Propofol for the Management of

Postoperative Nausea and Vomiting (PONV)

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ABSTRACT

Postoperative nausea and vomiting (PONV) is one of the most common complications following surgery. Despite better anaesthetic techniques, and the availability of newer generations of antiemetics, the incidence of PONV is still as high as 60–70% in high-risk subjects. Patients rated symptoms of nausea and vomiting as highly undesirable and are willing to pay out of pocket a substantial amount for an effective antiemetic. PONV also has major economic implications, prolonging recovery room and hospital stay, and in some cases, increases patient morbidity.

Propofol is an intravenous anaesthetic which gained rapid popularity due to its favourable pharmacokinetic and pharmacodynamic profile. In particular, it is associated with rapid recovery, making it the intravenous anaesthetic agent of choice especially in ambulatory anaesthesia. Previous studies have demonstrated that total intravenous anaesthesia with propofol is associated with a lower incidence of PONV when compared with inhalational anaesthetic. However, it is unclear regarding the dose response of propofol when used as an antiemetic, and how propofol should be administered in the perioperative period for its antiemetic effects.

The over arching goal of this MD thesis is to examine the use of propofol for its antiemetic properties. First, we assessed the extent of clinical practice of using propofol for its antiemetic effects among US anaesthesiologists. Next, we determine the dose response of propofol for its antiemetic effects. We examined the efficacy of propofol when used as

antiemetic prophylaxis as well as for the treatment of established PONV. Different regimens

of propofol administration were assessed for its prophylactic antiemetic effects. Treatment

of established PONV was assessed using a patient controlled antiemetic system. We also

determined the use of propofol in a multimodal PONV prevention strategy as well as its use

in paediatric population.

The main objective of these series of investigations was to systematically determine

the antiemetic effects of propofol and recommend how propofol should be used in clinical

practice.

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CHAPTER 1

Postoperative Nausea and Vomiting

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications following surgery. Despite significant advances in the management of PONV and the introduction of new antiemetic agents, the overall incidence is currently estimated to be around 30 %.[1] In certain high-risk patients, this incidence may be as high as 70 %.[2]

Nausea and vomiting are also among the most unpleasant experiences associated with surgery and one of the most common reasons for poor patient satisfaction rating in the postoperative period.[3] Macario et al. quantified patients' preferences for postoperative outcomes. Postoperative nausea and vomiting were among the ten most undesirable outcomes following surgery. Indeed, patients allocated the highest amount (about $30) to avoid PONV out of a total of $100 they were allowed to spend to avoid all complications.[4] Gan and colleagues also reported that surgical patients were willing to pay up to $100, at their own expense, for an antiemetic that would abolish their symptoms of PONV.[5] In addition, patient preference for the avoidance of specific side effects from anaesthesia may be different from that of anaesthesia care providers. In one survey, anaesthesiologists

responded that incision-site pain was patients' most undesirable outcome, when in reality,

the patients' chief concern was postoperative vomiting.[4]

PONV can have economic consequences. Previous studies have demonstrated that

PONV can prolong post-anaesthesia care unit (PACU) stay and unanticipated admissions

following ambulatory surgery, therefore increasing medical costs.[6] It was estimated that

each vomiting episode delays discharge from the recovery room by about 20 minutes.[7]

Although PONV is almost always self-limiting and non-fatal, it can cause significant

morbidity, including dehydration, electrolyte imbalance, suture tension and dehiscence,

venous hypertension and bleeding, subcutaneous emphysema, oesophageal rupture, and life-

threatening airway compromise[8,9,10], albeit the more severe complications are rare[11,12].

Definition and Classification of PONV

PONV encompasses three main symptoms that may occur separately or in

combination after surgery. *Nausea* is the subjective sensation of an urge to vomit, in the

absence of expulsive muscular movements; when severe, it is associated with increased

salivary secretion, vasomotor disturbances, and sweating. *Vomiting* or *emesis* is the forcible

expulsion through the mouth of the gastric contents. Vomiting results from coordinated

activity of the abdominal, intercostal, laryngeal and pharyngeal muscles, including

retrograde giant contraction of the intestines, relaxation of the gastric fundus, closure of the

glottis and elevation of the soft palate.[11] This activity is associated with increased heart rate

and breathing and with sweating.[13] *Retching* is an unproductive effort to vomit.[11] Retching

and vomiting are collectively termed *emetic episodes*.

PONV may take place in single or multiple episodes, which may last minutes, hours,

or even days. It is classified as early, occurring up to 2 to 6 hours after surgery, or late,

occurring up to 24 or 48 hours after surgery, with the exact cut-off times depending upon the

individual investigator's definition.[11] As may be inferred from this lack of a standard cut-off

time, the delineation is somewhat arbitrary and related to the patient's location at the time of

evaluation for the symptoms, e.g., the post anaesthesia care unit (PACU), surgical or other

ward, or home. However, there are suggestions that early and late PONV may differ at least

somewhat in their pathogenesis. The use of volatile anaesthetics may be a main cause of

early PONV[11,12]. Opioid-induced symptoms and motion sickness caused by transportation

from the PACU to the ward or from the hospital to the home may account for much of late

PONV.[14,15,16] However, for the most part, PONV research has focused on identifying risk

factors themselves rather than their time of activity.

Mechanism of Vomiting and Nausea

Vomiting is elicited through a complex series of autonomic changes that interact in

the hindbrain at the level of the medulla oblongata, located between the level of the obex

(opening of the central canal into the fourth ventricle) to the level of the rostral portion

(compact zone) of the nucleus ambiguous.[13] Vomiting may be triggered through a variety of

different input mechanisms, including PONV, pregnancy sickness, radiation-induced emesis,

cancer chemotherapy-induced emesis, food poisoning, psychogenic vomiting, motion

sickness, and blood poisoning.[13] Afferent sources of emetic input include the abdominal

viscera, heart, vestibular system, brain stem area postrema chemoreceptor trigger zone

(CTZ), and higher brain centres.[13]

There are a series of events associated with the act of vomiting. Motor changes

during vomiting occur in both gastroesophageal and respiratory muscles. Gastrointestinal

changes include reductions in gastric tone and mobility, changes in gastric myoelectric

activity, and a large retrograde contraction that, prior to expulsion, serves to push the

contents of the small intestine back into the stomach.[13] The oesophagus longitudinally

contracts, pulling open the gastroesophageal junction so that there is an open funnel

sufficiently wide to allow for retrograde contraction of the cervical oesophagus. Respiratory

muscles, especially the diaphragm and abdominal muscles, contract, thereby providing the

muscular impetus for retching and expulsion while the glottis remains closed.[13]

Signals from the peripheral afferent input may also trigger vomiting. For PONV,

enterochromaffin cells in the gastrointestinal (GI) tract release serotonin, which binds to

visceral receptors (5-hydroxytryptamine type 3 [5-HT$_3$]), causing stimulation of vagal

afferents in the GI tract to conduct impulses that reach the CTZ, also known as the *area*

postrema (Figure 1).[17]

Figure 1. Neuroanatomical areas associated with postoperative nausea and vomiting with peripheral input from the gastrointestinal enterochromaffin cells, medulla and dorsal vagal complex (DVC). NTS = nucleus tractus solitarius.
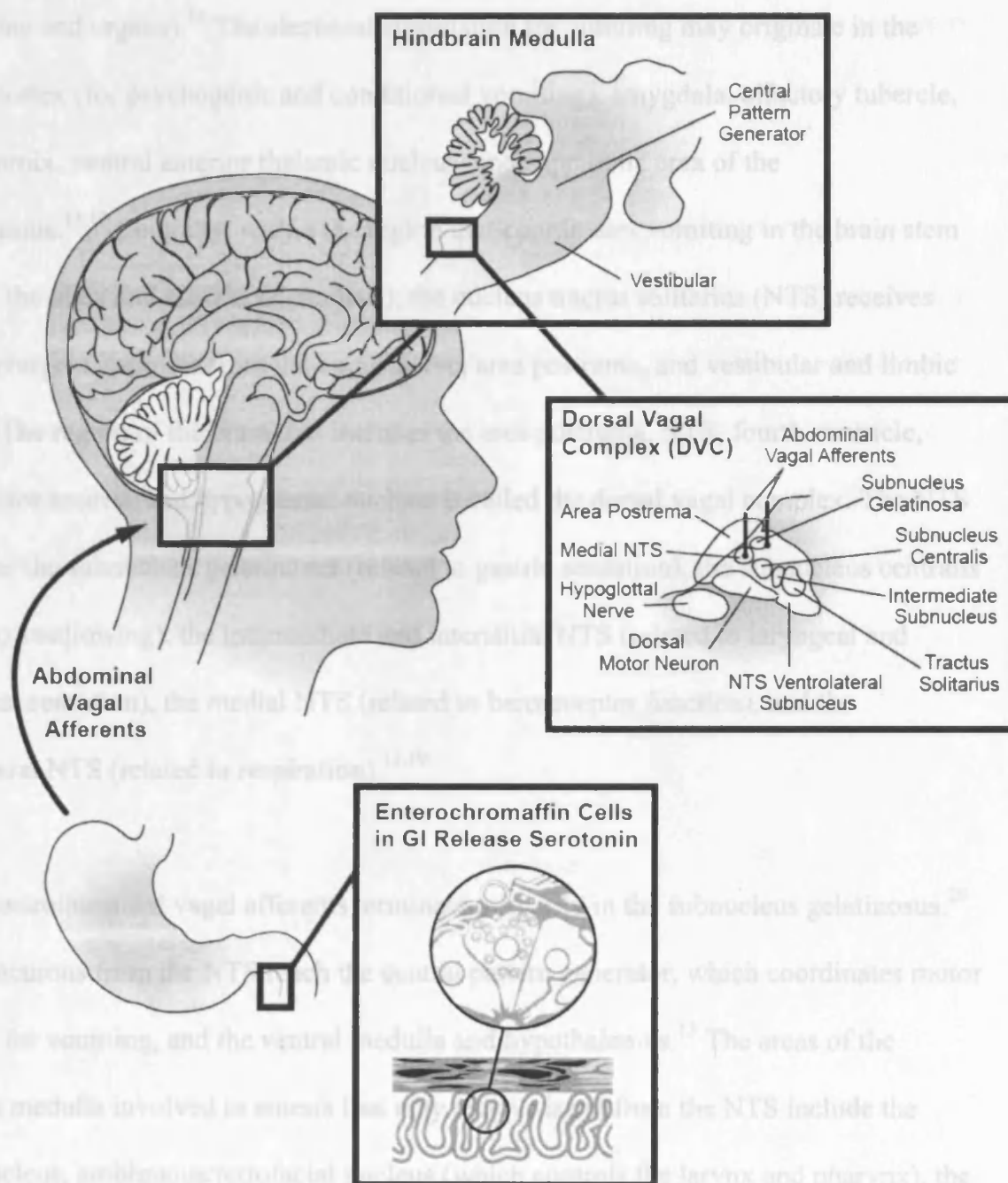
Pivotal in the central mechanism of vomiting is the area postrema, located on the

dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle.[17,18] Lacking

a blood-brain barrier, it is capable of detecting emetic agents in both blood and cerebrospinal

fluid and is more sensitive to toxic stimuli than motion sickness, which is associated with

labyrinthine end organs).[13] The electrical stimulation for vomiting may originate in the

cerebral cortex (for psychogenic and conditioned vomiting), amygdala, olfactory tubercle,

septum fornix, ventral anterior thalamic nucleus, and supraoptic area of the

hypothalamus.[13,19] Centrally, within the region that coordinates vomiting in the brain stem

(between the obex and retrofacial nucleus), the nucleus tractus solitarius (NTS) receives

these convergent impulses from the vagus nerve, area postrema, and vestibular and limbic

systems. The region of the brain that includes the area postrema, NTS, fourth ventricle,

dorsal motor neuron, and hypoglossal nucleus is called the dorsal vagal complex. The NTS

consists of the subnucleus gelatinosus (related to gastric sensation), the subnucleus centralis

(related to swallowing), the intermediate and interstitial NTS (related to laryngeal and

pharyngeal sensation), the medial NTS (related to baroreceptor function), and the

ventrolateral NTS (related to respiration).[13,19]

Gastrointestinal vagal afferents terminate primarily in the subnucleus gelatinosus.[20]

Efferent neurons from the NTS reach the central pattern generator, which coordinates motor

activities for vomiting, and the ventral medulla and hypothalamus.[13] The areas of the

hindbrain medulla involved in emesis that may receive input from the NTS include the

rostral nucleus, ambiguous/retrofacial nucleus (which controls the larynx and pharynx), the

Botzinger/ventral respiratory group (which controls respiratory behaviour), and the dorsal

motor nucleus of the vagus (which controls motor function of the lower oesophageal

sphincter and stomach). The sites involved in emesis therefore are scattered throughout the

medulla oblongata and are activated in a sequence of events described as a "central pattern

generator" (rather than a "vomiting centre"). The NTS also may send afferents to the

magnocellular hypothalamic neurons. leading to increases in plasma vasopressin and arterial

pressure.[13,17]

These signals are mediated primarily through 5 major neurotransmitter receptor

systems, including serotonergic, dopaminergic, histaminergic, cholinergic, and neurokinin.

[21,22] Antiemetics for prophylaxis and/or treatment of PONV act by blocking one or more of

these major receptors: type 3 serotonin receptor (5-HT$_3$), type 2 dopamine receptor (D$_2$),

type 1 histamine receptor (H$_1$), muscarinic cholinergic receptor, and type 1 neurokinin

receptor (NK$_1$) (Figure 2).[21,22,23]

Figure 2. Receptors involved in postoperative nausea and vomiting in the chemoreceptor trigger zone and the vomiting centre.
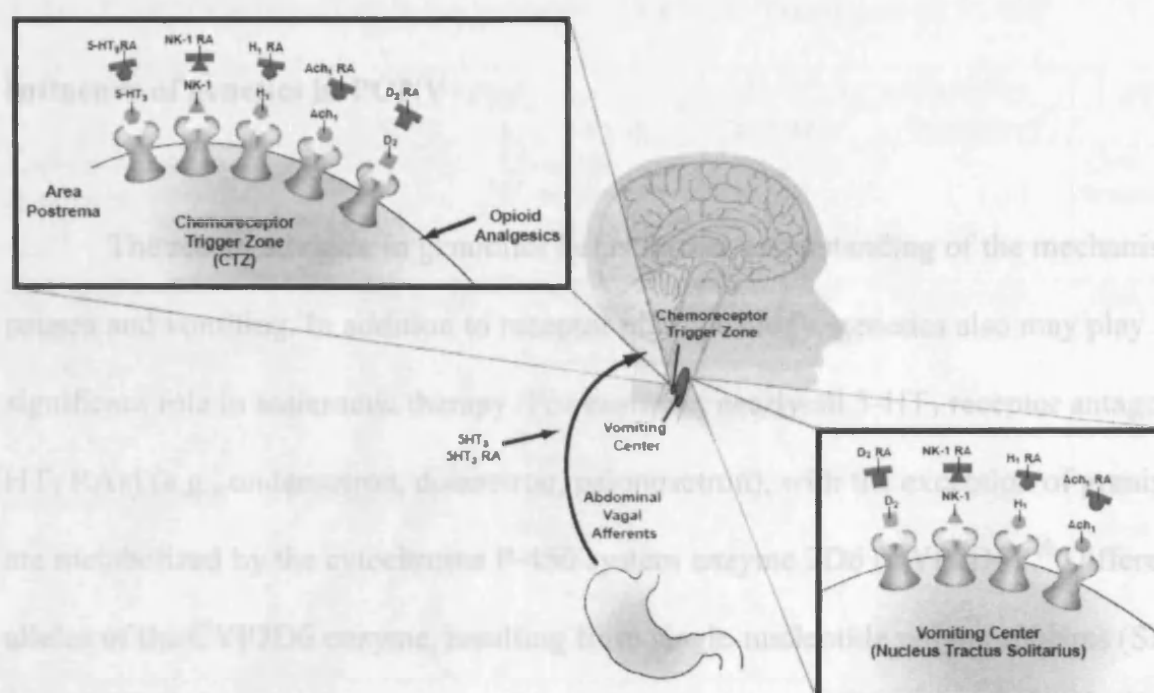
$5\text{-}HT_3$ = 5-hydroxytryptamine type 3; NK-1 = neurokinin-1; H_2 = histamine type 2; Ach = acetylcholine; D_2 = dopamine type 2; RA = receptor antagonist.

