kranke et al. 2002c). At a control event rate of 40–80 %, NNT for preventing nausea was approximately 6–7 and for preventing vomiting it was 5. No evidence for a dose response between 2 and 5 mg IV was found, this being in agreement with the recommendation of a 2 mg dose for prevention of PONV according to some earlier studies (Capouet et al.1996, Alon et al. 1998). However, Chan et al. (1998) demonstrated in their patients with a high incidence of PONV that the antiemetic effect of tropisetron 2 mg was too brief compared with a dose of 5 mg. As with ondansetron, tropisetron has better antiemetic properties than an antinausea effect (Morrow et al. 1995, Kranke et al. 2002c).

Compared with other antiemetics in the prevention of PONV, tropisetron has been shown to be as effective as ondansetron, granisetron, and dexamethasone (Naguib et al. 1996, Wang et al. 2002). In comparison with droperidol 1.25 mg IV, tropisetron 5 mg IV had no better efficacy in the prevention of postoperative nausea but resulted in a significantly lower incidence of vomiting after laparoscopic cholecystectomy (Jokela and Koivuranta 1999).

The side effects of tropisetron, such as headache, dizziness, and constipation, are similar to those of other 5-HT_3 receptor antagonists (Morrow et al. 1995, Gan 2005).

4.1.5 Corticosteroids

Corticosteroids, mostly dexamethasone and to some extent betamethasone, have been introduced into clinical practice during the last 10 years for the prevention of PONV. The precise mechanism of their antiemetic action is unknown but numerous theories have been presented (Fredrikson et al. 1992, Henzi et al. 2000a, Kovac 2000, Ho et al. 2004) (Table 3).

In the meta-analysis of Henzi et al. (2000a), dexamethasone, administered at a dose of 8–10 mg IV, effectively prevented nausea and vomiting (Table 3). Also smaller doses (2.5–5 mg) of dexamethasone have been found to be effective (Liu et al. 1999, Wang et al. 2000b). The recent multicenter study (Apfel et al. 2004b) found an equal antiemetic efficacy for dexamethasone 4 mg, ondansetron 4 mg and droperidol 1.25 mg IV, each of which reduced the risk of PONV by about 26 %. The effect of dexamethasone appeared

approximately 2 h after its administration and this may one reason for the finding that dexamethasone appears to be more effective when administered prior to induction of anesthesia rather than at the end of surgery (Wang et al. 2000).

4.1.6 Neurokinin-1 receptor antagonists

The neurokinin-1 (NK_1) receptor antagonists are a new class of antiemetics for the prevention of PONV. Substance P is the most likely endogenous ligand for the NK_1 receptor. Binding studies using radiolabelled substance P have demonstrated neurokinin receptors, including NK_1 receptors, in the nucleus of the solitary tract and dorsal motor nucleus of the vagus of the rat (Maubach and Jones 1997). Only one study has been published concerning the efficacy of the NK_1 receptor antagonist in the prevention of PONV (Gesztesi et al. 2000). In that study which was conducted in females undergoing abdominal hysterectomy, the NK_1 receptor antagonist (oral CP-122,721) decreased emetic episodes as compared with ondansetron 4 mg IV. Although NK_1 receptor antagonists showed very promising results in the animal studies, the published results in humans in the prevention of PONV have been somewhat disappointing (Raeder 2003).

4.2 Methods to reduce baseline risk for postoperative nausea and vomiting

A significant reduction in PONV can be achieved by decreasing perioperative risk factors for PONV (Tramer 2001b). This strategy in prophylaxis is useful on its own (Tramer 2001b), or combined with antiemetics, especially in patients at high risk (Gan et al. 2003). There are several methods which may help to maintain a low baseline risk of PONV.

4.2.1 Propofol

Propofol is a widely used intravenous anesthetic for induction and maintenance of general anesthesia and sedation (Smith et al. 1994). It was introduced into clinical practice in the late 1980's. Shortly after its introduction, propofol was found to prevent PONV (Raftery and Sherry 1992, Borgeat et al. 1992). The efficacy of propofol in preventing nausea seems to be better than its ability to prevent vomiting (Tramer et al. 1997a, Visser et al. 2001). The decrease of nausea is achieved at a much lower plasma level (343 ng/mL) than is required for sedation (1–1.5 μg/mL) and maintenance of general anesthesia (3–5 μg/mL) (Gan et al. 1997a). The exact antiemetic mechanism of propofol has remained unknown, although several studies in this area have been made. For instance, it has been suggested that propofol achieves its antiemetic action by modulation of some subcortical pathways (Borgeat et al. 1992). At present, however, there is increasing evidence that propofol may exert an antiemetic action by antagonizing the serotoninergic system (Hammas et al.1998, Cechetto et al. 2001). In their study in volunteers Hammas et al. (1998) found that propofol reduced the intensity of retching after oral intake of ipecacuanha syrup. Since ipecacuancha is known to release 5-hydroxytryptamine (5-HT), those workers concluded that propofol may have a weak 5-HT antagonistic effect. Cechetto et al. (2001) examined the effect of propofol on rat brain stem in the experiments using three techniques: immunohistochemistry, high-

performance liquid chromatography, and electrophysiology. They proposed that the reduced 5-HT levels in the area postrema and cerebrospinal fluid may explain the antiemetic property of propofol but that propofol may also act directly on the neurons in area postrema via the γ-aminobutyric acid-A ($GABA_A$) receptor to reduce their activity. Chassard et al. (2002) studied the effects of subhypnotic doses of propofol on gastric emptying in volunteers. They found that antiemetic properties of propofol were not peripheral, and stated that propofol cannot be considered a gastric prokinetic agent.

In their meta-analysis of 84 studies involving 6069 patients, Tramer et al. (1997a) compared the effect of either induction or maintenance with propofol and other anesthetics on PONV. The protective effect of propofol against PONV was not evident when it was used as an induction drug only. The decrease of early (0–6 h) PONV (NNT 5) was found when propofol was used both as the induction and maintenance agent within the control event rate of 20–60 %. However, after 6 hours, the beneficial effect of propofol was lost. Propofol for both induction and maintenance and without nitrous oxide i.e. in total intravenous anesthesia (TIVA) appeared to be promising also in the prevention of late (up to 48 h) PONV. However, the lack of relevant data did not allow any wide-ranging conclusions to be drawn (Tramer et al. 1997b). Sneyd et al. (1998) stated in their meta-analysis, sponsored by the manufacturer of propofol, that patients who received maintenance of anesthesia with propofol had a significantly lower incidence of PONV (NNT 7–8) in comparison with inhalational agents regardless of the induction agent, choice of inhalation agent, or presence/absence of nitrous oxide. Subsequently, the antiemetic efficacy of TIVA with propofol was confirmed in Apfel's multicenter study (Apfel et al. 2004b). In this study, substituting propofol for a volatile anesthetic reduced the risk of PONV by about 19 %, whereas substituting nitrogen for nitrous oxide reduced the risk by about 12 %. Combining these two anesthetic management strategies (i.e. TIVA with propofol) reduced the risk by about as much as could be achieved with any single antiemetic (ondansetron 4 mg, droperidol 1.25 mg, or dexamethasone 4 mg IV).

The continuous propofol infusion, also in subhypnotic doses, has been shown to possess antiemetic effects when used in combination with intravenous PCA with fentanyl (Kim et al.2000). In this study, the effective doses of propofol were 0.9 and 1.2 mg/kg/h, however, with the latter dose, more sedation was reported 4 h after surgery.

In conclusion, propofol has an antiemetic effect when used in the maintenance of anesthesia but not when administered only for induction of anesthesia.

4.2.2 Supplemental oxygen

The proposal that oxygen inhalation could prevent PONV was presented originally by Overdyk and Roy (1997) in a letter to the editor. In that letter they pointed out that the data of meta-analysis of Hartung (1996) concerning nitrous oxide as an emesis inducing anesthetic might support also an antiemetic efficacy of 100 % oxygen. Thereafter, Greif et al. (1999) showed in patients undergoing colon resection that supplemental 80 % oxygen intraoperatively and for 2 hours after surgery decreased the incidence of PONV from 30 % to 17 % compared with 30 % oxygen. The same study group (Goll et al. 2001) confirmed the beneficial effect of supplemental 80 % oxygen on PONV in the patients undergoing gynecologic laparoscopy. In that study, the

administration of supplemental 80 % oxygen was restricted to the intraoperative period, and oxygen was compared with ondansetron 8 mg IV administered immediately after the induction of anesthesia. The incidence of PONV decreased from 44 % after 30 % oxygen to 22 % after 80 % oxygen, and to 30 % after ondansetron. The investigators claimed that supplemental oxygen was effective in the prevention of PONV, and that ondansetron was no more effective than supplemental oxygen. In contrast to the results of Greif et al. (1999) and Goll et al. (2001), the antiemetic efficacy of supplemental oxygen has been questioned in three subsequent studies (Joris et al. 2003, Apfel et al. 2004b, Treschan et al. 2005). In patients undergoing thyroidectomy, administration of 80 % oxygen intraoperatively and for 2 h after surgery failed to prevent PONV, while droperidol did reduce the incidence of nausea (Joris et al. 2003). In the multicenter study by Apfel et al. (2004b) supplemental oxygen did not reduce PONV. In that study, a total of 280 patients received 80 % oxygen in nitrogen. The incidence of PONV was 31 % after 80 % oxygen and 24 % after 30 % oxygen in nitrogen. Further, after strabismus surgery, there was no difference in the incidence of PONV in patients (both adults and children) receiving 30 % or 80 % oxygen or 30 % oxygen with ondansetron IV (Treschan et al. 2005). Thus, on the basis of the published data, the antiemetic effect of supplemental oxygen has remained unresolved.

The mechanism by which supplemental oxygen might reduce PONV is unclear. It has been speculated that patients undergoing colon resection or laparoscopy are subject to subtle intestinal ischemia, and this ischemia might be ameliorated by supplemental oxygen (Greif et al. 1999, Goll et al. 2001). Any reduction in intestinal ischemia would presumably decrease the release of serotonin and other emetogenic substances from the compromised bowel (Marston 1977), and thus also decrease the risk of PONV. After thyroid surgery PONV may apparently arise by a different mechanism, for example, by vagal irritation due to the dissection of the recurrent laryngeal nerve during surgery, or via nociceptive reflexes from the pharynx and larynx after surgery (Joris et al. 2003).

Although supplemental oxygen has proven to be essentially risk-free (Greif et al. 1999, Goll et al. 2001), some undesired side events are linked with its use. First, high concentrations of oxygen are associated with absorption atelectasis (Magnusson and Spahn 2003). However, there are conflicting opinions about whether this atelectasis is clinically significant (Joyce and Baker 1995, Rothen et al. 1996, Akça et al.1999). Second, high inspired oxygen concentrations (i.e. 100 %) directly injure pulmonary tissue (Knight and Holm 2000). Subtle changes exist after 6 h of exposure, and they are clearly demonstrable after 24 h. However, such disadvantageous circumstances seem to be unlikely to occur in mostly short-term surgery. Third, the use of extra oxygen during surgery increases the risk of surgical fire (ECRI 2003).

Although the Consensus guidelines (Gan et al. 2003) recommend supplemental oxygen for the prevention of PONV, its efficacy in this respect is unclear and needs to be confirmed in further studies.

4.2.3 Other methods

Omitting nitrous oxide in anesthesia regimen can slightly decrease the risk of postoperative emesis, especially in patients at a high risk for PONV (Divatia et al. 1996,

Hartung 1996, Tramer et al. 1996, Apfel et al. 2004b). However, omitting nitrous oxide has no influence on nausea (Divatia et al. 1996, Tramer et al. 1996).

Antagonism of neuromuscular blockade with high doses of anticholinesterase drugs such as neostigmine and edrophonium has been claimed to be associated with PONV (Watcha 2002). Avoidance of high doses of neostigmine (> 2.5 mg) can reduce PONV but the risk of possible residual muscle paralysis has to be noted (Tramer and Fuchs-Buder 1999a, Fuchs-Buder and Mencke 2001). However, in the latest meta-analysis, the use of neostigmine, accompanied by either atropine or glycopyrrolate, showed no increased risk for PONV (Cheng et al. 2005).