Opioids, although not neurotransmitters, may have a significant effect on PONV, exerting both excitatory and inhibitory effects on the GI system (*e.g.*, inhibition of GI motility). Exogenous opioid agonists *(e.g.,* morphine) affect intestinal motility by modulating cholinergic transmission. When administered peripherally, exogenous opioid agonists decrease GI motility and delay gastric emptying by inhibiting central μ-receptors.[24] Exogenous opioid agonists may also modulate cholinergic transmission via the κ-receptor,

which may be more potent.[25] Opioid receptor antagonists that act centrally, such as naloxone, may counteract the inhibitory effect on gastric motility.[24]

Influence of genetics in PONV

The recent advance in genomics helps further understanding of the mechanism of nausea and vomiting. In addition to receptor pharmacology, genetics also may play a significant role in antiemetic therapy. For example, nearly all 5-HT$_3$ receptor antagonists (5-HT$_3$ RAs) (*e.g.*, ondansetron, dolasetron, palonosetron), with the exception of granisetron, are metabolized by the cytochrome P-450 system enzyme 2D6 (CYP2D6).[26] Different alleles of the CYP2D6 enzyme, resulting from single-nucleotide polymorphisms (SNPs), may create ultrametabolizers (UM), which rapidly metabolize the 5-HT$_3$ RA, leading to diminished duration of efficacy against PONV, or poor metabolises, which inefficiently metabolize the 5-HT$_3$ RA, leading to inadequate formation of the active metabolite and diminished efficacy.[26] Patients with three or more copies of the CYP2D6 gene and/or UM genotypes are more likely to develop postoperative vomiting, despite prophylaxis with ondansetron.[27]

Pharmacology of Antiemetics

There are a variety of different pharmacological agents, acting on one or more of the five major neurotransmitter categories (*i.e.*, serotonin [5-hydroxy-tryptamine], dopamine,

histamine, muscarinic cholinergic, neurokinin).[21,28] These antiemetics are used for the

prophylaxis and/or treatment of PONV. (Table 1)

Table 1. Antiemetic choices for prophylaxis and/or treatment of PONV

Class	Agent		Receptor site affinity		Formulations
	Generic	Trade	Primary	Secondary	
Anticholinergics (muscarinic)	Scopolamine	Scopace, Transderm Scop	Muscarinic cholinergic	—	Oral, transdermal
Histamine antagonists (H₁ RA)	Dimenhydrinate	Dimentabs, Dinate, Dramamine, Dramanate, Calm-X, Triptone	Histamine	Muscarinic cholinergic	Oral, injectable
(Antihistamines)	Promethazine	Anergan, Mepergan, Pentazine, Phenazine, Phenergan	Histamine	Muscarinic cholinergic Dopamine	Oral, injectable, rectal
Dopamine antagonists (D₂ RA)					
• Phenothiazines	Prochlorperazine	Compazine, Compro	Dopamine	Histamine Muscarinic cholinergic	Oral, injectable, rectal
• Benzamides	Metoclopramide	Clopra, Emex, Maxeran, Octamide, Reglan	Dopamine	Serotonin	Oral, injectable
• Butyrophenones	Droperidol	Inapsine, Droleptan	Dopamine	—	Oral, injectable
	Haloperidol	Haldol, Novo-Peridol, Peridol	Dopamine	—	Oral, injectable
Serotonin antagonists (5-HT₃ RA)	Granisetron	Kytril	Serotonin	—	Oral, injectable
	Ondansetron	Zofran	Serotonin	—	Oral, injectable
	Dolasetron	Anzemet	Serotonin	—	Oral, injectable
	Tropisetron	Navoban	Serotonin	—	Oral, injectable
Neurokinin antagonists	Aprepitant	Emend	Neurokinin	—	Oral

Class	Agent		Receptor site affinity		Formulations
	Generic	**Trade**	**Primary**	**Secondary**	
(NK₁ RAs)	GR205171		Neurokinin	—	—
	CP-122,721[1]		Neurokinin	—	—

Data from Scuderi,[12] Diemunsch et al.,[29] Gesztesi et al.,[30] and Gan et al.[31]

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[1] GR 205171 and CP 122721 are not being studied further.

Acetylcholine Receptor Antagonists

Anticholinergics, among the oldest antiemetic agents, block muscarinic cholinergic

CNS emetic receptors in the cerebral cortex and pons.[32] Scopolamine has been thought to

block cholinergic transmission from the vestibular nuclei to higher centres in the CNS and

from the reticular formation to the central pattern generator (vomiting centre).[32] Common

adverse events (AE) associated with anticholinergics include dry mouth and drowsiness; rare

AEs include disorientation, memory disturbances, dizziness, and hallucinations.[32]

A meta-analysis of 23 randomized controlled trials (RCT), which included 1963

patients (979 scopolamine, 984 placebo/control), compared transdermal scopolamine with

placebo or inactive controls for prophylaxis of PONV.[33] Scopolamine was significantly

superior to placebo or controls for prevention of vomiting and/or nausea and use of rescue

medication. The number needed to treat (NNT), defined as the number of patients who need

to be treated to prevent one adverse outcome, ranged from 5 to 8 (always rounded to higher

integer) for nausea and/or vomiting, and 8 for use of rescue medication.[33]

Histamine Receptor Antagonists

H_1 receptors exert peripheral effects, including contraction of smooth muscle and

dilation and increased permeability of capillaries, as well as induction of nausea and

vomiting via the NTS. Antihistamines, *i.e.*, H_1 receptor blockers, block acetylcholine in the

vestibular apparatus and H_1 receptors in the NTS.[21] Because antihistamines can effectively

treat motion sickness and nausea or vomiting after middle ear surgery, they are thought to

act on the central pattern generator and vestibular system.[21] Antihistamines used to treat

emesis include cyclizine, dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, and

promethazine. More frequent AEs include sedation, dry mouth, and constipation; less

frequent AEs include confusion, blurred vision, and urinary retention. The combination of

promethazine and opioid in the postoperative period may cause significant sedation and

respiratory depression.[21]

A meta-analysis 18 RCTs comparing dimenhydrinate (n = 1387 patients) with

placebo (n = 1658) for prophylaxis of PONV found that dimenhydrinate was significantly

superior to placebo for absence of nausea and/or vomiting.[34] During the early postoperative

period (defined by study authors as 0 to 6 hours), the NNT ranged from 8 to 9, whereas

overall (0 to 24 hours), the NNT ranged from 5 to 6.

Dopaminergic Receptor Antagonists

Dopaminergic receptors may be inhibited by D_2 receptor antagonists (D_2 RAs) acting

at the CTZ. D_2 RAs include the phenothiazines (*e.g.*, chlorpromazine, fluphenazine,

prochlorperazine), benzamides (*e.g.*, domperidone, metoclopramide), and butyrophenones

(droperidol, haloperidol).[32] Although the phenothiazines chlorpromazine and promethazine

have been used historically to treat PONV, AEs frequently associated with their use (*e.g.*,

sedation, lethargy, and skin sensitization) have limited their usefulness. Common AEs

associated with benzamides include sedation, restlessness, diarrhoea, agitation, and central

nervous system (CNS) depression. Less common AEs include extrapyramidal effects,

hypotension, neuroleptic syndrome, and supraventricular tachycardia. Phenothiazines,

particularly droperidol, have been commonly used in the past, either as a single agent or in

combination with 5-HT₃ RAs. In a dose of 1.25 mg, it was more cost-effective than

ondansetron 4 mg and was recommended as a first line agent for PONV prophylaxis (IA).[35]

In children, the recommended dose is 50-75 mcg/kg (IIA).[36] The recent Society of

Ambulatory Anesthesia (SAMBA) PONV consensus group recommends even lower doses

at 10-15 mcg/kg.[2] Droperidol received a "black box" warning from the US Food and Drug

Administration in December 2001 because of an association with fatal cardiac arrhythmias

of the torsades de pointe variety.[37] However, recent studies have shown no significant

increase in the incidence of QTc prolongation among patients undergoing prophylaxis for

PONV with low-dose droperidol compared with placebo[38] or ondansetron[39], adding to the

controversy of this ruling.[40] Recent debate on this topic weighed the rationale for the Food

and Drug Administration (FDA) action and the pros and cons of the implications of the

"black box" warning.[41,42]

Several meta-analyses have assessed the efficacy of dopamine receptor antagonists

for prevention of PONV.[43,44,45] Henzi et al. assessed 66 RCTs comparing 18 different

regimens of metoclopramide (n = 3260), at doses including 10 or 20 mg intravenous (IV), 10

mg intramuscular (IM), and 10, 20 or 30 mg orally (PO), with placebo or no treatment (n =

3006) during early (0 to 6 hours postoperative) and late (0 to 48 hours postoperative)

periods.[44] During the early period, the 10 mg IV and 10 mg IM doses of metoclopramide

significantly reduced the incidence of nausea and/or vomiting compared to placebo. During

the late period, the 10 mg IV also significantly reduced the incidence of nausea and/or

vomiting, whereas the 10 mg PO significantly reduced the incidence of nausea or vomiting,

but not nausea or vomiting alone. None of the other metoclopramide regimens significantly

differed from placebo. Hirayama et al.[45] found similar results in a smaller meta-analysis of 5

RCTs comparing metoclopramide (n = 153) with placebo (n = 165) from 24 to 36 hours

postoperatively. In the same meta-analysis, 11 RCTs comparing another dopaminergic

receptor antagonist, droperidol (n = 525), yielded a significantly less PONV from 24 to 36

hours postoperatively than placebo (n = 518). Domino et al.,[43] as part of a meta-analysis that

included ondansetron, directly compared droperidol with metoclopramide in 15 studies for

prevention of nausea (n = 1021) and in 20 studies for prevention of vomiting (n = 1374). In

both analyses, droperidol was superior to metoclopramide.

5-Hydroxytryptamine Receptor Antagonists

With noxious or mechanical stimuli, the neurotransmitter serotonin (5-

hydroxytryptamine [5-HT]), found in high concentrations peripherally in the

enterochromaffin cells of the gastrointestinal tract (and also in the central nervous system),

may be released, stimulating vagal afferent neurons, which in turn activate the vomiting

centre or directly activate the CTZ by binding to receptor sites.[32] Serotonin has many

different receptors, but the most important receptor for nausea and vomiting is subtype 3 (5-

HT_3). The greatest intensity of $5-HT_3$ receptors is in the NTS and CTZ. $5-HT_3$ RAs block

the nausea and vomiting cascade mediated by serotonin. As a class, $5-HT_3$ RAs are

considered the most potent antiemetic agents and are effective both for prophylaxis and

treatment of PONV.[46] However, their action occurs primarily during the early phase of

PONV. They are less efficacious during the delayed phase of PONV. 5-HT₃ RAs are highly

specific for the 5-HT₃ receptor, having little to no affinity for dopamine, muscarinic

cholinergic, or histamine receptor sites. These drugs include dolasetron, granisetron,

ondansetron, ramosetron, and tropisetron (not available in the United States); all are

metabolized by the CYP450 system in the liver. Granisetron, unlike ondansetron or

dolasetron, is not metabolized by the CYP2D6 isoform, which may be associated with

adverse drug interactions, poor metabolism in patients with CYP2D6 deficiency (leading to

significant accumulation of drug), or ultrametabolism in patients with increased CYP2D6

(leading to rapid metabolism of drug).[26] Frequently observed adverse effects (AEs) with 5-

HT₃ RAs include headache and asymptomatic prolongation of the QTc interval.[32] Less

common AEs include constipation, asthenia, somnolence, diarrhoea, ataxia, lightheadedness,

dizziness, and muscle pain.

Many published meta-analyses for treatment and/or prophylaxis of PONV have

centred on the use of serotonin antagonists (5-HT₃RAs), most often involving

ondansetron.[43,47,48,49,50,51,52] Tramer et al.[53] assessed early and late periods for further

prevention of PONV (defined as "success") in 4 RCTs (n = 1043) in patients who had

already experience nausea and/or vomiting. When at least 2 studies provided data, patients

treated with ondansetron 1, 4, and 8 mg IV achieved significantly greater success rates than

those receiving placebo. There was no evidence of a clinically relevant dose response

between ondansetron 1 and 8 mg IV. However, during the early period, the success rates did

not significantly differ between ondansetron and droperidol. Similarly, Figueredo et al.[54]

evaluated different schedules of ondansetron compared to placebo during the early and late

periods from data obtained from 48 RCTs (n = 12,078 patients). During the early period,

patients treated with ondansetron 4 mg or 8 mg IV experienced less vomiting than those

administered placebo. During the late period, patients treated with ondansetron 1, 4, or 8 mg

IV, or with 4, 8, or 16 mg PO had significantly less vomiting than those who received

placebo. There was no evidence of increased efficacy with ondansetron at doses greater than

4 mg, and the 1 mg dose was barely more effective than placebo. Subsequently, a meta-

analysis, by the same authors,[55] of 21 RCTs (ondansetron: n = 2446; placebo: n = 1538)

evaluated the effect of previous history of PONV on prophylaxis of PONV. Treatment with

ondansetron 4 or 8 mg IV prevented a significantly greater proportion of patients from

vomiting postoperatively than placebo, regardless of patient history of prior PONV. There

was no significant difference in absence of vomiting between patients who had a prior

history of PONV and those who did not, nor were there any significant differences between

ondansetron dose levels. However, a more recent, but smaller meta-analysis,[45] which pooled

results from 5 RCTs comparing ondansetron with placebo (n = 149 each) for prevention of

nausea and vomiting induced by morphine for postoperative pain, reported that ondansetron

was not significantly superior to placebo. Another meta-analysis evaluated the relative

efficacy of ondansetron to the dopamine receptor antagonists metoclopramide [N (number of

studies) = 19 RCTs; n = 2502 patients] and droperidol (N = 22; n = 1584).[43] Ondansetron

was significantly superior to both metoclopramide and droperidol for prevention of vomiting,

but did not significantly differ from either dopamine receptor antagonist for prevention of

nausea.

5-HT$_3$RAs other than ondansetron have been evaluated in meta-analyses. A pooled

analysis of three RCTs with patients treated with dolasetron (n = 1527) or placebo (n = 419)

evaluated complete response rate (defined as the proportion of absence of vomiting and of

need for rescue medication) and absence of nausea rate.[56] Dolasetron 12.5, 25, 50, and 100

mg IV doses had significantly greater complete response rates than placebo, and dolasetron

12.5, 25, and 100 mg IV doses had significantly greater absence of nausea rates.

There is no evidence that there is any difference in efficacy or side-effect profile

between the various 5-HT$_3$ receptor antagonists, when appropriate doses are used for the

management of PONV. In patients undergoing laparoscopic cholecystectomy, there was no

difference in antiemetic efficacy between ondansetron 4mg, tropisetron 5mg and granisetron

3mg given before induction of anaesthesia.[57]

Dolasetron 12.5mg was also found to have similar efficacy to ondansetron 4mg with

a similar side effect profile for the prevention of PONV.[58,59] In an earlier study, dolasetron

50 mg had similar efficacy to ondansetron 4 mg.[60] Similarly, in a multicentre trial, it was

demonstrated that 2 mg tropisetron intravenously had similar efficacy and side effect

profiles to those of ondansetron 4 mg.[61] This was confirmed in another two trials comparing

intravenous tropisetron 5 mg with ondansetron 4 mg and oral tropisetron 5 mg with

ondansetron 16 mg.[62,63]

Fujii and colleagues compared the antiemetic efficacy of granisetron 2.5-3 mg and

ramosetron 0.3 mg in three studies. There was no difference between the two agents in

achieving a complete response (no PONV and no antiemetic rescue) during the first 24

hours postoperatively. Between 24 and 48 hours, however, ramosetron provided better

prophylaxis.[64,65,66,67]

Several meta-analyses have examined 5-HT₃RAs in combination with droperidol (5-

HT₃RA/droperidol) and with dexamethasone (5-HT₃RA/dexamethasone) for prevention of

PONV. During both the early period and overall, Eberhart et al.[68] (N = 8; n = 881) observed

no significant difference in vomiting or nausea rates between 5-HT₃RA/droperidol

compared to 5-HT₃RAs or droperidol monotherapies. On the other hand, Habib et al.[69] (N =

33; n = 3447) observed significantly greater prevention of vomiting with 5-

HT₃RA/droperidol compared to droperidol monotherapy during the early period and overall,

and significantly greater prevention of nausea overall. The same study[69] also observed that

combination therapies of 5-HT₃RA/dexamethasone had greater prevention of nausea and

vomiting during both the early period and overall. A more recent meta-analysis by Kovac[70]

(N = 49; n = 12,752) evaluated the need for rescue medication with 5-

HT₃RA/dexamethasone compared to placebo, and to 5-HT₃RA and dexamethasone

monotherapies. For each comparison, a significantly smaller proportion of patients treated

with combination 5-HT₃RA/dexamethasone required rescue medication.

Leslie et al.[52] conducted a meta-analysis (N = 28; n = 3440) that examined the safety

of 5-HT₃RA combination therapies. The proportion of patients experiencing headaches was

significantly smaller with 5-HT₃RA/droperidol combination therapy than droperidol

monotherapy. Where calculable, the drowsiness, dizziness, or any AE rates of 5-

HT$_3$RA/droperidol did not significantly differ from 5-HT$_3$RA or droperidol monotherapies. As for combination 5-HT$_3$RA/dexamethasone therapy, the proportions of patients with headaches, dizziness, drowsiness, abdominal pain, or any AE did not significantly differ from 5-HT$_3$RA monotherapy, and was only greater than dexamethasone combination therapy for the proportion of patients with headaches.

However, the efficacy of 5-HT$_3$RAs, as monotherapy or in combination with dexamethasone or droperidol, occurs primarily during the early postoperative period and overall; little efficacy has been reported during the late postoperative period.[13] Delayed emesis remains a problem. This has led to significant interest in the use of neurokinin receptor antagonists, which appear to show efficacy during both the early and delayed chemotherapy-induced nausea and vomiting.[22,28,71]

Neurokinin Receptor Antagonists

Substance P, a member of the tachykinin family of neuropeptides, is an ubiquitous and important neurotransmitter in afferent pathways of the emesis.[28] Substance P may be released from enterochromaffin cells in the stomach and intestine (*e.g.*, postoperative trauma) or from sensory neurons (*e.g.*, radiation, chemotherapeutic agents).[28] Tachykinin peptide activity is tied to at least three G-protein–coupled receptor subtype found in the peripheral or central nervous tissue: neurokinin receptor subtype 1 (NK$_1$), subtype 2 (NK$_2$), and subtype 3 (NK$_3$). The NK$_1$ receptors are located in the area postrema and are thought to play a particularly important role in emesis. However, NK$_1$ receptor antagonists (NK$_1$ RAs) are

thought to exert their mechanism of action on neurons in the "afferent relay station" situated

between the medial NTS and the central pattern generator for vomiting, although this has not

been definitively isolated for humans. The potential NK_1 receptor blocking activity located

deeper in the brain stem is thought to prevent both acute and delayed emesis, whereas 5-HT$_3$

RAs are largely effective only against acute emesis. [28] This has led to considerable recent

interest in the use of NK_1 RAs for prophylaxis of PONV.

Only a few RCTs have been published in this expanding area of research. In a

double-blind randomized controlled trial (RCT), Diemunsch et al. [29] treated 36 patients who

experienced PONV following hysterectomy or ovariectomy with GR205171 (NK_1 RA) 25

mg IV or placebo. Patients in the GR205171 group exhibited significantly fewer emetic

episodes by 2 hours postoperative ($P = 0.006$) and less severe nausea at all times ($P \leq 0.025$,

exact Wilcoxon rank-sum test). Gesztesi et al.[30] reported on two double-blind RCTs

involving another NK_1 RA, CP-122,721. In the first part of the study, 86 patients were

treated with oral CP-122,721 at 100 or 200 mg or placebo 60 to 90 minutes before induction

of general anaesthesia. Patients who received CP-122,721 200 mg had a significant delay in

time to emesis compared with those receiving placebo ($P < 0.01$), and a significantly lower

proportion of patients exhibited emesis ($P < 0.01$). In the second part of the study, 157

patients were randomized to receive treatment with oral CP-122,721 200 mg, ondansetron 4

mg IV, or a combination of the two agents. A significantly lower proportion of patients

exhibited emesis within 24 hours postoperative with CP-122,721 or combination therapy

than with ondansetron alone (6% vs. 4% vs. 24%, $P < 0.05$). The median emesis-free time

for 75% of patients was significantly less with combination therapy than ondansetron alone

(362 vs. 82 minutes, $P < 0.05$). Gan et al.[31] recently reported on a multi-centre, phase III RCT in which 805 inpatients undergoing abdominal surgery received oral aprepitant (a NK_1 RA) at 125 or 40 mg or ondansetron 4 mg IV preoperatively. The proportion of complete responders (no vomiting or use of rescue medication) did not significantly differ among the treatment groups from 0 to 24 hours. More importantly, however, 95% of patients treated with aprepitant 125 mg and 90% of patients treated with aprepitant 40 mg experienced no vomiting compared with 74% of patients treated with ondansetron ($P < 0.001$ for both). A significantly greater proportion of patients treated with aprepitant 125 and 40 mg also had no vomiting from 0 to 48 hours (93% and 85%, respectively) compared with those receiving ondansetron (67%, $P < 0.001$ for both). The long-term safety of NK_1 RAs is under investigation.[31]

Other anti-emetics

Steroids

Following the successful use of dexamethasone in the prevention and treatment of chemotherapy induced emesis; this agent has been evaluated and found to be effective for the management of PONV.[72,73] The recommended dose is 5-10 mg in adults[74,75,76] and 150 mcg/kg in children.[75] More recently, smaller doses (2.5 – 5 mg) have been found to be effective.[74,77] Dexamethasone appears to be most effective when administered prior to induction of anaesthesia rather than at the end in preventing early PONV (0 – 2 hours).[77]

There are no reports of dexamethasone related adverse effects in the doses used for the

management of PONV.[75]

Benzodiazepines

Benzodiazepines were found to be effective for the prophylaxis of PONV.[67,78,79] The

successful use of midazolam in cases of persistent PONV and following failure of other

antiemetics has also been described.[80,81,82]

Ephedrine

Intramuscular ephedrine (0.5 mg/kg) has been shown to be effective for PONV

prophylaxis especially in the early postoperative period (0 – 3 hours).[83,84,85]

α_2 adrenergic agonists

α_2 adrenergic agonists also significantly reduced the incidence of PONV in both

children and adults.[86,87] It has been suggested that the antiemetic effect of clonidine might be

secondary to a reduction in the use of volatile agents and opioids, or a reduction in

sympathetic tone.[86]

High concentration of oxygen

Oxygen supplementation (80 %) intraoperatively or both intraoperatively and for two hours postoperatively have been shown to be effective in reducing the incidence of PONV compared to patients receiving 30 % oxygen.[88,89] These findings were not confirmed in a more recent study in females undergoing ambulatory gynaecologic surgery. In this study, 80 % oxygen was given intraoperatively and for up to one hour postoperatively.[90] A recent meta-analysis concluded that 80% FiO_2 should no longer be considered an effective or reliable method to reduce overall PONV.[91] This was adopted by the recent PONV consensus statement.

Fluid Administration

Adequate hydration is associated with a significant reduction in the incidence of PONV.[92] Liberal fluid regimen (median vol = 4.2 L) is associated with a lower incidence of vomiting and improved pulmonary function in patients undergoing knee arthroplasty compared with restricted fluid regimen (median vol = 1.7 L).[93] In a more recent study, 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 in patients undergoing major abdominal procedures.[94]

Non-Pharmacological Methods

Acupuncture

Several investigators have shown a useful effect of acupuncture in the management

of PONV. Acupuncture at the 6th acupoint along the pericardial meridian, traditionally

known as P6 or "neiguan" (Figure 3) has been shown to be effective in chemotherapy,

pregnancy induced as well as PONV.
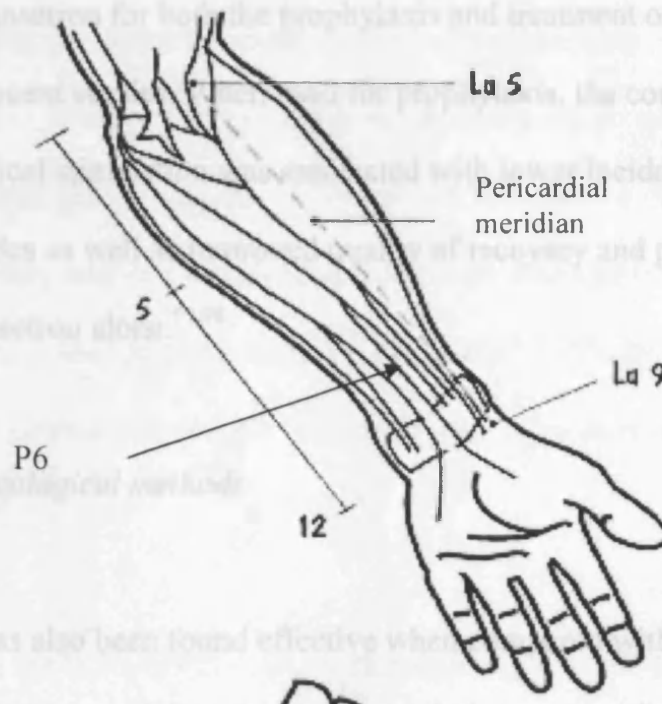
**Figure 3. Pericardial 6, an acupuncture point commonly used for the prevention of PONV.
Lu 5 and Lu 9 are acupuncture points along the lung meridian.**

Lee and Done performed a systematic review of 24 randomized trials of acupuncture,

electroacupuncture, transcutaneous electrical nerve stimulation, acupoint stimulation and

acupressure. They found that there was a significant reduction in early PONV (0 – 6h) in

adults treated with acupuncture compared with placebo and that antiemetics

(metoclopramide, cyclizine, droperidol, prochlorperazine) versus acupuncture techniques

were comparable in preventing early and late (0-48h) PONV in adults. These techniques

were more effective for controlling nausea than vomiting. In children, however, no benefit

was found.[95] More recently, in a randomized placebo controlled study in patients undergoing breast surgery, Gan and colleagues reported similar efficacy of electroacupuncture at the P6 point and prophylactic ondansetron. Of interest electroacupuncture patients reported less pain compared with the other groups.[96] The comparable efficacy of acupoint electrical stimulation to ondansetron for both the prophylaxis and treatment of PONV was also confirmed in two recent studies. When used for prophylaxis, the combination of ondansetron and acupoint electrical stimulation was associated with lower incidence of PONV, less need for rescue antiemetics as well as improved quality of recovery and patient satisfaction, compared to ondansetron alone.[97,98]

Other non-pharmacological methods

Hypnosis has also been found effective when compared with placebo.[99] Although some earlier reports suggested that ginger root might have a beneficial effect for PONV prophylaxis, this has not been confirmed in a recent meta-analysis.[100]

CHAPTER 2

Risk Factors for PONV

Administering prophylactic antiemetics to all patients may expose them to

unnecessary risks due to side effects of the drugs and may not be cost-effective. Hence, it is

important to recognize the various risk factors which increase the risk for developing PONV

and hence target a subgroup of patients for prophylactic management. PONV risk factors

have been described in the literature since the late 1800s[101]. Traditionally, investigation

focused on a single potential factor at a time, with little to no attempt to control for other

variables.

The modern era in PONV risk factor research began in the early 1990s, with

publication of the first studies that attempted to simultaneously identify multiple risk factors

and, in so doing, used regression models to control for a wide variety of variables.[1,102]

Nearly all these studies were prospective and relied on logistic regression analysis.[103]

Logistic regression analysis uses modelling in which a binary or dichotomous dependent

variable, that is, an outcome comprising two possible categories (e.g., PONV: yes or no), is

described as a function of one or more independent variables. Logistic regression analyses

generate an odds ratio (OR) for each factor examined. The OR is the ratio of the likelihood

of an outcome in a group with the given risk factor to the likelihood of the outcome in a

group lacking that factor. The statistical significance of each OR also is assessed. In

addition, the 95% confidence interval (CI) of the OR, i.e., that is, the range of values that is

95% likely to include the true OR in the study population, is calculated. When the lower

limit of the 95% CI of its OR exceeds 1.00, it is likely that a given factor increases PONV

risk.

The potential risk factors studied thus far (Table 2) may be classified as patient-,

surgery- or anaesthesia-related.[16,102,104] Most patient and surgical technique-related factors

are fixed; some other surgery-related factors and some anaesthesia-related factors are

variable.

Main Risk Factors for PONV

Table 2 classifies risk factors as well-established or possible as well as by

relationship to the patient, surgery, or anaesthesia.

Table 2. PONV risk factors.

Well-Established Risk Factors	Possible Risk Factors
Patient Related	
Female gender from puberty*[1,14,15,102,105,106,107,108,109,110,111,112,113,114]	Better ASA physical status[1,14]
Nonsmoking status [1,14,15,102,105,106,107,108,109,110,111,112,113,114,115,116]	History of migraine [nausea only][14,113]
History of PONV or motion sickness[1,14,15,102,105,106,107,108,109,110,111,112,113,114,117,118]	History of PONV or motion sickness in a parent or sibling (children only)[112]
Childhood after infancy and younger adulthood[1,14,15,102,105,106,107,108,109,110,111,112,113,114,117,118,119]	Preoperative anxiety[114]

Well-Established Risk Factors	Possible Risk Factors
	Ethnicity (Dutch/English versus Scandinavian)[120]
Surgery Related	

Well-Established Risk Factors	Possible Risk Factors
Increasing duration of surgical procedures[14,15,108,110,117]¶	Certain surgery types: •intraabdominal[1,14,15,102,105,106,107,108,109,110,111,112,113,114] • hernia repair [children][121] • laparoscopic[1,14,15,104,105,107,108,109,113,118,121,122,123,124,125] • orthopaedic[1,14,15,104,105,107,108,109,113,118,121,122,123,124,125] • major gynaecological (GYN)[1,14,15,104,105,107,108,109,113,118,121,122,123,124,125] • ENT [including adenotonsillectomy in children][1,14,15,104,105,107,108,109,113,118,121,122,123,124,125] • strabismus [children][1,14,15,104,105,107,108,109,113,118,121,122,123,124,125] • neurosurgery[109,121,126] • breast surgery[1,14,15,104,105,107,108,109,113,118,121,122,123,124,125] • plastic surgery[1,14,15,104,105,107,108,109,113,118,121,122,123,124,125]

Well-Established Risk Factors	Possible Risk Factors
Anaesthesia Related	
	Less pre- or intraoperative fluid administration[128,129]
	Intraoperative crystalloid versus colloid administration[94]
Volatile anaesthetics[21,107,114,130]	Increasing duration of anaesthesia[1,15,21,107,117,130]
Nitrous oxide[108,110,114,130,131]	General versus other forms of anaesthesia[15,113,132]
Balanced versus total IV anaesthesia[21,110,130,133]	Use of longer- versus shorter-acting opioids[134]
Large-dose (≥2.5 mg) neostigmine[135]	
Intraoperative opioids[110,136]	
Postoperative opioids[1,14,102,107,108,111,113,137,138,139]	

Patient-Related Factors

Probably the strongest risk factor identified is female gender from puberty on: all adult studies listed in Table 2[1,14,15,102,105,107,108,109,110,111,114,139,140,141] concurred in identifying female gender as a risk factor, and no study has contradicted this finding. All adult risk scoring systems include this factor. In most studies, ORs for this predictor have ranged from 2.0-4.0, reflecting a two-fold to four-fold increased PONV risk for adolescent and adult females (e.g.,[1,14,15,102,105,107,108,109,110,111,114,139,140,141]). That pre-pubescent girls apparently lack increased likelihood of PONV[117,119] could imply that the risk relates to hormonal factors. However, although early studies[142,143] reported increased susceptibility to PONV during the first week of the menstrual cycle, early stage of the menstrual cycle has been disproved as a risk factor by a subsequent study[144], and in a systematic review.[145]

Nonsmoking status has been identified as an independent PONV risk factor in numerous adult studies[1,14,15,107,110,113,140,146] as has history of either or both PONV or motion sickness[1,14,15,107,110,112,113,139,140,146]; intriguingly, a recent study in children also found history of PONV in a parent or sibling to be a risk factor.[117] There have been few contradictory reports.[102,111,139] Nonsmoking status is included in all but one adult risk scoring system, and history of PONV or motion sickness in all risk scoring systems. Most studies have found ORs of ~1.5-2.5 for nonsmoking status and of ~1.8-3.1 for history of PONV, motion sickness, or both.

A number of investigators also have identified childhood after infancy and younger adulthood as independent PONV risk factors[1,15,105,107,108,109,110,111,119] For example, 2 reports noted a >10% decreased risk for every decade of age in adults.[15,111] A study in children age

≤14 years found a sharp increase in PONV risk around age 3, with a 0.2%-0.8% per year

increase in risk thereafter, depending on the presence of other risk

factors[1,15,105,107,108,109,110,111,119] However, age is included in only a minority of risk scoring

systems (Table 3).

Possible PONV risk factors include better ASA physical status[14,147] and a history of

migraine (post-operative nausea only).[14,113] A recent adult study found higher scores on the

Spielberger State-Trait Anxiety Inventory anxiety scale or on the Amsterdam Preoperative

Anxiety and Information Scale anxiety section to be weak PONV risk factors (OR 1.01,

95% CI, 1.00-1.02, P = 0.04 and OR 1.04, 95% CI, 1.02-1.05, P = 0.02, respectively); their

inclusion in the investigators' risk scoring system did not improve its discriminating

power.[114] In contrast, a paediatric study found preoperative anxiety not to be a significant

PONV risk factor.[77] A meta-analysis of PONV after gynaecological surgery[120] and studies in

the laboratory-induced motion sickness setting[148] suggest that ethnicity (Dutch or English

versus Scandinavian and Chinese or Asian-American versus Caucasian- or African-

American, respectively) could be a PONV risk factor. However, two studies using

multivariable analyses do not support a role for this characteristic.[114,139]

Table 3. Overview of risk factors use in risk scoring systems

Risk Factor*	Adults, simplified or semisimplified systems			Adults, nonsimplified systems				Children, simplified system	Number of systems in which risk factor is used
	Apfel et al.[108]	Koivuranta et al.[14]	Van den Bosch et al.[149]	Apfel et al.[150]	Koivuranta et al.[14]	Palazzo and Evans[102]	Sinclair et al.[151]	Eberhart et al.[118]	
Patient-related									
Female	X	X	X	X	X	X	X		7/8
History of PONV or motion sickness	X	X	X	X	X	X	X	X	8/8
Nonsmoker	X	X	X	X	X		X		6/8
Age			X	X				X	3/8
Surgery-related									
Duration of surgery		X			X		X	X	4/8
Type of surgery			X				X	X	3/8

Risk Factor*	Adults, simplified or semisimplified systems			Adults, nonsimplified systems				Children, simplified system	Number of systems in which risk factor is used
	Apfel et al.[108]	Koivuranta et al.[14]	Van den Bosch et al.[149]	Apfel et al.[150]	Koivuranta et al.[14]	Palazzo and Evans[102]	Sinclair et al.[151]	Eberhart et al.[118]	
Anaesthesia-related									
Duration of anaesthesia				X					1/8
Anaesthetic technique			X				X		2/8
Postoperative opioids	X					X			2/8
Number of each type of risk factors	3 PR, 1 AR	4 PR, 1 SR	4 PR, 1 SR, 1 AR	4 PR, 1 AR	4 PR, 1 SR	3 PR, 1 AR	3 PR, 8 SR, 1 AR	2 PR, 2 SR	
Number of risk factors	4	5	6	5	5	4	12	4	

AR, anaesthesia-related; D&C, dilatation and curettage; ENT, ear nose and throat; GYN, gynaecologic; OPHTH, ophthalmologic;

ORTHO, orthopaedic; PONV, postoperative nausea and vomiting; PR, patient-related; SR, surgery-related, X, used in the

particular risk scoring system

Besides early stage of the menstrual cycle, obesity has been disproved as a patient-related PONV risk factor.[152] Interestingly, the systematic review that did so found that the belief in increased body mass index as a risk factor apparently largely stemmed from a "chain reaction" of 14 review articles misquoting or misinterpreting 4 original studies.