The use of the Bispectral Index (BIS) monitoring for titration of general anesthesia agents may allow the use of less anesthetics compared with a regimen without monitoring, thus possibly decreasing side effects such as PONV. In the recent meta-analysis into the effects of BIS monitoring on ambulatory anesthesia, the use of BIS reduced anesthetic consumption by 19 % but the incidence of PONV was reduced only modestly from 38 to 32 % (Liu 2004).

To avoid opioid-related nausea and vomiting, alternative methods for pain management have been proposed (Wheeler et al. 2002, Gan et al. 2003). Using local anesthetics or combining different analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol have been claimed to prevent PONV (Kehlet and Dahl 2003). Although their opioid sparing effect has often been demonstrated, the results in decreasing PONV have until now been less satisfying (Aubrun et al. 2003, Romsing et al. 2005, Straube et al. 2005). However, in a recent meta-analysis, including 2307 patients, Marret et al. (2005) demonstrated that NSAIDs combined with intravenous morphine PCA decreased significantly PONV by 30 %, and decreased nausea alone by 12 % and vomiting alone by 32 %.

When combined with the use of PCA opioid, low-dose infusions of centrally acting opioid receptor antagonists, like naloxone and nalmefene, have been shown to prevent nausea, vomiting, and the need for rescue antiemetics (Gan et al. 1997b, Joshi et al. 1999).

It is known that central opioid receptors inhibit emesis whereas peripheral receptors, also those in the CTZ, induce emesis (Bates et al. 2004). Peripherally acting opioid antagonists represent a new mechanism for antagonizing opioid related PONV. These drugs may block the peripheral actions of opioids without affecting centrally mediated analgesia. Methylnaltrexone, a peripheral opioid antagonist, when administered IV does not cross the blood brain barrier. It has been shown that methylnaltrexone decreases vomiting by 45 % in patients undergoing gynecologic laparoscopy (Moerman et al. 1995). Another antagonist, alvimopan, is absorbed after an oral dose only poorly (0.03 %), thus influencing mainly the intestinal opioid receptors (Schmidt 2001). In one study, oral alvimopan significantly reduced nausea and vomiting after laparotomy (Taguchi et al. 2001).

There is increasing data that perioperative IV administration of fluids is effective in decreasing of PONV (Yogendran et al. 1995, Ali et al. 2003, Magner et al. 2004, Maharaj et al. 2005). It has been speculated that the beneficial effect of hydration might be produced by a correction of intravascular volume deficits, thereby minimizing splanchic ischemia, a potential cause of PONV (Ali et al. 2003, Magner et al. 2004, Maharaj et al. 2005). In patients undergoing major non-cardiac surgery, a combination

of colloid and crystalloid fluid resuscitation was associated with less PONV and less use of rescue antiemetics compared with the administration of crystalloids alone (Moretti et al. 2003). However, further studies are needed to determine whether colloid fluids are better than crystalloid fluids in the prevention of PONV.

4.3 Miscellaneous therapies

The antiemetic effect of benzodiazepines in the prophylaxis of postoperative vomiting (POV) has been reported in children (Khalil et al. 1992, Splinter et al. 1995). In a recent study in adult patients, midazolam as a continuous infusion at a dose of 0.02 mg/kg/h was a more effective antiemetic than ondansetron at a dose of 0.1 mg/kg IV every 6 h in the prevention of PONV after cardiac surgery. The authors speculated that possible antiemetic mechanisms might be GABA receptor antagonism, inhibition of dopamine release, and anxiolytic effects (Sanjay and Tauro 2004).

Cannabinoids have been shown to have antiemetic effects, especially in chemotherapy-induced sickness (Tramer et al. 2001c). However, only one study about cannabinoids has been published in the prevention of PONV. According to that study, nabilone did not prevent PONV in women undergoing gynecologic laparotomy (Lewis et al. 1994). The psychotropic activity of cannabinoids can cause undesired side effects such as dysphoria, depression, hallucinations, and paranoia. These symptoms limit the usefulness of the present cannabinoid drugs in clinical practice (Tramer et al. 2001c).

Clonidine (an α_2-adrenergic agonist) given as a single dose of 2 μg/kg IV at induction of anesthesia increased the number of PONV-free women undergoing breast surgery compared with placebo (Oddby-Muhrbeck et al. 2002). The treatment group had in addition, a significant reduction in blood pressure and a lower heart rate after surgery but these effects were not judged to be of clinical importance. Further studies are needed to define the efficacy and side effect profile of clonidine in the prophylaxis of PONV.

As alternative methods to the pharmacological prevention of PONV, techniques in the area of acupuncture have been studied. These include traditional acupuncture, electro-acupuncture, laser acupuncture, trancutaneous electrical nerve stimulation, acupoint stimulation and acupressure (Lee and Done 2004). In particular, stimulation of the wrist at the Pericardium (P_6) acupuncture point has been studied in the prevention of PONV. The mechanism by which P_6 acupoint stimulation prevents PONV has not been established (Lee and Done 2004, Rowbotham 2005). A recent meta-analysis concluded that the use of P_6 acupoint stimulation was effective in the prevention of PONV compared with no antiemetic prophylaxis. In addition, compared with antiemetic prophylaxis, P_6 acupoint stimulation seemed to reduce the risk of nausea but not that of vomiting. The precise point of stimulation was suggested to be more important than the method itself (Lee and Done 2004). White et al. (2005a) studied the optimal timing (before or after surgery, or both) for P_6 acupoint stimulation in the prevention of PONV. They found that acustimulation at P_6 point was most effective when it was applied after surgery.

4.4 Combinations of antiemetics and a multimodal approach

None of the available antiemetics is definitely effective for preventing PONV, at least in high risk patients (Habib and Gan 2004b). The use of a single antiemetic agent typically reduces the incidence of PONV by up to 30 % because one agent cannot block all the receptors involved in the emetic process (Gan 2002a). A better prophylaxis may be achieved using a combination of agents acting at different receptor sites (Habib and Gan 2004b). The multifactorial study by Apfel et al. (2004b) showed that antiemetic interventions with different mechanisms of action have additive (rather than synergistic) effects on the incidence of PONV, and that they act independently of one another.

In the combination therapy for prophylaxis of PONV 5-HT_3 receptor antagonists, droperidol, and dexamethasone have been shown to be effective (Eberhart et al. 2000b, Henzi et al. 2000a, Habib et al. 2004a, Apfel et al. 2004b). In combinations, it is useful to utilize the advantages of each antiemetic drug. For instance, ondansetron has a better antivomiting than antinausea efficacy, and there is an increased risk for headache (Tramer et al. 1997b). With droperidol, there is more antinausea and less antivomiting efficacy, and some protection might exist against headache (Henzi et al. 2000b). Therefore, a combination of these two drugs might be beneficial. Combinations with older antiemetics have also shown to be advantageous, for instance cyclizine combined with ondansetron (Ahmed et al. 2000), and dimenhydrinate with droperidol (Turner et al. 2004).

A combination of several potentially beneficial interventions (multimodal approach) may further lead to an improved outcome in PONV prophylaxis (Gan et al. 2003). Apfel et al. (2004b) emphasized that multiple interventions should be reserved only for those patients at high risk, or in whom nausea and vomiting would be especially dangerous. Many algorithms have been presented for multimodal management of PONV (Gan et al. 2003, Apfel et al. 2004b, Habib and Gan 2004b). In the consensus guidelines (Gan et al. 2003), the first step in reducing PONV risk is to reduce the baseline risk. This can be achieved, for instance, as follows: propofol for induction and maintenance of anesthesia, administration of supplemental oxygen, adequate intravenous hydration, avoidance of emetic anesthetics such as nitrous oxide, volatile inhaled anesthetics and large doses of neostigmine, and minimizing the use of intraoperative and postoperative opioids. In addition, non-pharmacologic acupuncture therapies should be considered, and furthermore, a combination therapy with two or three prophylactic antiemetics from different classes should be administered. The multimodal approach has been shown to be very effective in the prevention of PONV (Scuderi et al. 2000, Eberhart et al. 2002b, Habib et al. 2004c). For instance, Scuderi et al. (2000) tested a multimodal approach in high risk patients undergoing gynecologic laparoscopy. Their algorithm consisted of midazolam premedication, induction and maintenance of anesthesia with propofol and remifentanil, no nitrous oxide, no neuromuscular blockade, use of 80 % oxygen, aggressive IV hydration (25 mL/kg), triple combination of prophylactic antiemetics (ondansetron 1 mg, droperidol 0.625 mg, and dexamethasone 10 mg), and ketorolac. Such a multimodal approach resulted in a 98 % complete response rate (no PONV and no rescue) in PACU. Post-discharge vomiting occurred in 12 % of patients in the multimodal group compared with 21 % in the ondansetron and 32 % in the placebo group.

In conclusion, a multimodal management strategy leads to the best results in the prophylaxis of PONV, and it should be focused mainly on patients at high risk for PONV.

5 Treatment of established postoperative nausea and vomiting

There is a paucity of data on the use of antiemetics for the treatment of PONV in patients who had unsuccessful prophylaxis or did not receive any antiemetic therapy (Habib and Gan 2004b). Before initiating pharmacologic intervention for treating established PONV, the first action should be to exclude the medical factors for the symptoms such as some emetic medication or mechanical factors such as PCA with opioids, blood draining down the throat, increased brain pressure, or abdominal obstruction (Gan et al. 2003). The 5-HT_3 receptor antagonists are the most commonly utilized drugs in rescue trials. Kazemi-Kjellberg et al. (2001) in their meta-analysis on the treatment of PONV did not find any evidence for a clinically relevant dose-response of the 5-HT_3 receptor antagonists. Therefore, they recommended the smallest effective dose should be used for the treatment: ondansetron 1mg, dolasetron 12.5 mg, granisetron 0.1 mg and tropisetron 0.5 mg. It is not known why minimal amounts of 5-HT_3 receptor antagonists block the receptors in the vomiting patient but much higher doses are needed when these drugs are used in prophylaxis. In the above mentioned meta-analysis, NNT to prevent further vomiting within 24 h with the 5-HT_3 antagonists was 4–5, however the anti-nausea effect was less pronounced. The results of propofol in the treatment of PONV were contradictory, and for other antiemetics there was a lack of data.

If antiemetic prophylaxis fails, and PONV occurs within 6 h after surgery, a drug from a different class has been suggested to be used for rescue (Kovac et al. 1999, Gan et al. 2003). Thus, for example the failure of prophylaxis with a 5-HT_3 antagonist should be treated with droperidol, promethazine or dimenhydrinate (Kreisler et al. 2000, Habib and Gan 2005). When PONV occurs more than 6 h after surgery, it should be treated with any of the agents used for prophylaxis except dexamethasone and scopolamine, which are longer lasting (Habib and Gan 2003b). In addition, the effect of dexamethasone may not begin until 2 h after its administration (Wang et al. 2000).

6 Costs in the prevention of postoperative nausea and vomiting

The increasing awareness of cost-effectiveness is important in an era of growing economic constraints on the health care budget (Watcha 2002). Economic evaluations of interventions have been undertaken to ensure that the best use is achieved with limited resources. Costs associated with PONV include drug acquisition costs, equipment to administer the medication, drugs and materials used to manage emesis, incremental costs for personnel time, and costs associated with delay in leaving the PACU and unplanned hospital admission (Watcha and White 1997, Hill et al. 2000).

One economically important aspect concerning the managing strategy of PONV is the issue of whether to use prophylactic drugs or wait for the patients to be treated when they have established the symptoms (White and Watcha 1999, Tramer 2004). With PONV prophylaxis, some patients will receive anti-emetic therapy without actually

needing it, whereas others will still experience PONV despite receiving prophylaxis. Prophylaxis to all patients entails extra costs. In a cost incremental analysis (cost/additional patient who benefits from a change in clinical practice), prophylaxis with ondansetron in all patients has been shown to be less cost-effective than treatments of existing PONV with the same drug (Tramer et al. 1999c). However, in selective surgical patients at high risk for PONV, it has been demonstrated that prophylactic antiemetic use is cost-effective and is associated with greater patient satisfaction compared to no prophylaxis (Hill et al. 2000). In this study of Hill et al. (2000), the use of 1.25 mg droperidol IV was associated with greater effectiveness, lower costs, and similar patient satisfaction compared with 0.625 mg droperidol IV and 4 mg ondansetron IV. In another study, both droperidol 0.625 mg and 1.25 mg IV were cost-effective when compared with ondansetron 4 mg IV and placebo (Tang et al. 1996).