Surgery-Related Factors

Increasing duration of surgery has been shown to be an independent PONV risk factor by a few well-conducted studies in adults[14,15,108,110] or children.[117] An outpatient study found that each 30 min increase in surgery duration increased baseline PONV risk by 60%.[15] However, while type of surgery has been identified as a risk factor in numerous reports[1,11,14,15,104,105,107,109,113,121], its status as such is still somewhat controversial, since the specific procedures implicated as particularly emetogenic sometimes vary among studies. Types of procedures that may be viewed as possible risk factors include intra-abdominal[1,11,14,15,104,105,107,109,113,121], laparoscopic, orthopaedic, major gynaecological, ear, nose and throat, thyroid, breast and plastic surgery[1,11,14,15,104,105,107,109,113,121] as well as neurosurgery[1,11,105,107,109,123,126], and, in children, hernia repair[121], adenotonsillectomy[121], strabismus or penile surgery, and orchiopexy.[121] Half of risk scoring systems include duration of surgery, and several incorporate one or more types of surgery (Table 3). Other possible surgery-related PONV risk factors include less pre- or intraoperative fluid administration[128,129] or intraoperative colloid versus crystalloid administration[94], when a large volume of crystalloid in a prolonged surgery may result in gastrointestinal tissue oedema leading to an increased incidence of PONV.

Anaesthesia-Related Factors

Numerous anaesthesia-related variables have been well established as PONV risk factors, including use of volatile anaesthetics[21,110,130,141], nitrous oxide[110,114,130,131], balanced inhalational versus total IV anaesthesia[110,130,131,133], and large-dose (≥ 2.5 mg) neostigmine.[135] The choice of volatile anaesthetic, e.g., isoflurane versus sevoflurane versus enflurane, appears not to affect the risk of PONV[130,141]. Use of intra-[110,136] or postoperative[1,14,102,107,111,113,137,138,139] opioids and larger peri and postoperative doses of these drugs also have been implicated as associated with PONV.[153,154,155,156] However, some contradictory findings have been reported with respect to post-operative opioid use in adults[114], intra- or post-operative opioid use in children[117] or intra-operative opioid use in a mixed adult and paediatric population.[107] Interestingly, despite the relatively large number of anaesthesia-related variables identified as risk factors, most risk scoring systems do not include any, while the remainder of the systems includes only a few (Table 3).

Administration of a long- rather than a short-acting opioid is, at best, a possible PONV risk factor. Although a small recent study observed an association between use of fentanyl versus remifentanil as an adjunct to propofol maintenance[134] and PONV, another similarly sized study found no association of alfentanil versus remifentanil use and PONV.[157] Moreover, a 5199-patient multi-national multifactorial designed study of anti-PONV interventions[130] failed to find fentanyl versus remifentanil as a PONV risk factor.

Far more likely, but not yet well established, anaesthesia-related PONV risk factors include longer duration of anaesthesia[1,15,105,107,117] or general versus other forms of anaesthesia, e.g., regional or sedation.[15,113,132] Together with postoperative opioid or isoflurane use, they comprise the anaesthesia-related risk factors used by current risk scoring systems (Table 3). Use of standard (30%) rather than supplemental (50% or 80%) oxygen seems to have been disproved as a risk factor[90,130,158,159], despite early evidence of its validity as such.[88,89]

Risk Factors in Paediatric Patients

In the paediatric population, only vomiting is reported due to difficulties in eliciting nausea in the young age group. The incidence of PONV increases after the age of 3 years with a peak incidence of about 40 % in the 11 –14 year age group.[15,104,119] Prior to puberty, gender differences for postoperative vomiting have not been identified.[7] Operations associated with a high incidence of postoperative vomiting in children include strabismus, adenotonsillectomy, hernia repair, orchidopexy and penile surgery.[104]

PONV Risk Scoring in Adult Patients

A number of PONV risk scoring systems have been developed. In 1993, Palazzo and Evans prospectively studied 147 patients undergoing minor orthopaedic surgery. Using logistic regression analysis, they concluded that the probability of postoperative sickness in the first 24 hours after surgery can be estimated using the following equation: logit

postoperative sickness = -5.03 + 2.24 (postoperative opioids) + 3.97 (previous sickness history) + 2.4 (gender) + 0.78 (history of motion sickness) − 3.2 (gender × previous sickness history).[102] This equation has not been validated further.

Subsequently, Koivuranta studied 1107 in-patients and used a logistic regression model to generate a score based on the strongest five predictors for PONV: score=0.93 (if female) + 0.82 (if previous PONV) + 0.75 (if duration of surgery over 60min) + 0.61 (if nonsmoker) + 0.59 (if history of motion sickness).[14]

More recently, in a study of 2,722 patients, Apfel et al developed a simplified risk score consisting of four predictors: female gender, history of motion sickness or PONV, non-smoking status and the use of opioids for postoperative analgesia. If none, one, two, three or four of these risk factors were present, the incidences of PONV were 10, 21, 39, 61 and 79 % respectively.[108]

Knowledge of independent PONV risk factors is crucial for the optimal use of antiemetic prophylaxis and multimodal management strategies. Modern multivariable studies, meta-analyses, and systematic reviews have greatly increased such knowledge. Independent risk factors identified by modern research, such as female gender from puberty, nonsmoking status, history of PONV or motion sickness, childhood after infancy or younger adulthood, lengthy or emetogenic surgery, or administration of nitrous oxide, volatile anaesthetics, or postoperative opioids, may be used in combination to predict, with moderate accuracy, the likelihood of PONV in a given patient. Additional PONV research examining

patient genetic characteristics and under-investigated potential clinical risk factors, and involving outpatients and children should lead to predictive systems with improved discriminating power and applicability. This development, in turn, will enable anaesthesiologists to better identify at-risk patients, further reduce the incidence of PONV and increase the safety and cost-effectiveness of PONV prophylaxis.

Strategies for the Management of PONV

None of the available anti-emetics is entirely effective for preventing PONV, especially in high-risk patients. Since at least 4 major receptor systems (serotonergic, cholinergic, histaminergic and dopaminergic) are involved in the aetiology of PONV, a better prophylaxis might be achieved by using a combination of agents acting at different receptor sites. This approach, introduced first in chemotherapy induced nausea and vomiting, is gaining more popularity for PONV prophylaxis. More than forty randomized controlled trials have been published comparing combination versus single agent for PONV prophylaxis. Most of these studies demonstrated improved prophylaxis using a combination of two or more agents acting at different receptor sites.[160] This has also been confirmed in systematic reviews.[75,160] Table 4 and Table 5, respectively, demonstrate the number needed-to-treat (NNT) for the common antiemetics as well as the side effects profile, or number needed-to-harm (NNH) for these drugs. In clinical practice, an NNT of >10 is considered as lack of efficacy that is of clinical significance and an NNT of ≤ 5 is considered as strong clinical efficacy and its used is advised.

Table 4: NNT (95 % CI) of antiemetics studied in systematic reviews

	Early Nausea	Late nausea	Early vomiting	Late vomiting
Anticholinergics				
Transdermal scopolamine[33]		5 (3.2 to 11.1)		5.9 (4.2 to 11.1)
Antihistamines				
Dimenhydrinate[34]	8 (3 to 20)	6 (3 to 33)	7 (4 to 50)	5 (3 to 8)
Butyrophenones				
Droperidol 0.5-0.75 mg[36]	4.8 (3.0 to 12)	11 (6.9 to 25)	10 (4.6 to 51)	3.4 (2.4 to 5.7)
Droperidol 1 – 1.25 mg[36]	6.1 (4.5 to 9.4)	6.8 (5.2 to 9.7)	7.6 (5.8 to 11)	8.2 (5.6 to 15)
Droperidol 1.5 – 2.5 mg[36]	5.9 (3.8 to 13)	5.8 (3.8 to 12)	6.9 (4.7 to 13)	7.1 (4.2 to 23)
Droperidol 5 – 20 mcg /kg [36]				7.3 (4.5 to 20)
Droperidol 50 mcg / kg [36]			7.4 (3.9 to 58)	4.4 (2.5 to 17)
Droperidol 75 mcg / kg [36]			4.2 (3.3 to 5.9)	3.8 (2.8 to 5.2)
Droperidol in PCA morphine[161]		5.1 (3.1 to 15)		3.1 (2.3 to 4.8)
5-HT$_3$ receptor antagonists				
Ondansetron[53,161]				
Ondansetron 1 mg	21 (9 to ∞)		9 (5.3 to 30)	15 (8 to 210)
Ondansetron 4 mg	5.6 (4 to 9)	4.6 (4 to 5.5)	5.5 (4.4 to 7.5)	6.4 (5.3 to 7.9)
Ondansetron 8 mg	11 (4.2 to ∞)	6.4 (4.6 to 10)	6.4 (4.7 to 10)	5.0 (4.0 to 6.7)
Ondansetron 100 mcg/kg			5 (3.7 to 7.6)	2.7 (2 to 4.2)
Ondansetron 150 mcg/kg			2.5 (1.9 to 3.6)	2.7 (1.7 to 7.6)
Ondansetron in PCA morphine		-67 (-5.8 to α)		5.1 (2.8 to 23)
Tropisetron				
Tropisetron 2 – 5 mg[162]		6.7 (4.8 to 11.1)		5 (3.6 to 8.3)
Benzamides				
Metoclopramide 10 mg[44]	16 (7.5 to -210)	12 (6 to -1587)	9.1 (5.5 to 27)	10 (6 to 41)
Propofol				
Propofol induction[163]	9.3	50.1	13.7	14.9

	(6.1 to 19.4)	(7.6 to ∞)	(8.1 to 45.4)	(6 to ∞)
Propofol maintenance[163]	8 (6.4 to 10.8)	5.8 (4.2 to 9.4)	9.2 (7.6 to 11.7)	10.1 (6.2 to 28.8)
Steroids				
Dexamethasone 8 mg[75]	5 (2.2 to -21)	4.3 (2.3 to 26)	3.6 (2.3 to 8)	4.3 (2.6 to 12)
Other interventions				
Omitting nitrous oxide[131]	30 (13.5 to ∞)	36.9 (11.8 to ∞)	11.8 (8.5 to 19.4)	13.8 (8.8 to 31.6)
Omitting reversal of neuromuscular block[135]	-636	14	417	23
Non-pharmacological techniques (0 – 48 h)[95]	4 (3 to 6)		5 (4 to 8)	14 (6 to ∞)

NNT = Number needed to treat[2]

Although data from systematic reviews provide us with an indicator of the relative efficacy

and side effects of the various antiemetics it is important to note that there are limitations to

the interpretation of these data. The studies analyzed are often heterogeneous with varied

study designs. The outcome variables may not have been the same between studies and the

duration of data collection may be variable. Allocation concealment tends to be dissimilar

between studies and the definition of nausea and vomiting may not be standardized.

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[2] The confidence intervals of the NNT and NNH values straddled between positive to negative numbers and at times infibity. This is because the NNT is a reciprocal function, or the inverse of absolute risk reduction (ARR). This function is not continuous. As the ARR crosses the "line of no effect" from positive to negative, the NNT crosses from plus infinity to minus infinity. When the ARR is non-significant, by definition its confidence interval includes or touches zero. The confidence interval for the corresponding NNT will straddle from plus to minus infinity.

Table 5: NNH (95 % CI) of antiemetics studied in systematic reviews

	Scopolamine[33]	Metoclopramide[44]	Ondansetron[53]	Droperidol[36]
Extrapyramidal symptoms (adults and children)		556 (72 to -98)		408 (171 to – 1061)
Extrapyramidal symptoms (children)				91 (38 to -241)
Restlessness or abnormal movements (adults)		245 (42 to -65)		39 (18 to -263)
Dizziness (adults)	50	10 mg iv : -42 (-14 to 44) 20 mg iv: 3.3 (1.9 to 12) All doses combined: -3862 (-30 to 31)		142 (26 to -41)
Headache (adults)		-45 (-18 to 90)	1 mg: 54 4 mg: 30 8 mg : 42 16 - 48mg: 38 All doses: 36 (22 – 89)	-25 (-14 to -137)
Sedation and drowsiness (Adults)		10 mg : 20 (8.7 to -65) 0.2 mg/kg: 3.9 (1.6 to -7.7) All doses (iv and im) combined: 58 (16 to -36)		0.25 - 6.25 mg : -57 (52 to -18) 1.25 mg: 24 (13 to 139) 2.5 mg: 7.8 (4.9 to 20)
Sedation and drowsiness (Children)		-9316 (-35 to 35)		24 (13 to 139)
Elevated liver enzymes			31	
Hypotension			4 mg : 12	
Constipation			23	
Visual disturbances	5.6			
Dry mouth	12.5			
Agitation	100			

NNH = Number Needed to Harm
When no dose is indicated, the NNH is for all the doses tested combined.

The most commonly studied combinations have included a 5-HT$_3$ receptor antagonist with either droperidol or dexamethasone. Both combination regimens appear to be equally efficacious.[69,164]

In addition to using a combination of anti-emetics acting at different receptor sites, the multifactorial aetiology of PONV might be better addressed by the adoption of a multimodal approach. This is especially important in patients at high risk for PONV. Table 6 summarizes different strategies for keeping the baseline risk of PONV low.

Table 6: Strategies to keep the baseline risk of PONV low

A) Use of regional anaesthesia[15]

B) Avoid emetogenic stimuli:

- Nitrous oxide[108,131]

- Inhalational agents[141]

- Etomidate and ketamine[165]

C) Minimize the following:

- Intraoperative and postoperative opioids.[107,136,137,138,146] Adequate analgesia should, however, be achieved by incorporating local anaesthetics, NSAIDS, and opioids as required)

- The dose of neostigmine.[135] Consider limiting the dose to a maximum of 2.5 mg in adults.

D) Multimodal therapy:

- Total intravenous anaesthesia (TIVA) with propofol[133,163]

- Adequate hydration[92], especially with colloids[94]

- Anxiolytics, e.g. benzodiazepines[67,78,79]

- Non-pharmacological techniques e.g. acupuncture[95]

- α_2-adrenergic agonists e.g. clonidine[86,87]

For instance, there is an 11 fold increased risk for PONV in patients receiving general anaesthesia compared to those receiving a regional anaesthetic.[15] TIVA with propofol has been shown to reduce the incidence of PONV, especially in the early postoperative period.[163] However, the dose response relationship of propofol for its antiemetic effects is unclear (see Chapter 5). Avoidance of nitrous oxide (which increases postoperative vomiting) and volatile agents (which cause PONV for up to two hours postoperatively), and minimizing intraoperative and postoperative opioids, also reduce the incidence of PONV.[107,108,131,136,137,138] The use of large doses of neostigmine (>2.5 mg) increases the risk of PONV.[135] Other strategies that might reduce the incidence of PONV adequate hydration especially using colloids,[92,94] anxiolysis with benzodiazepines,[79,82,166] and the use of α_2-agonists.[86,87]

Scuderi et al tested a multimodal approach to the management of PONV in females undergoing outpatient laparoscopy. Their multimodal critical care algorithm consisted of total intravenous anaesthesia with propofol and remifentanil, no nitrous oxide, no neuromuscular blockade, aggressive intravenous hydration (25 ml/kg), triple prophylactic antiemetics (ondansetron 1 mg, droperidol 0.625 mg and dexamethasone 10 mg), and ketorolac 30 mg. Control groups included standard balanced outpatient anaesthetic with or without 4 mg ondansetron prophylaxis. Multimodal management resulted in a 98% complete response rate (no PONV and no antiemetic rescue) in PACU. No patient in this group vomited before discharge, compared with 7 % of patients in ondansetron group (p=0.07) and 22 % of patients in the placebo group (p=0.0003).[167] Subsequently, more studies confirmed the efficacy of a multimodal approach, especially in high-risk patients.[168,169]

Recommended strategy for PONV prophylaxis

Figure 4. illustrates a suggested algorithm for PONV prophylaxis. The risk of PONV

should be estimated for each patient. No prophylaxis is recommended for patients at low risk

for PONV except if they are at risk for medical consequences from vomiting e.g. patients

with wired jaws. For patients at moderate to high risk for PONV, regional anaesthesia

should be considered. If this is not possible or contraindicated and a general anaesthetic is

used, a multimodal approach to the management of PONV should be adopted to keep the

baseline risk of PONV low (Table 6). Combination antiemetic therapy is superior to

monotherapy for PONV prophylaxis.[160] However, the best available combination and the

optimum doses of antiemetic agents when used in combination are yet to be established.

Figure 4. Strategies for the management of PONV.