The cost-effectiveness of prophylaxis depends on the underlying risk. The calculated risk scores may be beneficial in targeting prophylaxis toward those patients who actually need it, and this will have beneficial economical implications (Tramer 2004). In addition to the risk for PONV, the cost-effectiveness depends on the costs and effectiveness of the drugs used for prophylaxis. The incidence of PONV at which prophylaxis was more cost-effective than waiting till treating symptoms in the PACU was 33 % for ondansetron and 10 % for droperidol (Watcha and Smith 1994). Since the different 5-HT_3 receptor antagonists have comparable efficacy and safety profiles, it has been concluded that the acquisition cost would be the main factor that differentiates the 5-HT_3 compounds from one another, and the least expensive drug should to be used (Zarate et al. 2000, Gan et al. 2003). Dexamethasone is an inexpensive antiemetic, and it has been recommended for prophylaxis alone and in combinations (Henzi et al. 2000a, Apfel et al. 2004b). Propofol is regarded as an expensive anesthetic (Smith et al. 1999). In one study, the costs of propofol anesthesia (for induction and maintenance) were over three times greater than those of inhalational anesthesia with isoflurane-nitrous oxide (Visser et al. 2001). In that study, the costs of preventing PONV in one additional patient by using propofol anesthesia instead of isoflurane were $US174 in inpatients and $US75 in outpatients. At present, traditional antiemetics (for example haloperidol and antihistamines) have again become a target of interest because of their low costs (Buttner et al. 2004).

In the study of Hill et al. (2000) most of the costs (70–80 %) associated with PONV were from nursing labor costs from prolonged PACU stay as a result of persistent nausea and vomiting or the adverse effects of antiemetics. Thus, the cost-effectiveness of prophylactic antiemetic therapy will depend on where the procedure is performed. For instance, nursing labor costs are more likely to be directly related to the duration of PACU stay in an office-based setting, and to a lesser extent in an ambulatory surgery unit, whereas prolonged PACU stay may not have a significant impact on nursing labor costs in an inpatient hospital setting, unless the actual numbers of nursing staff can be reduced (Habib and Gan 2003b). However, in the study of Hill et al. (2000), the exclusion of nursing labor from the calculated costs did not alter the conclusion that droperidol 1.25 mg was superior over droperidol 0.625 mg and ondansetron 4 mg.

In a recent editorial, White (2004) stated that prophylactic use of antiemetics has become the standard approach to minimizing emetic symptoms after surgery because patients are more satisfied with this approach than with the treatment of symptoms

when they occur in the postoperative period. In addition, patients have expressed their willingness to pay out of their own pocket to avoid the discomfort of PONV (Gan et al. 2001). However, White (2004) advised caution with the use of the newer, more expensive antiemetics (5-HT_3 receptor antagonists and NK_1 receptor antagonists), and to resort to preferably even two inexpensive antiemetics (for example droperidol and dexamethasone). However, many factors that depend on local policies and cultural habits may influence the question as to whether prophylaxis or treatment of PONV is more cost-effective (Tramer 2004). The local circumstances should need to be taken into account when choosing drugs and strategies in the management of PONV.

AIMS OF THE STUDY

The purpose of this thesis was to evaluate different antiemetic interventions in the prophylaxis of PONV in women undergoing elective surgery under general anesthesia.

The more specific aims were:

- To compare the efficacy of two antiemetic drugs, tropisetron and droperidol IV, as single prophylaxis of PONV in gynecologic incontinence surgery. In addition, the side effect profile of both antiemetics was evaluated (Study I).

- To compare the antiemetic efficacy and costs of three different anesthesia regimens: propofol-air/O_2 anesthesia and isoflurane-nitrous oxide anesthesia with or without oral ondansetron (Study II).

- To test the hypothesis that perioperative supplemental 80 % oxygen is more effective than 30 % oxygen in the prevention of PONV after ambulatory gynecologic laparoscopy (Study III), or in breast surgery using ondansetron as an active control (Study V).

- To test the hypothesis that perioperative supplemental 50 % oxygen is more effective than 30 % oxygen in prophylaxis of PONV in breast surgery (Study IV).

- To determine whether patient satisfaction after surgery is associated with the incidence of PONV and the antiemetic intervention (Studies I–V).

PATIENTS AND METHODS

1 Patients

A total of 590 female patients were studied in five clinical studies (Studies I–V). All studies were approved by the Ethics Committee of Kuopio University Hospital. Informed (Study I) or written, informed (Studies II–V) consent was obtained from all patients. Women undergoing elective gynecologic incontinence surgery (Study I), gynecologic laparoscopy (Studies II–III), and breast surgery (Studies IV–V) under general anesthesia were recruited.

Exclusion criteria were as follows: nausea or vomiting or antiemetic drugs within 24 h before the surgery, contraindications to the anesthetics used (Studies I–V), pregnancy, breast feeding, obesity (BMI > 30 kg/m^2), pulmonary disease, abuse of alcohol or drugs (Studies III–V) or diabetes (Study V).

2 Study designs

All Studies I–V were prospective, randomized and controlled. Study I was double blind. Study II was double blind for ondansetron and single blind for the anesthetic technique used. In Studies II–V, the nurses assessing PONV were blinded to the antiemetic intervention that the patients had received. The patients were randomized using a computer-generated random number table. A summary of the study designs is presented in Table 4.

Study I. The aim of this study was to evaluate the antiemetic efficacy and adverse effect profile of tropisetron and droperidol compared with placebo. Altogether 150 women undergoing gynecologic incontinence surgery were randomly assigned to receive either tropisetron 5 mg (n = 50), droperidol 1.25 mg (n = 50), or saline IV (n = 50) within 15 min before the end of surgery. The antiemetic efficacy was measured by the proportion of patients with no PONV within the first 48 h after surgery. In addition, the incidences of nausea (without retching and vomiting), retching, vomiting, and adverse effects were recorded.

Study II. The study compared the antiemetic efficacy and costs associated with three different anesthesia regimens. A total of 150 women scheduled for gynecologic laparoscopy were randomly assigned to three study groups: 1) preoperative placebo tablet, propofol induction, propofol-air/O_2 maintenance (n = 50); 2) preoperative 8-mg ondansetron tablet, thiopental induction, isoflurane-nitrous oxide maintenance (n = 50); 3) preoperative placebo tablet, thiopental induction, isoflurane-nitrous oxide maintenance (n = 50). The primary outcome for the efficacy in the prevention PONV was the incidence of PONV (any nausea, vomiting/retching, or both) within the first 24 h after surgery. In addition, the costs of three anesthetic interventions PONV were compared.

Study III. The efficacy of supplemental 80 % oxygen in the prevention of PONV was evaluated in 100 women undergoing ambulatory gynecologic laparoscopy. The patients were randomly assigned to receive either routine 30 % oxygen (n = 50), or supplemental 80 % oxygen (n = 50) during surgery and up to 1 h after surgery. The

primary outcome was the incidence of PONV (any nausea, vomiting/retching, or both) within the initial 24 h after surgery.

Study IV. The efficacy of supplemental 50 % oxygen in the prevention of PONV was evaluated in breast surgery. One hundred women were randomly assigned to two groups: administration of routine 30 % oxygen (n = 50), or supplemental 50 % oxygen (n = 50). Oxygen was administered during surgery and up to 2 h afterwards. The primary efficacy variable was the incidence of PONV (any nausea, vomiting/retching, or both) within the first 24 h after surgery.

Study V. The efficacy of supplemental 80 % oxygen in the prophylaxis of PONV was studied. A dose of 4 mg of ondansetron was used as the positive control. Ninety patients were randomly assigned to three groups: 1) 30 % oxygen and saline 2 mL IV at the end of surgery, 2) 80 % oxygen and saline 2 mL IV, 3) 30 % oxygen and ondansetron 4 mg IV. The primary outcome was the incidence of the total response (no nausea, no vomiting or retching) over the initial 24 h after surgery.

3 Methods

3.1 Risk scores

The probability of the patients with postoperative vomiting (POV) was assessed with the risk score devised by Apfel et al. (1998) in Study III. The score is based on patient related risk factors and length of anesthesia (being female, young, nonsmoking, having a history of motion sickness or postoperative vomiting and duration of anesthesia). The probability of postoperative vomiting was estimated from the equation: postoperative vomiting = $1 / (1 + e^{-z})$, where z = 1.28 x (gender) - 0.029 x (age) - 0.74 x (smoking) + 0.63 x (history of POV or motion sickness) + 0.26 x (duration) - 0.92 when the variables are coded as follows: gender (male = 0, female = 1), age (in years), smoking status (no = 0, yes = 1), history of motion sickness and/or POV (no = 0, yes = 1) and duration of anesthesia (in hours).

The simplified risk score for PONV devised by Apfel et al. (1999) was used in Studies II, IV and V. The risk factors were female sex, nonsmoking status, history of PONV or motion sickness, and the use of postoperative opioids. The incidence of PONV with the presence of none, one, two, three, or all four risk factors was 10 %, 21 %, 39 %, 61 %, and 79 %, respectively. In Study II, the mean risk (%) for PONV in the study group was calculated as follows: at first the simplified risk score for every patient was calculated, then this score was converted to the corresponding risk percent, and finally the mean risk percent in the study group was calculated.

3.2 Anesthesia

All the studies were carried out using a standardized general anesthesia technique (Table 4). Patients were premedicated with oral diazepam or midazolam approximately 1 h before anesthesia (Studies I–II, IV–V). In Study III, the patients received midazolam IV at the induction. Anesthesia was induced with thiopental or propofol. For the

Table 4. Patients and study designs.

	Study I	Study II	Study III	Study IV	Study V
Number of patients	150	150	100	100	90
ASA	I–III	I–II	I–II	I–III	I–III
Type of surgery	Gynecologic incontinence surgery	Gynecologic laparoscopy	Ambulatory gynecologic laparoscopy	Breast surgery	Breast surgery
Study design	Prospective, randomized, double blind, placebo-controlled	Prospective, randomized, observer blind, controlled	Prospective, randomized, observer blind, controlled	Prospective, randomized, observer blind, controlled	Prospective, randomized, observer blind, controlled
Prophylactic antiemetic intervention	• Tropisetron 5 mg • Droperidol 1.25 mg	• Propofol-air/O_2 anesthesia and placebo • Isoflurane-nitrous oxide anesthesia and ondansetron 8 mg	• 80% oxygen	• 50% oxygen	• 80% oxygen • 30% oxygen and ondansetron 4 mg
Placebo or control	• Saline	• Isoflurane-nitrous oxide anesthesia and placebo	• 30% oxygen	• 30% oxygen	• 30% oxygen
Dosing regimen of antiemetic intervention and placebo/ control	IV within 15 min before the end of surgery	Oral ondansetron or placebo tablet 1 h before surgery	During surgery and up to 1 h after surgery	During surgery and up to 2 h after surgery	Oxygen during surgery and up to 2 h after surgery ondansetron or saline IV at the end of surgery
Premedication	Diazepam 10-20 mg PO	Midazolam 7.5-15 mg PO	Paracetamol 2 g PO	Diazepam 10-15 mg PO	Diazepam 10-15 mg PO
Induction of anesthesia	Thiopental 3-5 mg/kg Fentanyl 2 µg/kg	Thiopental 4-5 mg/kg or propofol 2-2.5 mg/kg Fentanyl 2 µg/kg	Propofol 2-2.5 mg/kg Midazolam 20 µg/kg Fentanyl 2 µg/kg, Glycopyrrolate 0.2 mg	Propofol 2-2.5 mg/kg Fentanyl 2 µg/kg	Propofol 2-2.5 mg/kg Fentanyl 2 µg/kg

	Study I	Study II	Study III	Study IV	Study V
Maintenance of anesthesia	70 % nitrous oxide in oxygen and isoflurane	67% nitrous oxide in oxygen and isoflurane or propofol infusion	Sevoflurane	Sevoflurane	Sevoflurane
Intraoperative analgesia	Fentanyl 1 μg/kg at the beginning of surgery and every 30 min thereafter	Fentanyl 1 μg/kg at the beginning of surgery and every 30 min thereafter	Ketoprofen 200 mg IV at the beginning of surgery	Fentanyl 1 μg/kg at the beginning of surgery and every 45 min thereafter	Fentanyl 1 μg/kg at the beginning of surgery and every 45 min thereafter
Muscle relaxation	Vecuronium	Vecuronium	Rocuronium	Rocuronium	Rocuronium
Reversal of muscle relaxation	Neostigmine 2.5 mg and glycopyrrolate 0.5 mg	Neostigmine 2-2.5 mg and glycopyrrolate 0.4-0.5 mg	Neostigmine 2.5 mg and glycopyrrolate 0.5 mg	Neostigmine 2.5 mg and glycopyrrolate 0.5 mg	Neostigmine 2.5 mg and glycopyrrolate 0.5 mg
FiO_2	30%	33% or 47%	30% or 80%	30% or 50%	30% or 80%
Fresh gas flow	3 L/min	3 L/min	3 L/min	3 L/min	1.5 L/min
Postoperative analgesia	Oxycodone 0.12 mg/kg IM or 0.06 mg IV	Fentanyl 1 μg/kg IV in the PACU, oxycodone 0.12 mg/kg IM on the ward Rectal ketoprofen 100 mg after surgery, then oral ketoprofen 100 mg every 8 h	Fentanyl 1 μg/kg IV in the hospital Oral ibuprofen or/ and paracetamol after discharge from the hospital	Oxycodone 0.1 mg/kg IM or 0.05 mg IV Propacetamol 2 g IV after surgery, then oral paracetamol 1g every 8 h	Oxycodone 0.1 mg/kg IM or 0.05 mg IV Paracetamol 1 g IV every 8 h
IV-fluids during surgery	Not standardized	Not standardized	Crystalloids 15 mL/kg/h during surgery	Crystalloids 10 mL/kg/h during the first hour, thereafter, 5 mL/kg/h until the end of surgery	Crystalloids 10 mL/kg/h during the first hour, thereafter, 5 mL/kg/h until the end of surgery

maintenance of anesthesia, the patients received isoflurane with nitrous oxide, sevoflurane or propofol infusion. Isoflurane was administered at end-tidal concentration 0.5–1.5 %. Propofol was given at an infusion rate of 6–12 mg/kg/h but changes were made when necessary, with bolus increments of 0.5 mg/kg to maintain adequate anesthesia. In Studies III–V, anesthesia was maintained with sevoflurane (end-tidal sevoflurane concentration was a minimum of 1 alveolar anesthetic concentration [MAC]). In cases of inadequate anesthesia, the sevoflurane concentration was increased in steps of 0.3 MAC, and after stabilization, the concentration was decreased to 1 MAC. In all studies, fentanyl was used for analgesia, and muscle relaxation was achieved with vecuronium or rocuronium. At the end of surgery, neuromuscular block was reversed with neostigmine and glycopyrrolate, and the stomach was emptied by suction before the tracheal extubation. Bradycardia (heart rate < 50 bpm) was treated with atropine 8 μg/kg in all studies. Hypotension (mean arterial pressure < 60–65 mmHg) was treated with ethylephrine 2mg IV (Study IV), or phenylephrine 0.1 mg IV (Study V).

Monitoring consisted of heart rate, ECG, noninvasive blood pressure, oxygen saturation (SpO_2), FiO_2, end-tidal carbon dioxide, and end-tidal anesthetic concentration. In addition, esophageal temperature was measured in Studies III–V.

3.3 Ventilation and administration of supplemental oxygen

In the beginning of anesthesia, all patients were ventilated with 100 % oxygen until tracheal intubation. Thereafter, they were normoventilated ($ETCO_2$ 4.2–5.3 kPa) with the gas mixture shown in Table 4. At the end of the operation, after reversing the neuromuscular block, the patients were ventilated with 100 % oxygen until tracheal extubation.

Supplemental oxygen was administered during surgery and up to 1–2 h afterwards in Studies III–V. In these studies, also a positive end-expiratory pressure (PEEP) of 6 mmHg was used during surgery. After surgery, the specified oxygen concentration was mixed in the oxygen blender of the Servo ventilator and given at a rate of 20 L/min. To prevent dilution of the gas composition with air, patients breathed through an adhesive continuous positive air pressure mask without a PEEP valve. A 40-cm piece of breathing tube was joined with a Y-connector to the mask to form the oxygen reserve. The fraction of inspired oxygen was measured under the mask at the beginning of postoperative oxygen administration (Studies III–V) and once again 1 h later (Studies IV–V).

3.4 Assessment and treatment of postoperative symptoms

Assessments of postoperative symptoms and the rescue antiemetics are presented in Table 5, and treatment of pain in Table 4.

3.4.1 Postoperative nausea and vomiting

Specifically trained nurses who were unaware of the antiemetic intervention assessed separately the incidence of nausea, retching and vomiting at the end of each study period. Vomiting was defined as a forceful expulsion of gastric contents involving

the rhythmic contraction of respiratory muscles including the diaphragm and abdominal muscles. Retching was the same as vomiting but without the expulsion of gastric contents.

Nausea was defined as an unpleasant sensation with the awareness of the urge to vomit. In Study I, nausea was included in retching or vomiting when they occurred simultaneously. Retching was included in vomiting except in Study I, where it was assessed separately. The number of emetic episodes (both retching and vomiting) was assessed to express the intensity of vomiting. The intensity of nausea was scored with a linear scale from 0 to 10 (0 = no nausea, 10 = nausea "extreme") (Studies II–V). All the data were collected in structured questionnaires. Patients discharged from the hospital during the study were interviewed by phone by trained nurses approximately 24 h after surgery (Studies II–III).

3.4.2 Pain and other symptoms

Assessment of pain and adverse events were conducted in connection with the assessment of nausea and vomiting. Pain (Studies I–V), anxiety (Studies I, III–V), drowsiness (Studies I–V) and sedation (Study I) were assessed with a numerical scale 0–10 (0 = none, 10 = extreme). In Studies III–V, sedation in the PACU was assessed by nurses on a four-point scale: 1 = awake, 2 = drowsy, 3 = asleep but easily arousable, and 4 = fast asleep. Side effects asked separately were: headache (Studies I–II), dyspnea (Studies III–V) and cough (Studies I, III–V). In addition, dizziness, tremor, pruritus, disturbances in hearing or seeing were inquired separately in Study I. Other adverse effects were recorded only if the patients spontaneously reported them.

3.4.3 Patient satisfaction

General satisfaction was assessed with a numeral scale 0–10 (0 = complete satisfaction, 10 = complete dissatisfaction) simultaneously with the assessments of PONV (Studies I–II). In Studies III–V, satisfaction with oxygen administration was evaluated at the end of the study, and in addition the patients were asked whether they would like to have the same kind of anesthesia in the future.

3.5 Recovery after surgery

The time from the end of surgery to extubation, ambulation, toleration of fluid and food (Studies II–V), and discharge from the hospital (Study III) was assessed. In addition, the time in the PACU was recorded (Studies I, III–V). Readiness to the Phase II unit was evaluated using the Aldrete score (Aldrete 1995) in ambulatory patients (Study III). In Study II, the time from the end of surgery to the time when the trained nurses evaluated the patients fit to return to the ward was noted.

Table 5. Assessments of symptoms and rescue antiemetics after surgery.

	Study I	Study II	Study III	Study IV	Study V
Assessment of PONV	Study periods 0-2 h, 2-6 h, 6-24, 24-48 h • nausea only (without retching or vomiting) • Retching • Vomiting	Study periods 0-1 h, 1-2 h, 2-24 h • Nausea with numerical scale (0-10) • Retching or vomiting (retching was included in vomiting category)	Study periods 0-30 min, 30-60 min, 60 min-time before admission to Phase II unit, time in Phase II unit, time from discharge from hospital-24 h • Nausea with numerical scale (0-10) • Retching or vomiting (retching was included in vomiting category) • Time from the end of surgery to the first PONV • Time from the end of surgery to the first rescue antiemetic	Study periods 0-1 h, 1-2 h, 2-6 h, 6-24 h • Nausea with numerical scale (0-10) • Retching or vomiting (retching was included in vomiting category) • Time from the end of surgery to the first PONV • Time from the end of surgery to the first rescue antiemetic	Study periods 0-1 h, 1-2 h, 2-6 h, 6-24 h • Nausea with numerical scale (0-10) • Retching or vomiting (retching was included in vomiting category) • Time from the end of surgery to the first PONV • Time from the end of surgery to the first rescue antiemetic
Rescue antiemetics	For nausea >10 min, retching, vomiting Metoclopramide 10 mg IV once per study period, except three times during the period 24-48 h	For nausea >15 min, retching, vomiting Metoclopramide 10 mg IV once per study period, except twice during the period 2-24 h	For nausea >15 min, the second emetic episode, at patients's request Ondansetron 1 mg IV twice, then droperidol 10 µg/kg once	For nausea >15 min, the second emetic episode, at patients's request Ondansetron 1 mg IV twice, then droperidol 10 µg/kg once	For nausea >15 min, the second emetic episode, at patients's request Droperidol 1.25 mg IV, then dexamethasone 5 mg, then ondansetron 4 mg

	Study I	Study II	Study III	Study IV	Study V
Other assessments	Numerical scale (0-10) • Pain • Anxiety • Drowsiness • Sedation (assessed by a nurse) • General satisfaction	Numerical scale (0-10) • Pain • Drowsiness • General satisfaction	Numerical scale (0-10) • Pain • Anxiety • Drowsiness • Satisfaction with oxygen administration Categorical scale • Sedation (assessed by a nurse in the PACU)	Numerical scale (0-10) • Pain • Anxiety • Drowsiness • Satisfaction with oxygen administration Categorical scale • Sedation (assessed by a nurse in the PACU)	Numerical scale (0-10) • Pain • Anxiety • Drowsiness • Satisfaction with oxygen administration Categorical scale • Sedation (assessed by a nurse in the PACU)

3.6 Costs

The costs of three different anesthesia regimens were compared in Study II. The acquisition costs of anesthetic drugs as well as costs of the disposables associated with their administration were recorded. Anesthetic drugs included ondansetron, hypnotics, opioids, muscle relaxants and their antagonists. Costs were based on the actual amount of drugs used. Isoflurane consumption was calculated with the formula: mL consumed = fresh gas flow rate (L/min) x % isoflurane) / 20 (Alhashemi et al. 1997). The volume of nitrous oxide was calculated from the fresh gas flow and the fraction of nitrous oxide during steady state anesthesia. The costs of rescue antiemetics were not included in the cost calculations of the anesthetic drugs.

3.7 Statistics

The power analyzes were executed in Studies II–V. In the estimation of the sample size, a 2-sided α level of 0.05, a power of 0.80 and an assumption that the incidence of PONV would decrease from 60 % (Studies II–IV) and 80 % (Study V) in the control groups to the half in the treatment groups were used. Continuous variables were analyzed by unpaired Student's t-test (Studies III, IV) or one-way ANOVA, followed by unpaired Student's t-test (Studies II, V). The non-parametric tests used were Mann-Whitney *U* test (Studies III, IV) or Kruskall-Wallis test followed by Mann-Whitney *U*-test (Studies I–II, V). Categorical variables were analyzed using χ^2 test. A Bonferroni correction for multiple comparisons was used when appropriate (Studies I–II, V). The level of significance was $P < 0.05$. All tests were performed using SPSS software.