A

B

- History of PONV

PONV
Reduction
Strategy

- Female gender
- Postoperative opioid
- History of motion sickness
- Emetogenic surgery
- Non-smoker
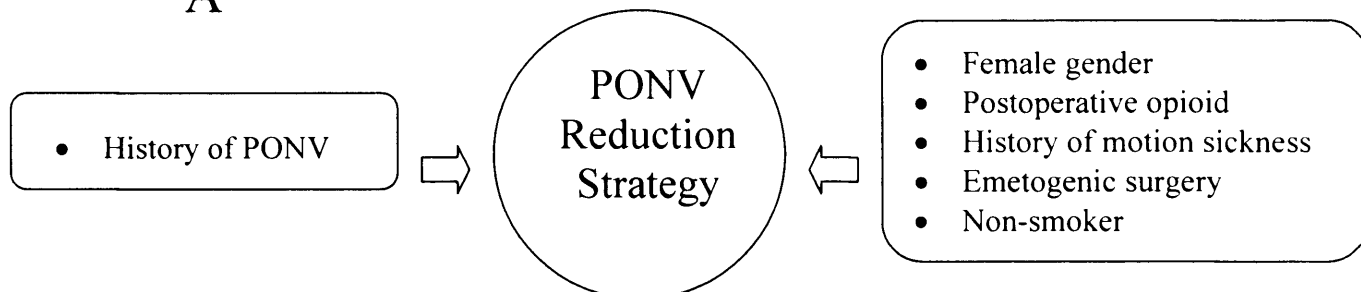
Consider

- Regional anaesthesia
- Adequate hydration
- Avoid nitrous oxide
- Avoid high dose neostigmine

A on **one** occasion
OR ≥ 2 factors
from **B**

A on **one** occasion
PLUS ≥ 1 factor from **B**
OR ≥ 3 factors from **B**

A on **more** than one occasions
PLUS ≥ 1 factor from **B**

Single Agent

Combination of 2 Agents

Multimodal

- 5-HT$_3$ antagonist
- Dexamethasone
- Scopolamine
- Promethazine
- Acupuncture

5-HT$_3$ antagonist
&
Dexamethasone
OR
5-HT$_3$ antagonist
& Acupuncture

≥ 2 antiemetics

PLUS

TIVA with Propofol

Recommendations for the treatment of established PONV:

There is a paucity of data on the use of antiemetics for the treatment of PONV in patients who failed prophylaxis or did not receive prophylaxis. This is due to the difficulty in performing such studies since a large number of patients would need to be recruited in order to obtain the required target of patients who eventually experience PONV.

The 5-HT$_3$ receptor antagonists were the most commonly tested drugs in rescue trials. Similar to their use in PONV prophylaxis, the anti-vomiting efficacy of the 5-HT$_3$ receptor antagonists is more pronounced than their anti-nausea efficacy. There is no evidence of dose-responsiveness for these agents when used for rescue. Therefore, small doses of these agents have been recommended for treatment: ondansetron 1 mg, dolasetron 12.5 mg, granisetron 0.1 mg and tropisetron 0.5 mg.[170] The NNTs for the different doses of the 5-HT$_3$ receptor antagonists when used for treatment are shown in Table 4.

In patients who fail ondansetron prophylaxis, there is evidence to suggest that the use of ondansetron for rescue is no more effective than placebo.[51] A drug acting at a different receptor might be more effective in this case.[35] There are some data from chemotherapy induced nausea and vomiting to suggest that granisetron might be efficacious for treating patients who fail ondansetron prophylaxis.[171,172] Such evidence is lacking in the PONV literature. There is also a striking lack of evidence on the therapeutic efficacy of older generation antiemetics in the treatment of established PONV. Droperidol was not different from ondansetron when used for the treatment of established PONV.[53] On the other hand,

ondansetron 4 mg was more effective than metoclopramide 10 mg in the treatment of established PONV.[138,173]

When evaluating PONV following surgery, the role of medication and mechanical factors should be considered first. Such contributing factors might include opioids, blood draining down the throat, or bowel obstruction. Then rescue therapy can be initiated. If PONV occurs within 6 hours postoperatively, patients should not receive a repeat dose of the prophylactic antiemetic; a drug from a different class should be used for rescue. Beyond 6 hours, PONV can be treated with any of the agents used for prophylaxis except dexamethasone and scopolamine, which are longer acting.

Summary

Identification of patients at increased risk for PONV allows targeting antiemetic prophylaxis to those who will benefit most from it. No prophylaxis is warranted for patients at low risk for PONV unless there is risk of medical sequelae from vomiting. The first step in reducing PONV risk is to reduce baseline risk factors. For patients at moderate to high risk, antiemetics should be used either as monotherapy or in combination for PONV prophylaxis. There is increasing evidence that a better prophylaxis might be achieved by using a combination of agents acting at different receptors. The adoption of a multimodal approach to the management of PONV should be considered in patients at high risk for PONV. In patients who develop PONV despite receiving prophylaxis, an antiemetic acting at a different receptor should be used for rescue within the first 6 hours following surgery.

After 6 hours, PONV can be treated with any of the drugs used for prophylaxis except

dexamethasone and scopolamine.

CHAPTER 3

Propofol

Propofol is a sedative-hypnotic that was introduced in 1986 in the UK as the first in a new class of agents known as the alkylphenols. Its distinctive pharmacokinetic and pharmacodynamic properties make it useful for a wide range of clinical uses. The injectable emulsion is indicated for induction and maintenance of general anaesthesia and monitored anaesthesia care with local or regional anaesthesia. Because it is characterized by a rapid onset of action, easy dose titration, and rapid recovery, propofol is frequently used for sedation in the intensive care unit and during office-based procedures such as colonoscopy. This chapter will discuss the pharmacokinetic and pharmacodynamic properties of propofol as well as its clinical uses and adverse effects.

Physical and Chemical Characteristics

Chemically, propofol is 2,6-diisopropylphenol (Figure 5). It has a molecular weight of 178.27. [174]. Propofol has only slight solubility in water and is formulated in an oil-in-water emulsion consisting of 10% soybean oil, 2.25% glycerol, 1.2% egg phosphatide, and disodium edetate (EDTA). [175] Propofol is isotonic with a neutral pH of 6 to 8.5, and a pKa in water of 11.[174 175]

Figure 5. Propofol chemical structure.
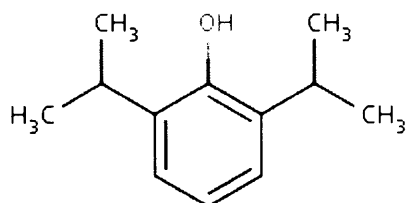
Pharmacokinetics

Propofol provides a rapid induction to anaesthesia, acting within 40 seconds of initiation of intravenous injection to induce hypnosis.[174] Propofol crosses the blood-brain barrier and is rapidly absorbed and extensively distributed. A 10-day infusion is associated with a volume of distribution of approximately 60 L/kg.[174] Propofol's initial distribution half-life is between 2-8 minutes, its slow distribution half-life is 30 to 70 minutes, and its terminal elimination half-life is 4-24 hours. Propofol's duration of action can vary based on the age of the patient, their medical status, and whether propofol is given as infusion or bolus dosing, as well as the duration of infusion.[175]

After the initial infusion, plasma levels decline rapidly as propofol is redistributed from the brain and other well-perfused sites into muscle, fat and other poorly-perfused tissue. [176] The initial distribution clearance of propofol is close to that of thiopental (3 to 4 L/kg/min). [176] However, propofol has a rapid metabolic clearance rate (nearly 10 times faster

than thiopental) and hence the recovery from its clinical effects is rapid.[175,177] As a result,

propofol concentrations decline rapidly in peripheral sites allowing for clinical recovery

from sedation and hypnosis while concentrations in the central compartment decline slowly

having little effect on the patient's clinical state. [176] The "context-sensitive half-time", which

is the time needed to reduce propofol concentrations in the central compartment by 50%, is

less than 25 minutes for infusions lasting up to three hours. [176] Recovery is even more rapid

when propofol infusion is titrated to effect, i.e. when plasma propofol levels are kept close

to the desired effect to ensure that a reduction of 10% to 20% will lead to awakening. [176]

Elimination, distribution clearance, and volume of central compartment are

decreased among elderly patients and are increased when normalized to body weight in

paediatric patients.[178] Thus, compared with adults, proportionally higher doses of propofol

are required to induce and maintain sedation in children and proportionally lower doses are

required for the elderly.[179] Propofol administration is typically titrated to effect in all

patients, however no extreme adjustments are necessary for patients who are obese or who

have moderate hepatic or renal dysfunction.[179]

Propofol is primarily metabolized in the liver through the cytochrome P450 system

and through glucuronidation.[180] One half to two thirds of propofol is excreted as propofol

glucuronide.[175] The primary catalysts for propofol glucuronidation are uridine diphosphate

glucuronosyltransferase I (UGT) family enzymes. The P450 isoforms that catalyze propofol

oxidation include CYP 2B6, 2C9, 1A2, 2A6, 2C8, 2C18, and 2C19 (2E1 and 3A4 are not

involved).[175] However, Oda and colleagues demonstrated that CYP2B6 is the predominant

CYP isoform involved in the oxidation of propofol by human liver microsomes.[181]

Propofol's metabolic clearance rate exceeds hepatic blood flow, which indicates the drug is also being metabolized in extrahepatic sites. [182] Hiraoka et al found that nearly one third of propofol clearance is renal.[183]

Pharmacodynamics

Mechanism of Action

Propofol's mechanism of action stems primarily from its effects on presynaptic and postsynaptic gamma-aminobutyric acid type A (GABA(A)) receptors which are found throughout the central nervous system and are associated with fast neuronal inhibition.[175] Propofol acts postsynaptically by enhancing the activity of the inhibitory neurotransmitter GABA at the $GABA_A$ receptor. When propofol is administered in clinically-relevant concentrations, chloride conductance increases and the postsynaptic membrane becomes hyperpolarized, which results in an anaesthetic effect. Studies evaluating the binding sites on the $GABA_A$ receptor indicate that propofol acts at a separate site of the $GABA_A$ receptor than benzodiazepines, barbiturates, or steroids.[175] Propofol's presynaptic effects occur through inhibition of GABA uptake and consequent accumulation of GABA in the synapse.[175] Propofol also interacts with different neurotransmitter receptors such as glycine, glutamate, and neuronal nicotinic ACh receptors.[175]

CNS Effects

Administration of propofol causes a generalized reduction in functional activity of the central nervous system, including sensory, motor, and limbic activity.[184] Propofol decreases cerebral blood flow and the cerebral metabolic rate in a dose-dependent manner.[185] When used during treatment of brain injury, propofol administration leads to a decline in regional cerebral blood flow, cerebral perfusion pressure, and intracranial pressure without causing changes in cerebrovascular resistance and cerebral arteriovenous oxygen content difference.[186]

Cardiovascular Effects

Propofol causes some cardiovascular depression during clinical use. Its cardiovascular effects include a decrease in mean arterial pressure and a reduced end-systolic quotient, most likely due to diminished afterload.[187] Global and segmental ventricular function appear to be unaffected by propofol. The cardiovascular depression associated with propofol appears to be due to decreased sympathetic tone with reduced vascular resistance.[175] It has been suggested that propofol-induced hypotension is related to its inhibitory effects on the sympathetic nervous system, impairment of the baroflex regulatory mechanisms, and reduced Ca^{2+} influx into arteries.[188] In an open-chested dog model, Puttick et al, found that propofol reduced left ventricular preload and contractility, as indicated by reductions in end-diastolic pressure and length. High infusion rates also

impaired relaxation. Reductions in preload and contractility contributed to the propofol-induced hypotension. However, regulation of coronary blood flow was not disrupted.[189]

Propofol has cardioprotective effects during myocardial surgery. It is believed to protect the heart from ischemia-reperfusion injury by preventing changes in adenine nucleotides, lactate, and amino acids during ischemia and by reducing cardiac troponin I release during reperfusion.[175] Propofol has antioxidant and free radical scavenging properties that promote further myocardial protection.[190] Another mechanism that adds to propofol's cardioprotective effect is its inhibition of the mitochondrial permeability transition pore (MPTP).[191] Opening the MPTP causes interference with ATP synthesis and other mitochondrial functions, which are a principle cause of reperfusion injury.

Respiratory System Effects

When propofol is administered for sedation it has a negative impact on ventilation. Propofol depresses ventilatory control causing depression of the ventilatory response to hypercapnia and the ventilatory adaptation to hypoxia.[192,193] This response is mediated through the central chemoreflex loop at the central chemoreceptors. Research shows propofol reduces central carbon dioxide sensitivity which has an effect on the control of breathing. $GABA_A$ receptors appear to play a role in the hypoxic ventilatory decline by inhibiting ventilation during sustained hypoxia.[194] Propofol may also cause airway obstruction by decreasing rib cage contribution to tidal volume and causing a decline in arterial oxygen tensions.[195]

Hepatic and Renal System Effects

Propofol sedation does not adversely affect renal or portal venous blood flow and it appears to increase hepatic arterial blood flow in a dose-dependent manner.[196] No impairment of proteinuria and glucosuria or protein/creatinine ratio were noted in the postoperative period following propofol anaesthesia.[197] After propofol administration, uric acid concentrations in urine are increased, causing the appearance of cloudy urine.[175]

Immuomodulatory effects

Propofol has several immunomodulatory effects. It decreases secretion of proinflammatory cytokines, changes nitric oxide expression, and impairs monocyte and neutrophil functions.[175] Propofol also has antioxidant radical scavenging activity that is similar to the actions of endogenous vitamin E.[198] This effect is dose dependent and is seen at doses significantly higher than those used for anaesthesia. However it has been suggested that propofol's antioxidant and anti-inflammatory effects may be beneficial in patients with sepsis and systemic inflammatory response from non-infective causes and in patients with ischemia-reperfusion injury. Propofol's neuroprotective effect may also be related to the antioxidant properties of its phenol ring structure.[175]

Clinical Uses

General Anaesthesia

For induction of general anaesthesia, adult patients typically receive 1.5 to 2.5 mg/kg of propofol whether unpremedicated or premedicated with benzodiazepines or opioids.[174] Propofol should be titrated upward by approximately 20-40 mg every 10 seconds until anaesthesia is achieved. Immediately after induction, anaesthesia can be maintained either by infusion or intermittent IV bolus injection. When delivered as a continuous infusion, from 100 to 200 mcg/kg/min is administered in a variable rate infusion with 60% to 70% nitrous oxide and oxygen. Typically, maintenance is initiated at 150 to 200 mcg/kg/min for the first 10 to 15 minutes, then decreased 30% to 50% during the first half-hour of maintenance. An overall rate of 50 to 100 mcg/kg/min should be achieved during maintenance. When delivered as an incremental bolus, 25 mg (2.5 mL) to 50 mg (5 mL) of propofol is given whenever alterations in vital signs suggest that the patient is responding to either surgical stimulation or light anaesthesia.

In clinical trials, propofol proved similar efficacy when used for induction of general anaesthesia as thiopental, methohexital or etomidate.[199] Compared with the other anaesthetics, propofol had a lower incidence of excitatory effects than methohexital, but was more likely to cause apnoea on induction than the other drugs. Due to its favourable pharmacological properties, propofol has replaced most other intravenous induction agents, such as thiopental and methohexital. It is also increasingly being used as maintenance agent during surgery instead of the inhalational agents.

Propofol is also commonly used for induction of general anaesthesia in paediatric

patients aged 3 years and older.[174] A dose of 2.5 to 3.5 mg/kg is typically administered over

20 to 30 seconds when patients are not premedicated or are lightly premedicated with

benzodiazepines or opioids. However the younger patients may need a higher induction

dosage. Patients classified as American Society of Anaesthesiologists Physical Status III or

IV require a lower dosage. Maintenance doses of propofol are given as a variable rate

infusion in conjunction with or without nitrous oxide. The maintenance therapy in children

with propofol is usually achieved at a rate of 200 to 300 mcg/kg/min immediately after the

induction dose. After the first half-hour of infusion, the rate can be lowered to 125 to 150

mcg/kg/min.

Induction of general anaesthesia with propofol in elderly, debilitated, or ASA-PS III

or IV patients should not be given as a rapid bolus due to an increased risk for

cardiorespiratory depression primarily due to vasodilatation.[174] Instead, such patients should

receive 1 to 1.5 mg/kg (approximately 20 mg every 10 seconds) until anaesthesia is achieved.

For maintenance of general anaesthesia, propofol should be administered at a rate of 50 to

100 mcg/kg/min.

Propofol has been widely used for induction of cardiac anaesthesia, especially

among patients with intact left ventricular function undergoing elective coronary artery

bypass grafting. Its use is more controversial in patients with impaired left ventricular

function due to its known risk for hypotension.[179] The recommended approach to

administration of propofol for induction of cardiac surgery is to avoid a rapid bolus and

administer boluses of 20 mg every 10 seconds to achieve a dose of 0.5 to 1.5 mg/kg.[174]

Among patients with impaired ventricular function, propofol is more frequently used for

maintenance rather than induction of cardiac anaesthesia. For maintenance of cardiac

anaesthesia, primary propofol (100 to 150 mcg/kg/min) is recommended with secondary

opioid therapy. Alternatively, a primary opioid can be given with secondary low-dose

propofol (50 to 100 mcg/kg/min).

Due to its capacity to elicit rapid recovery from sedation, propofol makes a valuable

tool for neuroanaesthesia. It allows for immediate post-operative assessment of CNS

function. Unlike volatile anaesthetic agents, propofol does not increase intracranial pressure

through cerebrovascular dilatation. Instead, it reduces intracranial pressure and intraocular

pressure, decreases cerebral metabolic requirement for O_2, and appears to provide cerebral

protection.[179] However, propofol should be given cautiously to patients with reduced

intracranial compliance and those receiving diuretic therapy to avoid acute haemodynamic

changes.[179] When administered for induction of neuroanaesthesia, propofol should be

administered at a rate of 20 mg every 10 seconds until induction onset (1 to 2 mg/kg).[174] For

maintenance, patients should receive 100 to 200 mcg/kg/min. Propofol has been the

anaesthetic drug of choice in awake craniotomy.