In Study II, the NNT to prevent PONV (which indicates how many patients had to have received propofol-air/O_2 anesthesia or ondansetron to prevent PONV) was calculated as 1/absolute risk reduction compared with the patients without propofol-air/O_2 anesthesia or ondansetron. In addition, the costs of anesthetic drugs in preventing PONV in one additional patient were calculated as the anesthetic drug acquisition cost per patient multiplied by the NNT.

RESULTS

1 Patients

Altogether 590 patients were recruited of whom 14 were excluded from the studies: two patients for missing data (Study I), one for a protocol violation (Study III), two for reoperation (one in each Study IV and V), two patients interrupted the study due to profuse emesis (Study I), and seven because of an uncomfortable oxygen mask (three in Study IV and four in V). Thus, 576 patients were left in the analysis. Patient demographics and the risk for PONV calculated using Apfel's simplified risk assessment (Apfel et al. 1999) are presented in Table 6.

Table 6. Patient demographics and duration of anesthesia.

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Type of surgery	Gynecologic incontinence surgery	Gynecologic laparoscopy	Ambulatory gynecologic laparoscopy	Breast surgery	Breast surgery
Number of patients after exclusion	146	150	99	96	85
Age (yr)	51 ± 9	34 ± 8	36 ± 6	54 ± 11	53 ± 3
History of previous PONV	83 (57)	43 (29)	18 (18)	37 (39)	26 (31)
History of motion sickness	55 (38)	63 (42)	27 (27)	37 (39)	31 (36)
Non-smokers	NA	122 (81)	70 (71)	75 (78)	74 (87)
Calculated mean risk (%) for PONV according to Apfel et al. (1999)	NA	61 ± 15	55 ± 16	67 ± 13	67 ± 14
Duration of anesthesia (min)	146 ± 55	68 ± 41	43 ± 19	123 ± 51	128 ± 70

Values are expressed as mean ± SD or n (%). NA = not applicable.

2 The incidence of postoperative nausea and vomiting without antiemetic intervention

The data of PONV in the control groups after the different surgical procedures are presented in Figure 3. The overall incidence of PONV without prophylaxis during 24 h was 60/99 (61 %) after gynecologic laparoscopy (Studies II and III), 39/49 (80 %) after gynecologic incontinence surgery (Study I), and 65/77 (84 %) after breast surgery (Studies IV–V). The data of nausea in gynecologic incontinence surgery is not presented because nausea was assessed differently than in other studies, as nausea only or combined with retching or vomiting.

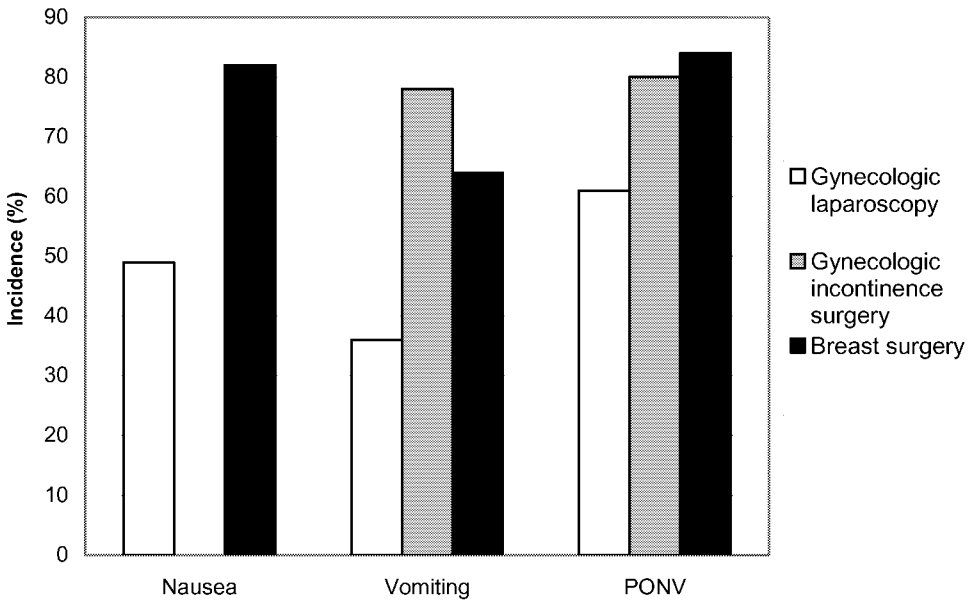

Figure 3. The incidence of PONV during 24 h after different types of surgery with no antiemetic intervention (Studies I–V).

3 Antiemetic interventions

3.1 Tropisetron compared with droperidol

After gynecologic incontinence surgery (Study I), there were more PONV-free patients after tropisetron 5 mg IV compared with placebo during the 24 h study period ($P < 0.05$) (Table 7). Tropisetron decreased vomiting (including retching) ($P < 0.05$), whereas droperidol failed to have any effect on PONV. The true incidence of nausea could not be defined because nausea was categorized to retching or vomiting when they occurred together. Nausea only (without retching and vomiting) did not differ between the study groups. The need of rescue antiemetic medications during the 24-h

observation period was decreased after both tropisetron and droperidol compared with placebo ($P < 0.05$).
During the first 2 h after surgery, the patients in the droperidol group felt drowsier than those in the placebo group, also the nurses evaluated the droperidol-treated patients as being more sedated than tropisetron-treated patients (Table 8). In addition, the patients felt more anxiety after droperidol compared with those after placebo during the study period 2–6 h. General dissatisfaction was more common in the patients after droperidol compared with tropisetron (0–6 h after surgery) and placebo (2–6 h after surgery). After 6 h from the end of surgery, there was no difference in the side effect profile between the study groups.

Table 7. The proportion (%) of patients without PONV, the incidence of nausea and vomiting (including retching), the need of rescue antiemetics, and NNT to prevent PONV in different study groups during 24 h after surgery.

	n	PONV-free %	Nausea %	Vomiting %	Emetic episodes per patient	NNT to prevent PONV	Rescue antiemetics %
Study I							
Tropisetron	48	31*	NA	50*	1.8†	9	42*
Droperidol	49	25	NA	71	3.3	∞	45‡
Placebo	49	20	NA	78	4.6		69
Study II							
Propofol + placebo	50	62	22	26	0.9	5	16
Isoflurane + ond	51	67§	27	22§	0.6§	4	22
Isoflurane + placebo	49	41	37	49	1.5		35
Study III							
80 % oxygen	49	45	53	25	0.9	14	27
30 % oxygen	50	38	62	24	0.8		20
Study IV							
50 % oxygen	47	11	85	51	1.5	-14	49
30 % oxygen	49	18	78	63	2.3		51
Study V							
80 % oxygen	29	17	79	66	2.7	17	48
30 % oxygen + ond	28	43‖	54¶	32**	0.9‖**	3	29
30 % oxygen	28	11	89	64	2.5		61

*$P < 0.05$ tropisetron versus placebo. † $P < 0.01$ tropisetron versus placebo. ‡$P < 0.05$ droperidol versus placebo. §$P < 0.05$ isoflurane + ond versus isoflurane + placebo. ‖$P < 0.05$ 30 % oxygen + ond versus 30 % oxygen. ¶$P < 0.01$ 30 % oxygen + ond versus 30% oxygen. **$P < 0.05$ 30 % oxygen + ond versus 80 % oxygen.
NNT = number needed to treat. NA = not applicable.
Isoflurane = isoflurane-nitrous oxide anesthesia. ond = ondansetron.

Table 8. Postoperative adverse effects during 24 h after gynecologic incontinence surgery evaluated with a numerical scale (0–10) (Study I).

	Tropisetron	Droperidol	Placebo
0-2 h			
• Pain	4 (2,7)	5 (5,7) *	5 (3,7)
• Anxiety	2 (0,5)	3 (1,5)	2 (1,5)
• Drowsiness evaluated by the patient	6 (4,8)	7 (5,8)†	5 (4,7)
• Sedation evaluated by the nurse	6 (4,7)	7 (6,8) ‡	7 (4,8)
• Dissatisfaction	2 (0,5)	4 (2,5)*	2 (1,4)
2-6 h			
• Pain	3 (3,5)	5 (3,7)	4 (3,6)
• Anxiety	1 (0,3)	2 (1,4) †	1 (0,2)
• Drowsiness evaluated by the patient	5 (4,8)	7 (4,8)	6 (5,8)
• Sedation evaluated by the nurse	5 (4,7)	6 (5,8)	6 (5,7)
• Dissatisfaction	1 (0,3)	3 (1,5)*†	1 (0,3)
6-24 h			
• Pain	3 (3,5)	5 (3,7)	4 (3,7)
• Anxiety	1 (0,3)	2 (0,4)	1 (0,4)
• Drowsiness evaluated by the patient	4 (2,6)	5 (3,7)	4 (2,6)
• Sedation evaluated by the nurse	4 (3,6)	5 (4,7)	4 (3,5)
• Dissatisfaction	4 (1,6)	3 (1,6)	3 (1,5)

Values are medians with the first and third quartiles in parentheses.
*$P < 0.05$ droperidol versus tropisetron. †$P < 0.05$ droperidol versus placebo. ‡$P < 0.005$ droperidol versus tropisetron.

3.2 Propofol-air/O_2 anesthesia compared with isoflurane-nitrous oxide anesthesia with or without oral ondansetron

In the patients undergoing gynecologic laparoscopy (Study II), the proportion of PONV-free cases was similar after propofol-air/O_2 anesthesia and after isoflurane-nitrous oxide anesthesia with oral ondansetron 8 mg, but less common than after isoflurane-nitrous oxide anesthesia without ondansetron (Table 7). Ondansetron was better at preventing vomiting, it had less of an anti-nausea effect. NNT to prevent PONV was 5 for propofol-air/O_2 anesthesia and 4 for ondansetron with isoflurane-nitrous oxide anesthesia compared with isoflurane-nitrous oxide anesthesia without

ondansetron. The need for rescue antiemetics did not differ significantly between the three anesthesia regimens.

There were no differences in sedation and satisfaction scores, or in other adverse effects between the different anesthesia regimens.

The median costs of anesthetic drugs were lowest in isoflurane-nitrous oxide anesthesia ($US18) compared with those in propofol-air/O_2 anesthesia ($US31) and isoflurane anesthesia with ondansetron ($US35). Thus, compared with isoflurane anesthesia, the additional median cost per surgical session was $US13 for propofol-air/$O_2$ anesthesia and $US17 for isoflurane-nitrous oxide anesthesia combined with ondansetron. Further, to avoid PONV during the first 24 h after surgery in one patient who would have suffered from PONV after isoflurane-nitrous oxide anesthesia, five patients would have to receive propofol-air/O_2 anesthesia (absolute risk reduction, 21 %; NNT = 5), totaling $US65 (5x$US13). Accordingly, to avoid PONV until 24 h in one patient who would have suffered from PONV after isoflurane-nitrous oxide anesthesia, four patients would have to receive prophylactic oral ondansetron (absolute risk reduction, 26 %; NNT = 4), an additional cost of $US68 (4x$US17).

3.3 Intravenous ondansetron

Intravenous ondansetron 4 mg used as an active control in Study V decreased PONV (NNT 3) compared with 30 % oxygen during 24 h after breast surgery (Table 7, Figure 4). It was effective also against nausea (Figure 5), and decreased the incidence of vomiting compared with 80 % oxygen (Figure 6) and the number of emetic episodes compared with either 30 % or 80 % oxygen (Table 7).

3.4 Supplemental oxygen

The data of the ambulatory patients (Study III) have been presented in a similar manner to those of the inpatients (Studies IV–V). Therefore, in Study III, the postoperative periods in the PACU (mean duration 123 min) and at hospital (mean duration 309 min) have been rounded down to 2 h and 6 h, respectively.

Supplemental oxygen administered as 50 % in breast surgery (Study IV) and 80 % in gynecologic laparoscopy and breast surgery (Studies III, V) did not decrease the incidence of PONV during 24 h after surgery (Figure 4). During the first 2 h after breast surgery, none of the 47 patients breathing 50 % oxygen vomited, whereas 6 of those 49 breathing 30 % oxygen did vomit ($P < 0.05$) (Figure 6). Supplemental oxygen had no effect on nausea (Figure 5), the need of rescue antiemetics (Table 7), or the time from the end of surgery to the first dose of rescue antiemetic (Figure 7). The times to the first symptoms of PONV were similar after supplemental and 30 % oxygen, except in gynecologic laparoscopy, where this time was shorter after 80 % oxygen than after 30 % oxygen ($P < 0.05$) (Figure 7).

The occurrence of cough and dyspnoea, which was specifically inquired from each patient, was not different after supplemental oxygen compared with 30 % oxygen. Also the incidence of those adverse effects which the patients spontaneously reported did not differ between the oxygen groups.

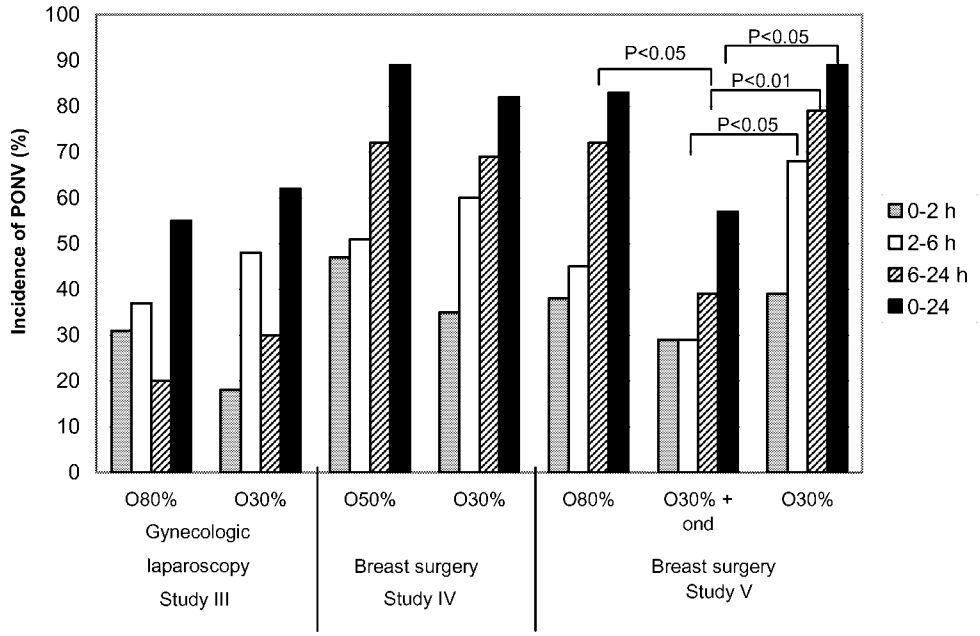

Figure 4. The incidence of PONV during 24 h after surgery (Studies III–V). O30 % = 30 % oxygen. O50 % = 50 % oxygen. O80 % = 80 % oxygen. Ond = ondansetron.

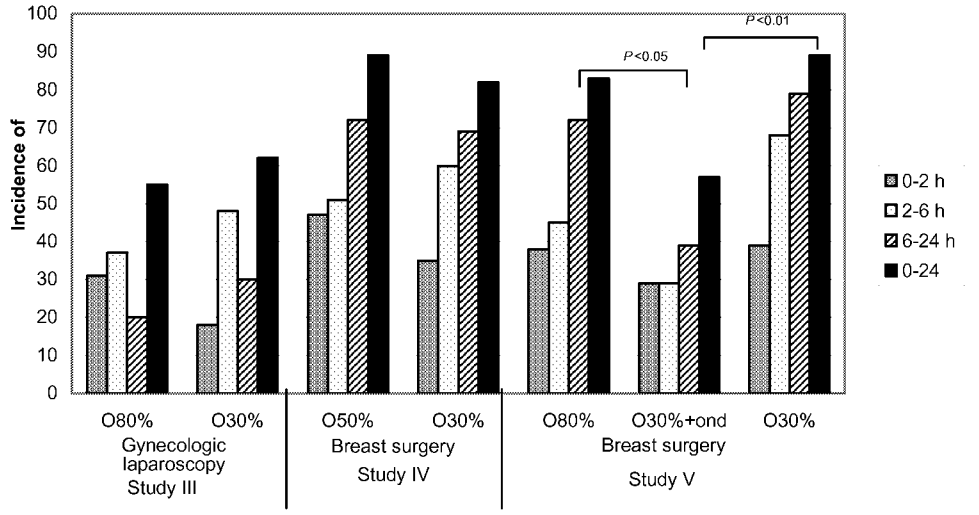

Figure 5. The incidence of nausea during 24 h after surgery (Studies III–V). O30 % = 30 % oxygen. O50 % = 50 % oxygen. O80 % = 80 % oxygen. ond = ondansetron.

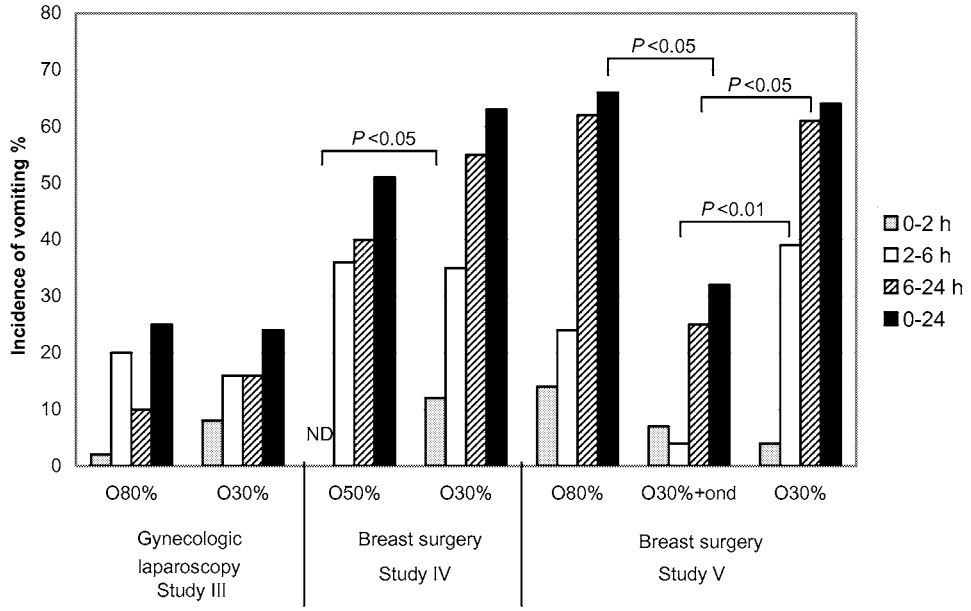

Figure 6. The incidence of vomiting during 24 h after surgery (Studies III–V). O30 % = 30 % oxygen. O50 % = 50 % oxygen. O80 % = 80 % oxygen. ond = ondansetron. ND = not detected.

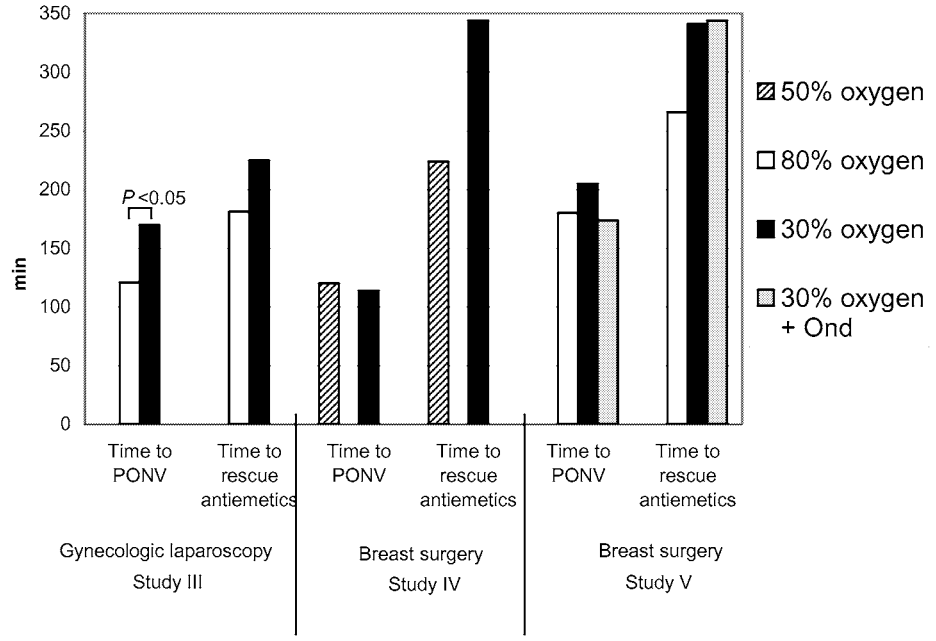

Figure 7. Median times (min) from the end of surgery to the first PONV and rescue antiemetics (Studies III–V). ond = ondansetron.

The overall satisfaction scores with the oxygen therapy were similar between the study groups. There were also no differences in the willingness of the patients to choose the same anesthesia if they were to undergo surgery in the future.

4 Pain and postoperative analgesics

Pain scores were not different between the study groups except during the first 2 h after gynecologic incontinence surgery (Study I) where the patients in the droperidol group reported higher pain scores than those in the tropisetron group (Table 9). Also the need of postoperative opioids did not differ between the study groups. In general, more patients needed opioids after gynecologic incontinence surgery (98–100 %) and breast surgery (86–97 %) than after gynecologic laparoscopy (63–76 %).

Table 9. Pain scores (median with the first and third quartiles in parentheses), proportion (%) of patients needing postoperative opioids, and the amount of opioids (mg or μg, mean ± SD) administered per patient during 24 h after surgery.

	Pain 0–2 h	**Pain 2–24 h**	**Need of postoperative opioids (% of patients)**	**Oxycodone (mg)**	**Fentanyl (μg)**
Study I					
Tropisetron	4 (2,7)	5 (4,6)	100	39 ± 17	-
Droperidol	5 (5,7)*	6 (5,8)	98	35 ± 17	-
Placebo	5 (3,7)	5 (4,7)	100	40 ± 20	-
Study II					
Propofol + placebo	3 (2,5)	2 (1,4)	66	4 ± 6	70 ± 79
Isoflurane + ondansetron	4 (1,5)	2 (1,3)	65	2 ± 4	66 ± 67
Isoflurane + placebo	3 (1,5)	2 (1,5)	76	4 ± 7	68 ± 62
Study III					
Oxygen 80 %	3 (2,6)	4 (2,5)	63	-	77 ± 89
Oxygen 30 %	4 (3,6)	3 (2,5)	70	-	95 ± 107
Study IV					
Oxygen 50 %	3 (2,4)	4 (2,5)	89	18 ± 13	-
Oxygen 30 %	3 (2,4)	3 (1,6)	94	14 ± 13	-
Study V					
Oxygen 80 %	4 (2,5)	3 (1,5)	97	16 ± 12	-
Oxygen 30 % +	4 (2,6)	3 (1,5)	86	14 ± 13	-
ondansetron	5 (3,6)	3 (1,6)	96	16 ± 9	-
Oxygen 30 %					

*$P < 0.05$ droperidol versus tropisetron. Isoflurane = Isoflurane-nitrous oxide anesthesia.

5 Recovery after surgery

The recovery data are presented in Table 10. After gynecologic laparoscopy, the patients receiving isoflurane-nitrous oxide anesthesia with ondansetron achieved readiness to ward transfer later than those with the same anesthesia without ondansetron (Study II). Otherwise, there were no differences in the recovery parameters between the study groups. After ambulatory gynecologic laparoscopy, readiness for discharge from the hospital was achieved in a median time of 5 hours after both 80 % and 30 % oxygen, and no one had to remain in the hospital overnight because of PONV (Study III). In Study IV, during the 24 h study period, five patients (4/49 after 30 % and 1/47 after 50 % oxygen) were unable to eat because of intense PONV. The times recorded for these patients to tolerate food were recorded to be 24 h, although they were actually longer.

Table 10. Recovery times during the initial 24 h after surgery (Studies II–V).