In a clinical trial, a propofol/fentanyl combination had fewer side effects and proved

as effective as two different volatile anaesthetic regimens in patients undergoing elective

craniotomy for supratentorial mass lesions.[200] In the first study group, propofol 1 to 2 mg/kg

was given, followed by propofol 50 to 300 mcg/kg/min infusions and fentanyl 0.03 to 0.05

mcg/kg/min. The second study group received thiopental 4 to 6 mg/kg followed by

isoflurane-N_2O anaesthesia. The third study group received thiopental followed by fentanyl-

N_2O anaesthesia with supplemental isoflurane to maintain haemodynamic stability as

needed. The group receiving isoflurane- N_2O had higher heart rate during induction and

lower mean arterial pressures during maintenance than the other groups and had the slowest

emergence rates. The fentanyl- N_2O group had the fastest emergence rates but also the

highest rate of vomiting (17%) compared with a rate of 2.5% in the propofol-fentanyl group.

No significant differences in neurologic outcome were found between the three groups.

The potential for seizure-like activity is a concern when propofol is used in

neurosurgery since propofol can induce dose-dependent changes in EEG.[179] While propofol

appears safe in patients with no history of epilepsy, its use is controversial in patients who

do have a history of epilepsy. There have been reports that propofol causes convulsions and

involuntary movements in such patients.[201] However, these seizure-like activities may be

opisthotonos and subcortical depression and do not appear to cause seizure-like activity on

EEG.[202] In other studies, propofol has been associated with anticonvulsant activity. It

decreases the duration of seizures in patients receiving electroconvulsive therapy.[203]

Sedation in the Intensive Care Unit (ICU)

Sedation in the ICU is primarily administered to reduce patient anxiety, facilitate

mechanical ventilation, and promote sleep. One of the primary attributes of a sedative used

in the ICU is rapid clinical recovery. When propofol 30 mcg/kg/min was compared with

midazolam 1.7 mcg/kg/min for sedation of 101 critically ill patients, recovery was more

rapid with propofol. [204] Patients were also discontinued from ventilatory support in a mean

of 5 minutes in the propofol-sedated group versus a mean of 148 minutes in the midazolam

group. In other studies, no clinical differences were found between propofol and

benzodiazepine infusion or bolus in the medical and post-surgical ICU.[174]

After cardiac surgery, propofol is often used for sedation in the ICU. A study

comparing midazolam (0.1 to 0.5 mg/kg/hr) with propofol (1 to 6 mg/kg/hr) found a

significantly shorter weaning time with propofol compared with midazolam.[205] Time from

midazolam discontinuation to extubation was 97.9 +/- 54.6 hrs (48.9 +/- 47.2 hrs to the first

disconnection, and 49.0 +/- 23.7 hrs to extubation). With propofol, time from

discontinuation to extubation was 34.8 +/- 29.4 hrs (4.0 +/- 3.9 hrs to the first disconnection,

and 30.8 +/- 29.2 hrs to extubation) (p < .0001).

However, concerns about cardiovascular stability with propofol remain. Several

studies reported a reduction in mean arterial pressure of 15% to 20% when a loading dose of

propofol (0.24 to 1.0 mg/kg) was administered following cardiac surgery.[206,207] Although the

mean arterial pressure remained low throughout the duration of one of the studies (10 hours),

Roekaerts et al. found the level acceptable in this population (patients with an ejection

fraction ≥ 40% prior to surgery).[207]

The use of propofol for sedation of paediatric patients in the ICU remains

controversial due to reports of neurologic sequelae following withdrawal of propofol and the

occurrence of metabolic acidosis following propofol infusions in patients with upper

respiratory tract infections.[179]

Sedation in Monitored Anaesthetic Care

Several sedative regimens have been used as supplements to local or regional

anaesthesia in monitored anaesthesia care but most have limitations. Benzodiazepines are

effective for sedation but their effects are often long-lasting and delay recovery. Opioid

analgesia has been combined with midazolam for monitored anaesthetic care, but this

combination can cause respiratory depression.[208] Propofol is a reliable alternative as a

supplement to monitored anaesthetic care sedation. Its ability to produce euphoria-like

mood alterations make it useful for procedures that require conscious sedation.[179] To achieve

monitored anaesthetic care, propofol can be used alone or in combination with low-dose

midazolam (2 to 3 mg) and fentanyl (50 to 75 mcg) or alfentanil (0.5 to 1 mg).[179]

A comparison between propofol and midazolam during monitored anaesthetic care

showed that propofol was associated with a lower incidence of ongoing sedation, drowsiness,

confusion, clumsiness, and amnesia than midazolam.[209] Although it was noted that

midazolam provided a greater degree of intraoperative amnesia, residual amnesia continued

for $\geq$ 60 minutes postoperatively. Another study compared remifentanil, (0.5 mcg/kg

followed by 0.05 mcg/kg/min) with propofol (0.5 mg/kg followed by 50 mcg/kg/min).[210]

Mean arterial pressure, heart rate and end-tidal CO_2 remained stable in both groups.

Respiratory rate and oxygen saturation values were lower in the remifentanil group than in

the group receiving propofol and one patient in the remifentanil group required airway

support. Patients receiving propofol had higher sedation levels, better amnesia and less

frequent nausea and vomiting during the recovery phase while those in the remifentanil

group had better pain and discomfort scores. Discharge times were similar in the two groups.

Propofol sedation has been given as an adjunct to local infiltration in a variety of

procedures including oral surgery, venous catheter placement, and breast biopsy.[211,212]

Propofol has also been used for upper gastrointestinal endoscopy. Compared with

midazolam, propofol had a more rapid recovery time and fewer symptoms of ongoing

sedation and grogginess following surgery.[213]

For initiation of monitored anaesthetic care, propofol should be administered either

as an infusion or using a slow injection method. During initiation of monitored anaesthetic

care, cardiorespiratory function should be closely monitored. When propofol is

administered as an infusion, the recommended rate is 100 to 150 mcg/kg/min for 3 to 5

minutes then it is titrated to the desired clinical effect.[174] Administration of propofol via the

slow injection method requires approximately 0.5 mg/kg administered over 3 to 5 minutes

and titrated to clinical responses. Rapid bolus dosing should not be used in the elderly,

debilitated, or ASA III or IV patients.

For maintenance of monitored anaesthetic care, it is preferable to use a variable rate

infusion method instead of intermittent bolus doses.[174] Maintenance rates of 25 to 75

mcg/kg/min during the first 10 to 15 minutes of sedation are recommended and infusion

rates should be decreased over time to 25 to 50 mcg/kg/min and adjusted to clinical

responses. Alternatively, incremental bolus doses of 10 mg or 20 mg can be used. In the

elderly, debilitated, or ASA-PS III or IV patients, the rate of administration should be over 3

to 5 minutes and 80% of the adult dose should be used.

Office-Based Sedation

Propofol is frequently used for office-based sedation because recovery is predictable

and rapid after a single bolus dose as well as after continuous infusion. Clarke et al. studied

the safety of propofol for office-based sedation over a five year period in two endoscopy

centres performing gastroscopy and/or colonoscopy.[214] Of the 28,472 procedures performed,

there were 185 sedation-related adverse events (6.5 per every 1000 procedures; 95%

confidence interval (CI): 5.6-7.4): 107 for airway or ventilation problems (3.8 per every

1000 procedures; 95% CI: 3.1-4.5) and 77 hypotensive episodes (2.7 per every 1000

procedures; 95% CI: 2.1-3.3). Four patients required transfer or admission to hospital,

however there were no patients who required endotracheal intubation and no deaths. The

authors concluded that general practitioners can safely use propofol for in-office sedation.

Another study evaluated the use of propofol for office-based plastic surgery in 4,778

outpatient plastic surgery procedures.[215] The anaesthesia protocol included sedation with

midazolam, propofol, and a narcotic. The average duration of the procedures was 111

minutes. No deaths, ventilator requirements, deep venous thromboses, or pulmonary emboli

occurred. Dyspnoea occurred in 0.05 percent (n = 2) of patients, protracted nausea and

vomiting occurred in 0.2 percent (n = 6) of patients, and unplanned hospital admission

occurred in 0.05 percent (n = 2) of patients.

Although office-based sedation is increasingly popular in the US, it is not practised

in the United Kingdom. Most of the procdures requiring minor sedation are performed in a

hospital or an ambulatory facility.

Adverse Effects

Pain on Injection

One of the most common problems with propofol sedation is the occurrence of pain

on injection, which has been reported in about 70% of patients.[216,217 218] The sensation of

pain is thought to be due to activation of the kinin cascade system caused by propofol.[219]

Several approaches have been used to reduce pain on injection. Local analgesics have been

administered at the injection site including lidocaine 40 mg, metoclopramide 10 mg, and

flurbiprofen axetil 50 mg. When preceded by venous occlusion for 2 minutes, these drugs

proved comparable for reducing pain during the injection of propofol. [220] In another study,

investigators compared premixture with lidocaine, premedication with remifentanil, and a

combination of the two.[221] The incidence of pain on injection in the group receiving 2%

lidocaine premixed with propofol (40 mg lignocaine in 180 mg propofol) was 35%.

Pretreatment with remifentanil 2 mcg/kg IV over 30 seconds had a pain incidence of 36%.

In contrast, the combination of lignocaine and remifentanil abolished moderate and severe

pain on propofol injection and reduced the incidence of pain to 10% (P = 0.003). Another

approach is to administer a propofol formulation with a 10% emulsion of long- and medium-

chain triglycerides (LCT/MCT), however this approach appears to be less effective than

propofol 1% with IV lignocaine pretreatment.[216]

Hypotension

Between 3% to 10% of adults experience hypotension during monitored anaesthetic

care with propofol.[174] The incidence increases to 17% in paediatric patients.

The rate is higher during ICU sedation with propofol. In that setting 26% of adults

experience hypotension. During induction of anaesthesia, arterial hypotension can result

from administration of propofol if spontaneous ventilation is maintained, however this is

typically not associated with a change in heart rate and minimal decrease in cardiac

output.[174] With positive pressure ventilation, cardiac output may become depressed,

especially if an opioid is added as premedication, which can cause a further decline in

cardiac output and respiratory drive. Patients who are at increased risk for hypotension

during propofol sedation include those with compromised myocardial function, intravascular

volume depletion, or abnormally low vascular tone (e.g., sepsis).[174] Other factors that

increase risk for hypotension include administration techniques. A rapid bolus injection of

propofol can result in undesirable cardiorespiratory depression. Similarly, if an infusion rate

of 50 mcg/kg/min or higher is required to achieve adequate sedation in medical ICU patients

or patients who have recovered from the effects of general anaesthesia or deep sedation, this

may also increase the likelihood of hypotension. To minimize hypotension in intubated,

mechanically ventilated adult patients, ICU sedation should be initiated slowly with a

continuous infusion so propofol can be titrated to desired clinical effect without increasing

the risk for hypotension.

Respiratory Depression

Both adults and paediatric patients are at increased risk for apnoea when propofol is

used for induction of anaesthesia. In clinical trials, 7% of adult patients receiving propofol

(2 to 2.5 mg/kg) on induction had apnoea lasting less than 30 seconds, 24% had apnoea

lasting between 30 and 60 seconds, and 12% had apnoea lasting longer than 60 seconds.[174]

When propofol was administered to paediatric patients for induction of anaesthesia, 12% of

patients who received bolus doses of propofol (1 to 3.6 mg/kg) had apnoea lasting less than

30 seconds, 10% had apnoea lasting between 30 and 60 seconds, and 5% had apnoea lasting

more than 60 seconds.

If propofol is given as a rapid bolus injection during monitored anaesthetic care,

cardiorespiratory depression can occur including hypotension, apnoea, airway obstruction,

and oxygen desaturation.[174] Elderly, debilitated, and ASA III or IV patients are at increased

risk for respiratory depression as they may have exaggerated haemodynamic and respiratory

responses to rapid bolus doses. The risk of cardiorespiratory depression with propofol is

also greater when infusion rates are rapidly increased. Thus, it is recommended that slow

infusion or injection techniques are used during initiation of monitored anaesthetic care and

variable rate infusion is used during maintenance of monitored anaesthetic care. This is

especially true for elderly or debilitated patients. When administered during maintenance of general anaesthesia, propofol can reduce spontaneous minute ventilation and increase carbon dioxide tension.[174] This effect can become more pronounced during rapid injection of propofol or when it is administered in conjunction with opioids or other sedatives.

Propofol Infusion Syndrome

In rare instances, prolonged propofol administration (>48 hours) at high doses (>4 mg/kg/h) may cause a fatal complication called propofol infusion syndrome.[222] This syndrome is associated with onset of metabolic acidosis, rhabdomyolysis of skeletal and cardiac muscle, and arrhythmias that can manifest as bradycardia, atrial fibrillation, ventricular and supraventricular tachycardia, bundle branch block and asystole.[222,223] In most cases, myocardial failure, renal failure, hepatomegaly, and death occur. In one recent report, propofol infusion syndrome occurred at a low infusion rate (1.9-2.6 mg/kg/h) and proved fatal.[222] Characteristic findings for propofol infusion syndrome include myoglobinuria, downsloping ST-segment elevation, an increase in plasma creatine kinase, troponin I, potassium, creatinine, azotaemia, malonylcarnitine and C5-acylcarnitine. If these characteristic findings are observed, propofol should be immediately stopped and cardiocirculatory stabilization should be initiated along with corrections of metabolic acidosis. When treating critically ill children and adults, propofol should not be administered for an extended period time (>48 hours) and doses should not exceed 4 to 5 mg/kg/h.[222]

CHAPTER 4

The use of propofol for its antiemetic effect: a survey of clinical practice in the United States.

Abstract

Introduction

Propofol is widely used for induction and maintenance of anaesthesia. The choice for the selection of propofol over other induction and maintenance agents depends on a number of factors. This project investigates the use of propofol by anaesthesiologists for its antiemetic effect, and to compare this with published evidence.

Methods

This survey was conducted with a random group of anaesthesiologists at the 1995 American Society of Anaesthesiologists annual meeting. One hundred and fifty anaesthesiologists were surveyed on how they use propofol to achieve an antiemetic effect.

Results

A large majority (84%) of the anaesthesiologists surveyed use propofol for its antiemetic effect: 63% of these use propofol for induction only for cases > 1 hour to achieve an antiemetic effect. In addition 37% use a 'sandwich' technique, utilizing propofol at the beginning and end of a case for a similar purpose. Simulation data demonstrate that

following propofol 2 mg/kg its concentration will drop below 350 ng/ml at 32 minutes.

Following 2 mg/kg and 20 mg within 10 minutes of the end surgery, its concentration will

drop below 350 ng/ml by 7 minutes after the 20mg bolus dose. This suggests that the plasma

concentrations of propofol when used in these cases may be below the effective range of

antiemetic effect.

Conclusions

Many anaesthesiologists use propofol for its antiemetic effect. However,

pharmacokinetic data suggest that the use of propofol purely for induction of anaesthesia, or

as part of a 'sandwich' technique is unlikely to confer an antiemetic benefit. However, there

is strong evidence for its antiemetic efficacy following anaesthesia maintained by a propofol

infusion, and also for its use in the post-anaesthesia care unit (PACU).

Introduction

Total intravenous anaesthesia before the introduction of propofol was not widely

practiced and was associated with prolonged recovery with many side effects. This was

primarily due to the long duration of action of the older intravenous sedatives as well as

older generation of opioids. Since the introduction of propofol into clinical practice in the

eighties, practitioners have embraced it enthusiastically due to its many favourable

properties which are associated with rapid and better quality of recovery from general

anaesthesia. Not only was wakeup more rapid and predictable, patients also achieved

recovery milestones much more rapidly, with more clear headedness and less drowsiness.[176]

Another phenomenon that was noted with propofol maintained anaesthetic was the

lower incidence of PONV. A meta-analysis of studies involving propofol found a significant

reduction in the incidence of PONV when compared with inhalational agent maintained

anaesthetic.[133] Thus practitioners have been increasingly using propofol either at induction

of anaesthesia[224,225], during maintenance of anaesthesia[226,227,228], or as a 'sandwich'

technique (at induction and again towards the end of anaesthesia) [124,229], with the hope of

achieving an antiemetic effect. There was a widespread belief that propofol use, regardless

of duration confers an antiemetic benefit. Hence, the purpose of this questionnaire survey

was to investigate how practitioners use propofol for its antiemetic effect and if the

perception of antiemetic properties of propofol when used in different settings is evidence

based.

Method

We surveyed practising anaesthesiologists at random, attending the American

Society of Anaesthesiologists (ASA) annual meeting. One hundred and fifty questionnaires

were handed out to anaesthesiologists standing in line to register at the meeting over a three-

day period. Completed surveys were collected after registration. The survey was anonymous.

Questions were asked concerning the use of propofol specifically to reduce PONV.

(Appendix 1) The respondents were asked to check all boxes, which apply to their practice.

Plasma concentrations of propofol were simulated based on a practice regimen using

pharmacokinetic simulation software [230] for a) an induction dose of 2 mg/kg, and b) an

induction dose of 2 mg/kg, and a bolus of 20 mg one hour later or 2 hours later. The second

simulation represents two examples of a simple 'sandwich' technique. The simulation was

based on the pharmacokinetic parameters for propofol reported by Gepts and colleagues.[230]

Descriptive statistics were used to describe the data from the questionnaire.

Results

A total of one hundred and fifty questionnaires were returned, which included 72

respondents working in an academic institution and 78 working in private (i.e. non-academic)

practice.

The antiemetic potential of propofol is a commonly cited reason for its use for

induction and maintenance of anaesthesia. In our survey, 84% of respondents used propofol

for this reason. Of these, 75% used propofol for induction only, and 37% for induction and

emergence. Total intravenous anaesthesia with propofol is practiced by up to 61% of this

group for at least a proportion of their anaesthetics. The numbers do not add up to 100%

because more than one response was allowed (i.e. an anaesthesiologist may use propofol for

induction of anaesthesia for some patients, but may also use the 'sandwich' technique on

occasion for others). The results are shown in Table 7.

Table 7. The use of propofol during anaesthesia, in expectation of an antiemetic effect.

Methods of propofol use		% propofol users
Induction only : cases less than 60 min		75
: cases greater than 60 min		63
Induction/emergence : cases less than 60 min		37
(i/e "sandwich") : cases greater than 60 min		36
Propofol-based : cases less than 60 min		61
: cases greater than 60 min		47

Tables 8 and 9 show the dose, frequency, and the time before the end of the case that propofol was administered by those using a sandwich technique. A majority (75%) uses a small dose (10-20 mg), and start using propofol within 10 minutes of the end of the anaesthetic. Many anaesthetists in this group (40%) use only a single dose of propofol at the end of the case.

Table 8. Propofol dose per bolus given towards the end of the case, and the frequency of dosing.

Bolus doses	%	Dose Frequency	%
10mg	29	once	40
20mg	45	1-4 min	35
30mg	10	5-10 min	14
40mg	5	11-15 min	6
>40mg	11	>15 min	5

Table 9. Of those administering bolus doses of propofol towards the end of the case, the time before the end that the bolus is administered.

Time to end case:	%
1-5 min	27
6-10 min	40
11-15 min	17
16-30 min	12
31-45 min	4

Fifty-eight percent of the respondents combined an additional antiemetic to enhance efficacy. Table 10 lists the various antiemetics and how often they were used. Of this group,

92

65% administer the additional antiemetic at the beginning of the case, and 35% towards the

end.

Table 10. Additional antiemetics given.

Antiemetic	%
Droperidol	29
Ondansetron	30
Metoclopramide	27
Promethazine	3
Prochlorperazine	0
Other	1

Simulation of propofol plasma and effect site concentration over time following a 2

mg/kg bolus and 20 mg at 1 hour is illustrated in Figure 6. Propofol concentrations fall

below 350 ng/ml within 32 minutes of the initial bolus and by 7 minutes following the

second 20 mg. bolus. An initial bolus of either 20 or 40 mg of propofol followed by an

infusion of 1 mg/kg/hr will maintain a propofol plasma concentration between 350 and 500

ng/ml.

Figure 6. Simulated plasma propofol concentration (ng/ml) following an intravenous (IV) induction dose of 2 mg/kg, with a further bolus of 20 mg iv given at 60 minutes. The therapeutic plasma concentration (dotted line) is shown at 350 ng/ml.
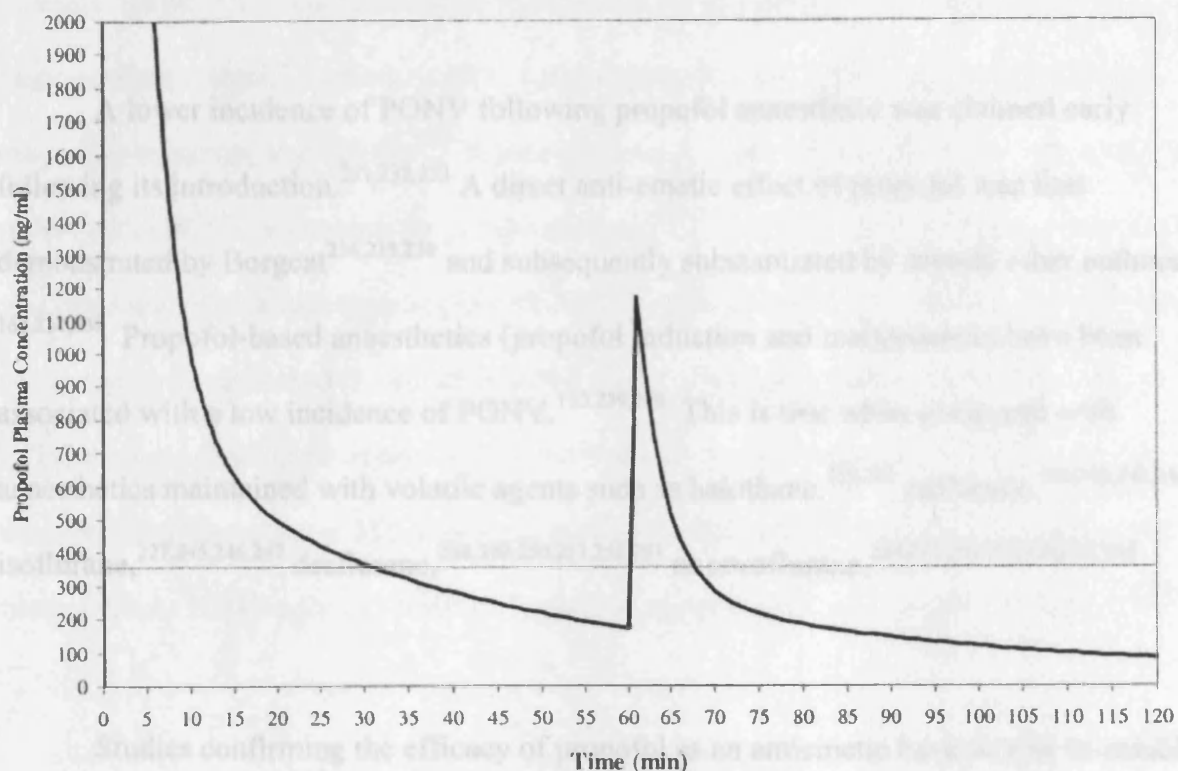
Discussion

This survey demonstrated that 84% of anaesthesiologists use propofol in the intraoperative period with the hope that it will reduce PONV. Propofol was used as either a single induction dose (63-75%), as a 'sandwich technique' (36-37%), or as a continuous infusion (47-61%). The percentages represent the response for longer cases and shorter cases respectively. The most common dose of propofol used in the sandwich technique was 20 mg. Simulations of propofol disposition indicate that following an induction dose of 2 mg/kg the

propofol concentration at 32 minutes will fall below its anti-emetic therapeutic concentration,

or by 7 minutes after a second dose of 20 mg administered at 1 hour following induction

(Figure 6).

A lower incidence of PONV following propofol anaesthetic was claimed early

following its introduction.[231,232,233] A direct anti-emetic effect of propofol was first

demonstrated by Borgeat[234,235,236] and subsequently substantiated by several other authors.

[163,237,238] Propofol-based anaesthetics (propofol induction and maintenance) have been

associated with a low incidence of PONV.[133,239,240] This is true when compared with

anaesthetics maintained with volatile agents such as halothane,[239,241] enflurane,[240,242,243,244]

isoflurane,[227,245,246,247] desflurane,[248,249,250,251,252,253] or sevoflurane.[254,255,256,257,258,259,260]

Studies confirming the efficacy of propofol as an antiemetic have almost invariably

involved the use of a propofol infusion, or an intermittent bolus technique for maintenance

of anaesthesia.[163,245,261,262] This survey found that a large majority of practising

anaesthesiologists use propofol at induction for long and short cases, with the hope of

achieving an antiemetic effect. However the scientific evidence for this is lacking. The lack

of efficacy of a single dose of propofol has been shown in many studies.[241,242,250,263] Indeed,

some studies suggest that even a short intermittent bolus technique with propofol may not be

superior to other intravenous induction agents, following cases with a relatively low emetic

potential such as therapeutic termination of pregnancy.[224,264] A few studies show a trend for

a reduction in PONV when patients were given propofol for induction of anaesthesia only.

The duration of procedure in these studies were all relatively short (less than 30 minutes).

Moreover this apparent trend failed to reach statistical significance in most of the studies.[245,265,266,267,268] There are exceptions, however. Rutter et al found, in patients undergoing minor gynaecological procedures, a significant reduction in PONV following incremental propofol, compared with incremental methohexital.[233] Mirakhur et al demonstrated a significant reduction in early nausea, but not vomiting, following minor surgical procedures in children.[269] Myles et al in a retrospective study found a modest reduction in PONV following propofol induction.[270] These conflicting findings may be due in part to the relative emetogenic potential of the operative procedure, individual differences in pharmacodynamic and the duration of the cases. There is evidence that the antiemetic efficacy of propofol is associated with a defined plasma concentration range.[263] We demonstrated (see chapter 5) that plasma propofol concentration for a 50% reduction in nausea scores is 343 ng/ml (10-90% CI, plasma propofol concentration 200-600 ng/ml).[271]

Interestingly 63% of respondents admitted to using propofol as an induction agent for longer cases primarily with the expectation of an antiemetic effect. In addition approximately one-third of respondents utilized a 'sandwich' technique with the same expectation. Of those using this technique a majority used a low dose of propofol (10-20 mg) and a significant number (40%) used only a single dose of propofol. Figure 6 demonstrates the serum propofol level following a bolus of propofol 2 mg/kg (a standard induction dose) declines rapidly and falls below 350 ng/ml after 32 minutes.[271] A single bolus of 20 mg propofol at 60 minutes leads the plasma level to rise into the therapeutic range for only 7 minutes (Figure 6), which simulates the situation if a 'sandwich' technique is employed. In another study (see chapter 7) where we compared the use of intraoperative propofol at

different times during surgery with ondansetron administered at the beginning of an

isoflurane maintained anaesthetic, we found that a 'sandwich' technique did not confer any

advantage with respect to PONV or more rapid recovery[124] The group that had propofol at

induction as well as maintenance had significantly greater efficacy compared with the

ondansetron group. The incidence of emesis and rescue antiemetic use was lower in the

propofol group compared to the ondansetron group. However the group where propofol was

administered at induction and towards the end of surgery (sandwich technique) did not show

a reduction in PONV compared with propofol used as the induction and throughout surgery.

Simulations of plasma propofol concentrations suggested that this group had a

subtherapeutic level. Campbell and Thomas studied the efficacy of a bolus dose of propofol

0.3 mg/kg given at the completion of surgery in a group of patients having gynaecological

laparoscopy, following thiopental induction and volatile maintenance of anaesthesia.[272] Not

surprisingly, in light of our simulation data, no benefit was found, probably because an

insufficient serum propofol concentration was achieved. Hence, it appears that propofol has

a concentration response relationship for the prevention of PONV.

In contrast to the findings above, Song et al have demonstrated a significant

reduction in early (but not late) PONV using a 'sandwich' technique with sevoflurane

anaesthesia, following laparoscopic cholecystectomy.[273] This may be due to the shorter

duration of surgery in this study. If the anti-emetic effect of propofol is related to its plasma

concentration, our simulations indicate that any possible benefit of a single dose either at

induction or near the end of surgery would disappear fairly rapidly. To achieve a therapeutic

concentration post-operatively, a bolus of 20-40 mg propofol followed by an infusion of 1-2

mg/kg/hr must be used. Another alternative is to administer propofol 20 mg intermittently via a patient controlled device with a lock out interval of 5 minutes.[274] (see chapter 6)

It is interesting to note that 58% of respondents routinely add another antiemetic to their anaesthetic. Table 10 indicates that droperidol, metoclopramide, and ondansetron are given with approximately equal frequency. A majority (65%) gives the additional antiemetic at the beginning of the case. Combining an additional antiemetic increases efficacy especially in high risk patients, as combinations of a variety of antiemetics have been shown to be more efficacious than using a single agent alone.[160,275,276,277,278,279] More recently, Apfel and colleagues demonstrated an additive effect of the various antiemetics, including propofol when used throughout the surgical procedure. Each antiemetic reduces the risk for developing PONV by about 25%.[130]

A limitation of the study is the applicability of the findings from this relatively small sample to a wider anaesthesiologist cohort. It is possible that anaesthesiologists attending an anaesthesiology meeting may have been better informed about the antiemetic effects of propofol. Previous meetings have shown roughly equal attendance of participants from academic and private practice background and hence strengthen the validity of our results.

In conclusion, this study demonstrates that many anaesthesiologists use a single dose of propofol to induce anaesthesia in expectation of an antiemetic effect, even though scientific evidence supporting this is lacking. The lack of efficacy of a single induction dose of propofol

may be explained by the subtherapeutic concentration of propofol. To achieve, and sustain a

therapeutic antiemetic level, especially for longer cases (>1 hour), a propofol infusion at

concentration levels used to maintain anaesthesia should be used.

CHAPTER 5

Determination of Effective Plasma Concentrations of Propofol for The Treatment of Postoperative Nausea and Vomiting

Abstract

Background

Propofol is widely used as the anaesthetic maintenance agent and is associated with a lower incidence of PONV. Small doses of propofol appear to possess direct antiemetic properties. The doses used were arbitrary and not based on dose response analysis. We sought to determine the plasma concentrations of propofol as an antiemetic for the effective treatment of postoperative nausea and vomiting.

Methods

Adult patients with ASA physical status 1 or 2, who had surgery under general anaesthesia were approached to take part in the study. Only patients who had nausea with a verbal rating score (VRS) >5, retching or vomiting in the Post Anaesthetic Care Unit (PACU) participated in the study. Propofol was administered to target plasma concentrations of 100, 200, 400 and 800 ng/ml by a computer assisted continuous infusion (CACI) device. If the preceding concentration of propofol did not adequately relieve symptoms, then the next step in incremental plasma concentration was taken. Treatment success was defined as having a 50% or more reduction of symptoms on the VRS. Fifteen minutes after achieving each target

concentration, the patient was assessed on a VRS for nausea and an arterial blood sample was obtained. The measured plasma propofol concentrations were used for analysis of data. Blood pressure, heart and respiratory rates, arterial blood saturation and sedation score were recorded. An overall satisfaction of treatment was assessed.

Results

Of the total of 89 patients consented for the study, 15 patients (17%) met entry criteria and were enrolled into the study. Five of these patients also experienced retching/vomiting at the entry of the study. Fourteen patients responded successfully to treatment. One patient did not achieve the required response at target plasma concentration of 800 ng/ml. Hence, the success rate for the treatment of PONV was 93%. The median plasma concentration that was associated with antiemetic response was 343 ng/ml. There was no difference in sedation scores from baseline and no episode of desaturation. Haemodynamic parameters were stable during the study period.

Conclusions

Propofol is efficacious for the treatment of postoperative nausea and vomiting at plasma concentrations that do not appear to produce increased sedation. Propofol is associated with minimal side effects and a great degree of patient satisfaction. Simulations indicate that to achieve plasma propofol concentration of 343 ng/ml, a bolus dose of 10 mg followed by 10 $\mu g.kg^{-1}.min^{-1}$ would be necessary.

Introduction

Intraoperative maintenance of anaesthesia with propofol is widely practiced and is associated with a lower incidence of PONV compared to inhalational agent maintained anaesthetic.[228,242,267,280,281] More recently, propofol in smaller doses had been used with success for the treatment of chemotherapy-induced emesis[234] as well as PONV.[235] In the PONV study, Borgeat and colleagues randomized patients who developed PONV in the recovery room into either receiving propofol 10 mg i.v. or placebo (intralipid) bolus. Patients who received propofol had a significant greater success rate (81% vs. 35%, p<0.05) when compared with placebo, but this response is short-lived. The doses that have been employed in these studies[234,235] were chosen empirically and not based on any systematic dose response analysis. It was further demonstrated that the antiemetic action of propofol was not due to the intralipid emulsion in the formulation and propofol has a direct antiemetic effect.[282] Schulman et al in a case report, determined the plasma concentration of propofol for the successful treatment of nausea in a postoperative patient to be 197 ng/ml.[283]

Given that propofol possesses antiemetic properties and studies to date have not systematically define the dose response relationship of propofol for its antiemetic effect, this study's aim was to determine the effective plasma concentration of propofol when used as treatment for postoperative nausea, retching and/or vomiting using a Computer Assisted Continuous Infusion (CACI) device. The primary objective was to determine the 50th percentile of the plasma propofol concentrations for the reduction of nausea score of at least 50%.

Methods

After Institutional Review Board approval, ASA physical status 1 or 2 male or non pregnant female patients between the ages of 18 and 70 who were scheduled to have surgeries under general anaesthesia were approached to participate in this study. Patients who had received drugs with an antiemetic effect within 24 h prior to initiation of anaesthesia, had previous allergy to propofol, had received an investigational drug within the past 30 days, had vomited or retched within the preceding 24 h, were twice their ideal body weight, or have significant organ dysfunction were excluded from the study. As this was a treatment study, we obtained informed consent from all potential study subjects in the preoperative screening clinic. Patients were provided with detailed explanation on the study protocol. Only subjects who met inclusion criteria as defined below were enrolled.

Patients were given a standardized general anaesthetic regimen. Fentanyl up to 100 mcg and midazolam up to 2 mg was used as premedication. Thiopental or propofol was used for induction of anaesthesia. General anaesthesia was maintained with fentanyl up to 5 mcg/kg/h, with nitrous oxide, oxygen and isoflurane to maintain haemodynamic variables within 20% of baseline. The choice of neuromuscular blocking drugs and reversal of neuromuscular blockade were left to the discretion of the anaesthesia care providers. Patients were extubated at the end of the surgery and transferred to the PACU when awake, obey commands and met clinical criteria for extubation.

A research personnel was with the patients at all time during their stay in the PACU. While in the PACU, patients were assessed on their presence of nausea and vomiting symptoms. Those patients who developed symptoms of severe nausea as judged by the Verbal Rating Score (VRS) score >5 retching or vomiting and requesting an antiemetic were formally studied.

A CACI device was used to deliver the propofol. CACI device is an infusion pump programmed with a pharmacokinetic model for the drug being infused.[284] A pump control algorithm used a simulation of the model, computed at frequent intervals, to determine the infusion rates required to theoretically achieve and maintain the specified plasma drug concentration[285] and the pharmacokinetic data set used (Appendix 2) in this study was based on that by Gepts et al.[230]

Plasma concentration of propofol or intralipid was achieved in an incremental step-up fashion, with the first target plasma concentration of propofol at 100 ng/ml, followed by 200, 400 and 800 ng/ml if the preceding concentrations of propofol did not adequately relieve symptoms. (Figure 7) Each target concentration was maintained for a minimum of 15 minutes. Patients were assessed on their nausea scores every 15 min during the study period.