	Extubation (min)	**Duration of PACU stay[a](min)**	**Patient tolerates fluids (h)**	**Patient tolerates food (h)**	**Time to ambulation (h)**
Study II					
Propofol + placebo	7 (4,10)	61 (60,103)	3 (3,3)	6 (5,8)	6 (5,9)
Isoflurane + ond	7 (5,9)	90 (64,120)*	3 (3,3)	6 (5,8)	7 (5,8)
Isoflurane + placebo	8 (5,11)	64 (60,104)	3 (2,3)	7 (5,14)	8 (5,11)
Study III					
Oxygen 80 %	14 (12,16)	110 (84,141)	1 (1,2)	3 (2,4)	3 (2,5)
Oxygen 30 %	15 (11,17)	114 (95,158)	2 (1,2)	3 (2,4)	3 (2,4)
StudyIV					
Oxygen 50 %	13 (3,28)	188 (124,482)	4 (3,6)	17 (7,20)	10 (7,14)
Oxygen 30 %	11 (5,24)	175 (110,457)	4 (4,7)	11 (8,20)	8 (6,14)
Study V					
Oxygen 80 %	17 (12,21)	176 (160,228)	5 (4,10)	18 (9,20)	8 (6,15)
Oxygen 30 % + ond	14 (9,21)	175 (153,250)	5 (3,9)	9 (6,19)	9 (4,10)
Oxygen 30 %	16 (11,20)	163 /145,216)	4 (3,7)	17 (7,20)	9 (7,15)

Values are expressed as median with the first and third quartiles in parentheses.
*$P < 0.05$ Isoflurane + ond versus Isoflurane + placebo. Isoflurane = isoflurane-nitrous oxide anesthesia. ond = ondansetron. [a]In Study II, the time from the end of surgery to the readiness for ward transfer.

6 Patient satisfaction with and without postoperative nausea and vomiting

The general dissatisfaction was higher in the patients with PONV compared with those without it (Studies I–II) (Table 11). Similarly, the patients without PONV were more satisfied with oxygen administration than those with PONV (Studies III–V).

Table 11. Satisfaction of the patients with and without PONV during 24 h after surgery (Studies I–V).

	Patients with PONV	**Patients without PONV**	***P***
General dissatisfaction (0-10)			
• Study I	5 (3,8)	3 (1,5)	<0.01
• Study II	1 (0,4)	0 (0,1)	<0.001
Satisfaction with oxygen administration (0-10)			
• Study III	9 (7,10)	10 (9,10)	<0.001
• Study IV	8 (6,10)	9 (9,10)	<0.05
• Study V	8 (5,10)	10 (9,10)	<0.005

Values are medians with the first and third quartiles in parentheses.

DISCUSSION

1 Methodology

This thesis evaluated the effectiveness of different interventions in the prophylaxis of PONV in prospective, randomized and controlled studies. Study I and Study II for ondansetron were double blinded. Double blinding is recommended for study designs, whenever possible (Tramer 2001b). Anesthesia with propofol-air/O_2 (Study II), and the concentration of administered oxygen during anesthesia (Studies III–V) were difficult to mask properly, thus they were not blinded for the personnel delivering anesthesia in the operation room. However, all the studies were observer blinded in order to avoid observer bias which might lead to overestimation of the effect of the antiemetic intervention (Schulz et al. 1995).

Placebo drugs were used in Studies I–II. Also in the control groups, isoflurane-nitrous oxide anesthesia without ondansetron (Study II) and the groups receiving 30 % oxygen (Studies III–V), the patients did not receive any antiemetic intervention. The use of placebo in the studies focused on PONV is controversial. Some investigators claim that it is unethical to use placebo, especially in patients at a high risk for PONV (Aspinall and Goodman 1995). On the other hand, it has been stated that it is necessary to use placebo for a realistic determination the efficacy of an antiemetic intervention because there is no "gold antiemetic standard" in the area of PONV (Goodman 1999, Tramer 2001b). In addition, prophylaxis of PONV with one antiemetic intervention is only marginally more effective than no prophylaxis and then treating PONV should it occur (Tramer et al. 1999c). We consider that the use of placebo/control groups in our studies was not unethical.

PONV has a multifactorial etiology (Kovac 2000). Therefore, it is important to have an appropriate study design where all known confounding factors are controlled and evenly distributed between the study groups (Apfel et al. 2002c). In our studies, the patient related risk for PONV, evaluated with the risk score by Apfel et al. (1999) or risk for POV evaluated with the risk score of Apfel et al. (1998), did not differ between the study groups. The studies were carried out in one hospital and only three surgical procedures were studied. Anesthesia in every study was well controlled and standardized, and there was only one anesthesiologist delivering anesthesia in Studies I–II, and from 2 to 3 anesthesiologists in Studies III–V.

The sample sizes of the studies included in this thesis were relatively small. However, a prior power analysis was conducted (Studies II–V) to determine the number of patients needed to be enrolled to avoid a type 2 error in the conclusions (Apfel et al. 2002c). The power analysis in our studies was based on the differences in the incidence of PONV between the antiemetic intervention and the placebo (or control) groups. In the mutual comparison of two different antiemetic interventions (Studies II, V), the estimation of the number of the required patients should have been based on assumed differences in the incidence of PONV between the interventions to be compared, not between each intervention group and a placebo group as was done. Consequently, small differences in the antiemetic efficacy between the interventions might have been lost along with the possible loss of power.

The number of patients completely free of any symptoms of PONV was determined in all studies. In addition, in the latter studies, nausea and vomiting were analyzed and reported separately (Studies II–V) as has been recommended by Tramer (2001b). These two symptoms, although appearing very often together, are not the same entity. Study I differed from the other Studies II–V in that if the patients experienced nausea, retching, or vomiting together, they were categorized as having the most severe symptom (vomiting > retching > nausea). Therefore, it was impossible afterwards to determine the true incidence of nausea. In studies II–V, retching was included in vomiting as is commonly the case in most studies nowadays. The intensity of nausea was assessed with a numerical scale (0–10), and that of vomiting or/and retching by the amount of emetic episodes (retching and vomiting together). This is in accordance with the recommendations for studies of PONV (Korttila 1992, Tramer 2001b).

The study period of 48 h in Study I was longer than that of 24 h in all other studies. At present, the 24 h study period after surgery is commonly used, and regarded to reflect well the antiemetic effect of the intervention concerned (Tramer 2001b). For the sake of standardization, in this thesis the results of all studies have been presented up to 24 h after surgery.

2 The incidence of postoperative nausea and vomiting without antiemetic intervention

When the patients did not receive any antiemetic prophylaxis, the incidences of PONV after gynecologic and breast surgery were unexpectedly high (61–84 %). This can be attributable to many factors. First, the pre-evaluated risk of our patients for PONV was high. The mean risk of PONV in the control groups varied from 55 to 69 % according to the risk score by Apfel et al. (1999). All our patients were women and many of them had also other risk factors included in this risk score such as previous PONV, motion sickness, or nonsmoking status. Apfel et al.'s risk score showed good predictive accuracy in the patients undergoing gynecologic laparoscopy. However, in the patients undergoing breast surgery, the actual risk was underestimated. This might indicate that in this patient population, the scoring system may need to be adjusted to local circumstances (van den Bosch et al. 2005). Second, a high proportion (70–100 %) of the patients received postoperative opioids. The higher incidence of PONV after gynecologic incontinence surgery and breast surgery compared with gynecologic laparoscopy may be attributable to the higher use of postoperative opioids after those procedures (Wheeler et al. 2002). Third, the durations of anesthesia were rather long, thus the patients were exposed to the volatile anesthetics which are considered to be the main reason for early PONV after surgery (Apfel et al. 2002a). In addition, nitrous oxide was used in Studies I–II. However, omitting nitrous oxide in anesthesia has been shown to have only a negligible decreasing effect on PONV (Apfel et al. 2004b). In accordance, the incidence of PONV remained high after anesthesia without nitrous oxide in breast surgery. One possible cause for the increased incidence of PONV could be dehydration (Ali et al. 2003, Magner et al. 2004). However, the infusion of crystalloids 10–15 mL/kg/h during surgery should have been sufficient to prevent dehydration, and thus PONV (Studies III–V).

In general, gynecologic and breast surgery has been associated with a high risk for PONV (Koivuranta et al. 1997, Sinclair et al. 1999). Although the reported incidences of PONV after gynecologic and breast surgery have been mainly lower than those in the present study, also high incidences from 84 to 88 % have been published (Zomers et al. 1993, Chan et al. 1998, Hammas et al. 2002). However, recently the type of surgery as a risk factor for PONV has been questioned (Gan et al. 2003, Apfel et al. 2004c). It has also been claimed that although there might be an association between the type of surgery and PONV, the causal effect of the type of surgery on PONV is unclear (Apfel et al. 1999).

All in all, the high incidences of PONV in the placebo/control groups of the present study are not acceptable, and thus our results point to the need for combination of 3–4 antiemetic interventions to reduce this distressing postoperative symptom.

3 Antiemetic interventions

3.1 Droperidol

Droperidol 1.25 mg IV failed to decrease the incidence of nausea, vomiting, or both compared with placebo in gynecologic incontinence surgery. This is not in agreement with the claim that droperidol at this dose is an effective antiemetic (Henzi et al. 2000b, Apfel et al. 2004b). The sample sizes in Study I were rather small, thus there might not be enough power to detect efficacy if such existed. Droperidol has also been shown to have an anti-nausea efficacy superior to its anti-vomiting properties (Henzi et al. 2000b). We categorized nausea to retching/vomiting if these symptoms occurred together. Therefore, we assessed the incidence of those patients with nausea only. Consequently, the true effect of droperidol on nausea could not be determined, and thus its possible anti-nausea effect might have been lost. The antiemetic effect of droperidol is supported with our finding that the need of antiemetic rescue drug was decreased after droperidol compared with placebo during the first 24 h after surgery.

Our study showed clearly that even this relatively small dose of droperidol can cause adverse effects such as drowsiness, sedation and anxiety. The anti-nausea effect of droperidol is not dose-dependent, but the appearance of adverse effects does depend on the dose (Henzi et al. 2000b) and therefore, minimal effective doses of droperidol are recommended for prophylaxis. Valanne and Korttila (1985) showed that droperidol at a dose of 1–1.25 mg IV caused some delay in recovery from anesthesia. They recommended that droperidol in doses exceeding 1.25 mg should not be used in outpatient anesthesia. In the meta-analysis of Henzi et al. (2000b), with droperidol 1.25 mg, the additional risk for drowsiness or sedation was only one in 24.

Our patients felt more anxiety after droperidol compared with placebo during the study period 2–6 h. This is in accordance with the findings of Melnick et al. (1989) who reported that 23 % of their patients receiving droperidol 1.25 mg IV developed anxiety and became restless after their discharge from the ambulatory care unit. However, in their meta-analysis, Henzi et al. (2000b) reported extrapyramidal symptoms after droperidol only in one of 408 patients. The great variation in the incidences of the adverse effects may be influenced by the different follow-up. Melnick et al. (1989) asked their patients every 15 min, "Are you comfortable?" In our study, we asked our

patients to rate their drowsiness and anxiety on a scale from 0 to 10 at the end of every study period. This kind of focused questioning may elicit reporting of trivial detrimental symptoms which would not otherwise be described spontaneously. Another possible reason for the high incidence of anxiety in our patients might be a synergism of droperidol and metoclopramide which was used as a rescue antiemetic in about half of the study patients. Both drugs are dopamine$_2$ receptor antagonists and thus possess a similar side effect profile. Although there was statistically more anxiety after droperidol than after placebo, it is dubious whether the short-term increase of 1 point on an 11-point scale in the median anxiety is clinically significant.

The pain scores were higher after droperidol than tropisetron during the first 2 h after surgery. This finding could be explained by the greater presence of sedation in the droperidol group to the extent that the patients were too confused to request analgesics. On the other hand, there is some evidence that tropisetron, and 5-HT$_3$ receptor antagonists in general, might possess an analgesic effect on chronic pain (McCleane et al. 2003, Riering et al. 2004). However, in acute pain, such as that occurring after surgery, the mechanisms of pain and analgesia are different. Therefore, it might be an exaggeration to claim that the lower pain scores were attributable to an analgesic effect of tropisetron. One cannot exclude the possibility that the different pain scores may be a result of chance, as the sample size in this study was rather small.

At the time when the data for Study I were collected, there was no knowledge that the use of droperidol might produce arrhythmia by prolonging the QT interval (FDA 2001). Thus the patients were not monitored postoperatively with ECG, and possible arrhythmias have nor been registered.

In the present study, droperidol alone did not reduce PONV. In addition, it caused sedation and anxiety. Therefore, regardless of its low cost ($US1.60 for a dose of 1.25 mg IV), droperidol does not seem to be a useful drug for single prophylaxis of PONV in patients who have a high risk (60–80 %) of PONV.

3.2 Tropisetron and ondansetron

The antiemetic effect of tropisetron was confirmed with the present study. Tropisetron 5 mg IV decreased the incidence of PONV by reducing vomiting. In addition, it reduced the need of rescue antiemetics compared with placebo. These findings are in accordance with previous studies where tropisetron was especially effective against vomiting (Kranke et al. 2002c). In our study, the true antinausea effect could not be assessed because of the study setting. Tropisetron was well-tolerated but its high cost ($US30 for a dose of 5 mg IV) does not make it an attractive option as the first choice antiemetic in the prophylaxis of PONV.

In our patients undergoing breast surgery, ondansetron 4 mg IV decreased the incidence of PONV compared with placebo. This is in accordance with many studies where the dose of ondansetron 4 mg IV has proven to possess antiemetic efficacy (Derschwitz et al. 1998, Sadhasivam et al. 1999). It was a surprise that in our patients, the anti-nausea efficacy of ondansetron was superior to its anti-vomiting efficacy. This is contrary to the previous findings which have indicated that ondansetron is more effective against emesis than against nausea (Tramer et al. 1997b). Ondansetron was

also well-tolerated but as with tropisetron, its high cost ($US23 for a dose of 4 mg IV) is an obvious disadvantage for its widespread use.

3.3 Anesthesia regimens

One strategy in the prevention of PONV is to keep the baseline risk low (Tramer 2001b). This baseline risk for PONV can be decreased by a choice of a less emetic anesthesia method. The use of propofol for induction and maintenance of anesthesia has been proven to reduce PONV compared with inhalation anesthesia (Tramer et al. 1997a, Sneyd et al. 1998, Visser et al. 2001). The choice of induction agents in Study II can be criticized. However, propofol and thiopentone for induction of anesthesia are not thought to differ in increasing the risk for PONV (Tramer et al. 1997a, Sneyd et al. 1998). We chose thiopentone-isoflurane-nitrous oxide anesthesia because it was our routine practice in laparoscopies at that time. Omitting nitrous oxide in anesthesia decreases the incidence of PONV only slightly (Tramer et al. 1996, Apfel et al. 2004b). In Study II, the incidence of PONV after propofol-air/O_2 anesthesia was not statistically different from that seen with isoflurane-nitrous oxide anesthesia with and without ondansetron. However, the absolute decrease of 21 % (NNT 5) in the incidence of PONV after propofol-air/O_2 anesthesia compared with isoflurane-nitrous oxide anesthesia alone can be regarded as clinically significant. This finding is in accordance with previous studies (Tramer et al. 1997a, Sneyd et al. 1998, Visser et al. 1999, Apfel et al. 2004b). In the factorial trial, Apfel et al. (2004b) found that substituting propofol for a volatile anesthetic reduced the risk of PONV by about 19 %, and substituting nitrogen for nitrous oxide reduced the risk by about 12 %. Thus combining these to strategies (propofol-air/O_2 anesthesia) should reduce the risk of PONV by about 30 %, which is rather near to the reduction achieved in our set-up. These investigators recommended the use of propofol-air/O_2 anesthesia for prophylaxis of PONV so that antiemetic drugs could be reserved for the treatment of PONV should it occur.

Oral ondansetron 8 mg combined with isoflurane-nitrous oxide anesthesia prevented PONV effectively compared with isoflurane-nitrous oxide anesthesia without ondansetron. Its better anti-vomiting than anti-nausea effect was detected in accordance with the findings in previous studies (Tramer et al. 1997b). In the large meta-analysis conducted by Tramer et al. (1997b), the optimal dose for oral ondansetron was 16 mg (corresponding to 8 mg IV). In our study, the lower oral ondansetron dose of 8 mg (corresponding to 4 mg IV) was effective in reducing PONV. This agrees with the findings of Derschwitz et al. (1998) where the optimal dose for ondansetron was 4 mg IV. We used an oral preparation of ondansetron administered approximately 1 h before surgery because at that time it was a common practice at our hospital. However, it has been demonstrated that the optimal administration time for an intravenous administration of ondansetron is at the end of surgery (Sun et al. 1997, Tang et al. 1998). It is unknown whether ondansetron 4 mg IV at the end of surgery would have been more effective in decreasing PONV than our oral ondansetron 8 mg given before surgery.

Prophylaxis of PONV has economical impact. Ondansetron is an expensive antiemetic, and at that time when the study was carried out the cost of oral ondansetron 8 mg was similar to that of a 4 mg IV dose. Also maintaining anesthesia with propofol

is associated with higher costs than those with inhalation anesthesia (Smith et al. 1999, Tang et al. 2003). Isoflurane-nitrous oxide anesthesia without ondansetron had the lowest costs compared with the same anesthesia with ondansetron and propofol maintenance anesthesia. However, the incidence of PONV after this type of anesthesia was predictably the highest. This study demonstrated that in the prophylaxis of PONV, the additional cost per one PONV-free patient was similar regardless of which of the two anesthesia strategies was chosen, combining oral ondansetron with isoflurane anesthesia, or using propofol-air/O_2 anesthesia instead of isoflurane-nitrous oxide anesthesia alone. Our study can be criticized because the personnel costs were not included in the calculations. In ambulatory surgery, as much as 70–80 % of the costs associated with PONV can be attributable to personnel costs (Hill et al. 2000). However, our patients were mainly inpatients whose possible prolonged stay in the PACU had no direct economical impact on the personnel costs. Further, there were no unanticipated hospital admissions which produce the highest costs associated with PONV.

It is important to note that the costs of drugs greatly vary between different countries and hospitals. Therefore, every anesthesia unit should calculate the local costs associated with PONV before making decisions about its own anesthesia strategy.

3.4 Supplemental oxygen

Recently, the effect of oxygen on postoperative outcome has been under intense scrutiny. Greif et al. (1999) found that perioperative supplemental 80 % oxygen decreased PONV by about 50 % when compared with 30 % oxygen after abdominal surgery. That study was primarily designed to investigate the effect of supplemental oxygen on reducing surgical wound infections (Greif et al. 2000). The study group of Goll et al. (2001) confirmed the efficacy of supplemental oxygen to decrease PONV. In their study, intraoperative 80 % oxygen decreased the incidence of PONV from 44% to 22 % compared with 30 % oxygen, whereas the incidence of PONV after ondansetron 8 mg IV was 30 %. Subsequently, administration of supplemental oxygen has been recommended for prophylaxis of PONV (Gan et al. 2003). In contrast to the reports of Greif et al. (1999) and Goll et al. (2001), in our studies perioperative supplemental 80 % and 50 % oxygen failed to decrease PONV. However, our findings are in accordance with three studies which could not find any antiemetic effect for supplemental oxygen in thyroid surgery (Joris et al. 2003), mixed surgery (Apfel et al. 2004b), and strabismus surgery (Treschan et al. 2005). We found a lower incidence of vomiting during the first 2 h in patients breathing 50 % oxygen after breast surgery but this may have been a result of chance, as the sample size was rather small (Study IV). The possibility of this being a chance finding is supported by the finding that in Study V, with a similar study setting as used in Study IV, there was more vomiting after 80 % oxygen compared with 30 % oxygen during the first 2 h after surgery.

The decrease in the incidence of PONV has been shown only after abdominal surgery. It has been speculated that in this type of surgery, intestinal ischemia would be the cause of PONV, and that supplemental oxygen could produce its beneficial effect on PONV by relieving this ischemia (Greif et al. 1999, Goll et al. 2001). In our patients, also in those undergoing gynecologic laparoscopy as the patients in the study of Goll et

al. (2001), there was no benefit from supplemental 80 % oxygen. However, the degree of oxygenation in the tissue level was not measured in any of these studies.

The number of patients in our oxygen studies was rather small, and was powered to find a 50 % decrease in the incidence of PONV according to the findings of Greif et al. (1999) and Goll et al. (2001). Therefore, it is possible that we have underestimated the mild antiemetic effect of supplemental oxygen.

Although supplemental oxygen is cheap and easily available in circumstances where anesthesia is being performed, it can also have deleterious influences. For instance, it can cause atelectasis. However, the clinical significancy of this risk of atelectasis is unclear (Joyce and Baker 1995, Rothen et al. 1996, Akça et al.1999, Magnusson and Spahn 2003). Dyspnoea and cough are symptoms of atelectasis. We did not find any differences in the occurrence of these symptoms after supplemental oxygen compared with 30 % oxygen. In our oxygen studies, in order to prevent atelectasis, obesity and pulmonary diseases were exclusion criteria, and PEEP of 6 mmHg was used during anesthesia (Neumann et al. 1999). Administration of supplemental oxygen is associated also with surgical fires (ECRI 2003). These are uncommon but potentially devastating complications.

In conclusion, administration of supplemental oxygen cannot be recommended for prophylaxis of PONV. More evidence for its possible antiemetic efficacy needs to be gathered. In addition, administration of supplemental oxygen may not be risk-free.

4 Patient satisfaction

In his editorial, Fisher (1997) emphasized that patient satisfaction is a more meaningful measure of outcome than the incidence of PONV. Patient satisfaction is more difficult to achieve than the decrease in the incidence of PONV because many factors can influence satisfaction, for example the occurrence of adverse effects (Fisher 1997). Accordingly, in the droperidol treated patients, the increased general dissatisfaction during the first 6 h after surgery occurred at the same time when these patients had more adverse effects than those who received tropisetron or placebo. It may be that the dissatisfaction was caused by side effects such as pain, drowsiness and feelings of anxiety.

In all studies, the patients without PONV were more satisfied than those with the symptoms. However, we could not find any increased patient satisfaction in those study groups where a significant decrease in the incidence of PONV after antiemetic intervention was achieved (tropisetron in Study I, ondansetron in Studies II and V). There is no contradiction between these findings because, although our aim was to determine patient satisfaction and its connections to PONV and to the use of antiemetics, it was not a powered end point in our studies. On the other hand, the lack of increased patient satisfaction may reveal that our antiemetic interventions at their best had too mild an effect on PONV. Indeed, the incidence of PONV after tropisetron (69 %) and ondansetron (33 % and 57 %), remained unacceptably high. Our findings are in accordance with the current knowledge that in high risk patients, prophylaxis of PONV with one antiemetic intervention is not effective and combinations of different methods (multimodal approach) need to be used (Gan et al. 2003, Apfel 2004b).

CONCLUSIONS

- In patients who have a 60–80 % risk for PONV, tropisetron decreased PONV, but its efficacy was modest. Droperidol alone failed to exhibit any antiemetic effect. Both drugs decreased the need for rescue antiemetics. Therefore, the use of droperidol alone for prophylaxis of PONV is not sufficient, and in addition, it can cause adverse effects such as drowsiness, sedation, and anxiety.

- Propofol-air/O_2 anesthesia and isoflurane-nitrous oxide anesthesia with oral ondansetron had similar efficacy and costs in the prevention of PONV.

- Perioperative supplemental 80 % oxygen had no antiemetic efficacy compared with 30 % oxygen after gynaecologic laparoscopy or breast surgery. The addition of intravenous ondansetron increased the proportion of PONV-free patients compared with 30 % oxygen alone after breast surgery.

- Perioperative supplemental 50 % oxygen did not differ from 30 % oxygen in the prophylaxis of PONV in breast surgery.

- Patient satisfaction was similar between the patients with and without antiemetic intervention. However, patient satisfaction was higher in those without PONV compared with those with PONV.

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