Figure 7. Study design. Targeted plasma propofol concentrations (ng/mL). Each plasma concentration was held for 15 min.
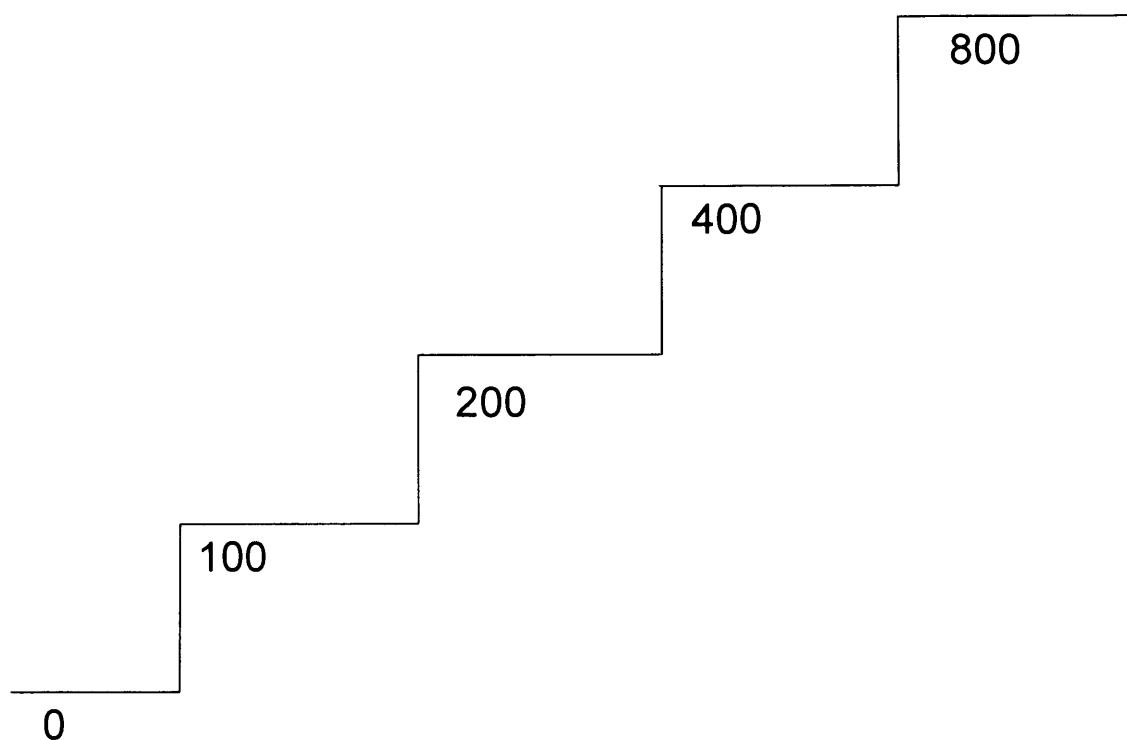
When the patients consented for the study, they were told that they would first

receive propofol if they had symptoms of nausea, retching and/or vomiting in the recovery

period and would like to have an antiemetic to relieve or treat their symptoms. However,

they could request for rescue antiemetic at any time during the study period. The 11 point

VRS, 0-10 whole number linear scale to assess their severity of symptoms, was also

explained to them. Zero (0) described 'no nausea' and 10 described 'nausea as bad as it

could be'.

Prior to the commencement of the propofol infusion, a baseline VRS for nausea was assessed. A separate intravenous cannula was established to deliver the study medication. A radial arterial cannula was inserted if it had not already been placed for surgical indications. An arterial blood sample was taken to determine the baseline plasma propofol concentration. The propofol infusion was set at a target plasma concentration of 100 ng/ml. Fifteen minutes after achieving each target concentration, the patient was assessed on a VRS for nausea and further arterial blood samples were obtained. Episodes of retching and vomiting were recorded. Treatment was considered successful if there was a 50% reduction of symptoms or greater on the VRS. Otherwise, the next higher plasma concentration was targeted until 800 ng/ml was reached. Successfully treated patients had the infusion continued at that target concentration for a further 2 hours. If the patients' VRS scores increased during the study period, the next higher target propofol concentration was delivered up to a maximum of 800 ng/ml.

Blood pressure, heart and respiratory rates, arterial blood saturation with the use of a pulse oximeter and observer assessment of sedation score (Table 11) were recorded prior to the commencement of the study, 15 minutes after each target plasma concentration and half hourly during the study period. An overall satisfaction of treatment was assessed at 24 h after the study period.

Blood samples and assays for propofol concentrations

Arterial samples were collected for whole blood propofol in heparinised tubes amd

placed on ice. They were refrigerated at -4°C and the concentrations were measured by high-

performance liquid chromatography (see appendix 3).

Table 11. Sedation scores

0	completely awake
1	awake but drowsy
2	asleep but responds to verbal commands
3	asleep but responds to physical stimulus
4	unarousable

Statistical Analysis

Steady state plasma concentrations were correlated with nausea scores for each

individual at the various time points. These data were then examined for plasma

concentrations that bracketed the transition from "no response" to "response". The mean of

resulting two plasma concentrations was computed for each individual. The median and

percentiles of the individual means were taken to represent the study population. All

calculations were performed with an Excel spreadsheet (Excel 7.0, Microsoft Corporation,

Redmond WA. 1995).

Results

A total of 89 patients consented for the study. Fifteen patients (17% of total) met

entry criteria and were enrolled into the study. Fourteen patients completed the study. One

patient did not achieve the required response at a target level of 800 ng/ml and was not

included in the analysis. Hence, the success rate was 93%. Five of these patients also

experienced retching/vomiting at the entry of the study and no patient had retching/vomiting

at the end of the study period. There were 2 male and 12 female patients. The Mean ± SD

for age was 41.2 ± 12, for weight was 78.8 ± 15.4 kg and intraoperative fentanyl use was

454 ± 187 µg. Nine patients received propofol intraoperatively for induction only.

The median (interquartile range) plasma concentration that was associated with

antiemetic response was 343 (246-507) ng/ml. Other concentrations and associated study

population percentiles are given in Table 12.

Table 12. Plasma propofol concentrations associated with a successful treatment response in various percentiles of population.

Percentile of population	Propofol plasma concentrations (ng/ml)
10	71
25	246
50	325
75	507
90	578

The targeted and measured propofol plasma concentrations were close and there was no overlap between the different target and measured propofol concentrations (Figure 8).
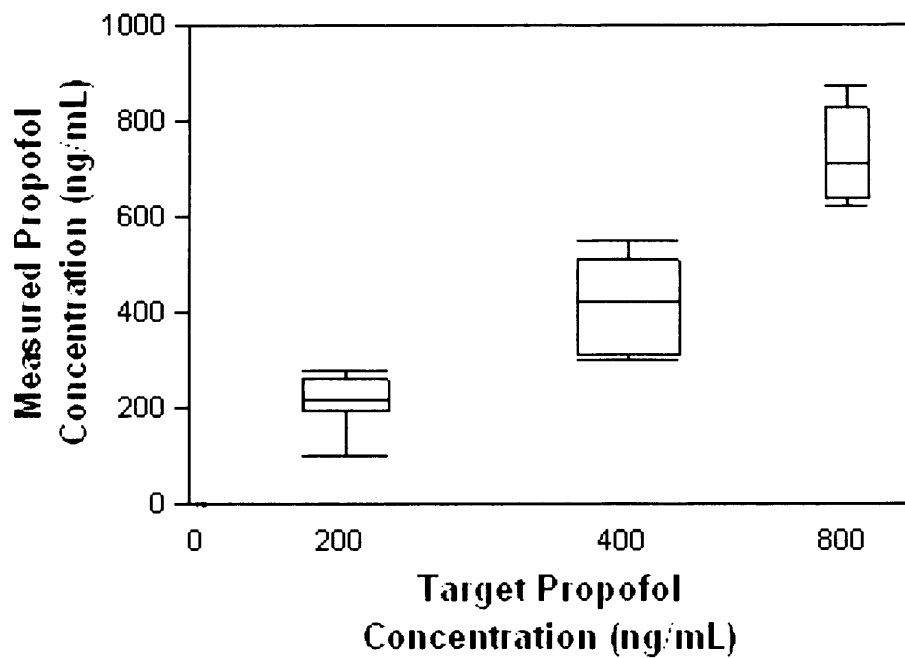
Data on measured plasma propofol concentrations that bracketed the transition from

"no response" and "response" vs. VRS for nausea are shown in figure 9. Nausea VRS at

various time periods and plasma propofol concentrations immediately before response, at

response and their arithmetic means for each subject are shown in table 13.

Figure 9. Raw nausea score vs. measured plasma propofol concentrations that bracketed the transition from "no response" to "response" for each patient. Below: Plasma propofol concentrations and probability of response.
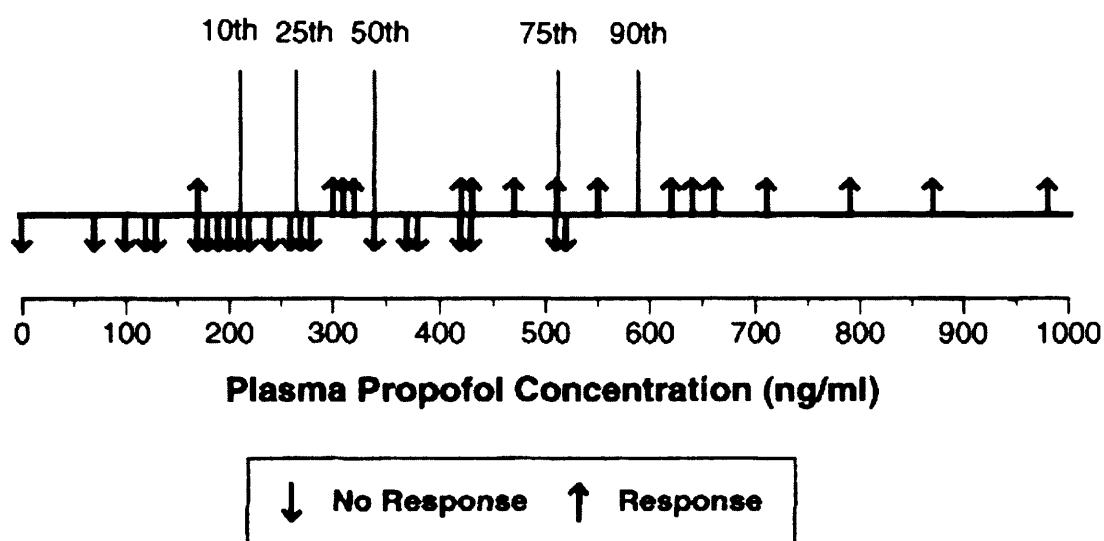
There was no request for rescue antiemetic during the study period and no patient had a sedation score of > 2 or an episode of desaturation. There were no significant changes with respect to time in sedation score (Table 14), neither were there changes in haemoglobin oxygen saturation, systolic and diastolic blood pressures and heart rate during the study.

Raw data on individual propofol concentrations are shown in figure 10. Only one patient had breakthrough nausea after initial control at plasma propofol concentration of 200 ng/ml but symptoms were controlled when the next higher plasma concentration (400 ng/nL)

was achieved. Thirteen out of 14 patients rated the treatment as satisfactory or very
satisfactory. One patient rated it as not satisfactory.

Figure 10. Individual plasma propofol concentrations at various nausea scores.
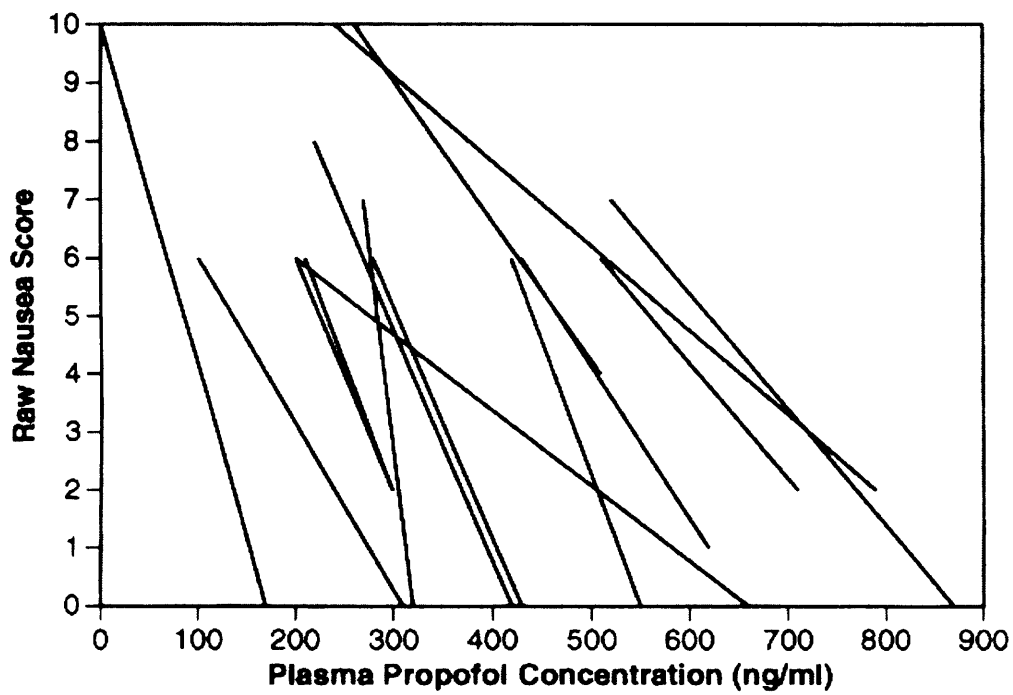
Table 13. Individual data on baseline VRS, VRS at treatment response and at the end of study period, measured plasma propofol concentrations at bracketed transition from "no response" to "treatment response" and the arithmetic means of the two propofol concentrations.

Patient No.	Baseline VRS	Treatment Response VRS	Final VRS (2 h)	[propofol] No response	[propofol] Treatment Response	Arithmetic Mean
1	6	0	0	280	430	355
2	7	0	0	270	320	295
3	6	1	0	420	550	485
4	10	3	0	0	170	85
5	6	2	2	210	300	255
6	6	0	0	100	310	205
7	7	2	2	200	300	250
8	7	0	0	200	660	330
9	10	0	0	220	420	320
10	10	5	4	260	510	385
11	7	0	0	520	870	595
12	8	1	2	430	620	525
13	10	2	2	240	790	585
14	6	0	2	510	710	610

[propofol]: Plasma propofol concentration in ng/ml

Table 14. Sedation scores at the various target plasma concentrations.

Target Plasma Propofol Concentrations (ng/ml)	No. of Patients	Median Sedation Scores	$25 - 75^{th}$ Percentile Sedation Scores
0	15	1	0-2
100	15	1	0-1
200	15	1	0-1
400	10	1	0-1
800	5	1	0-1
End of Study	15	0	0-1

Discussions

The median (10th-90th percentile) concentration of propofol for an antiemetic effect is 325 (71-578) ng/mL. Propofol when administered in these concentration ranges did not result in significant sedation or change in haemodynamics and was well tolerated.

Propofol has been widely used for the maintenance of anaesthesia. More recently, propofol has been used as an antiemetic for treatment of both PONV[235] as well as chemotherapy-induced[234] nausea and vomiting. Borgeat and colleagues used 17 µg/kg/min of propofol infusion in a group of patients receiving cisplatinum chemotherapy that had previously failed ondansetron and steroid during their initial chemotherapeutic treatment cycle. They found an incidence of 89% success in this group of patients. In the PONV settings, the same group of investigators reported the efficacy of propofol 10 mg (1 mL) vs.

intralipid for the treatment of established PONV. They found a high success rate of 81% in the propofol group (versus 35% in the intralipid group). However, the effect was relatively short lasting and 28% and 22% of the propofol and intralipid patients, respectively, had relapse within 30 min following treatment. We demonstrated that the antiemetic effects of propofol could be maintained if the plasma concentration was within the therapeutic range. These results suggest that propofol efficacy is likely to be related to its plasma concentrations.

We performed a simulation based on Borgeat et al's[235] propofol dosing regimen of 17 µg/kg/min which resulted in a high degree of efficacy in chemotherapy patients. The plasma concentrations of propofol were between 300–500 ng/ml for most of the 24 hour period. This is very similar to the median concentrations associated with successful PONV relief found in the present study. The 25%-75% plasma propofol concentrations for this study were between 246 and 507 ng/mL.

In a recent study, Pavlin et al[237] investigated the clinical effects of the sedative doses of propofol and alfentanil, alone and in combination. Interestingly, no subject experienced nausea or vomiting during the study period in the propofol and the propofol/alfentanil groups. However, there was an incidence of nausea of 50% in the alfentanil only group. The plasma propofol concentrations in their subjects ranged 150–600 ng/ml. The propofol concentrations in that study were almost identical to our results of the 90% confidence level of the anti-emetic action of propofol.

One of the concerns of using propofol in this setting is its sedative effects. However, the range of the propofol concentrations associated with antiemetic effects (10th to 90th percentile concentrations are 71-578 ng/mL) appear to be much lower than the propofol concentrations needed for sedation (1500-2000 ng/ml)[286] and maintenance of general anaesthesia (3000-10,000 ng/ml).[176,287] None of the patients in this study demonstrated sedation. Hence, although propofol has the potential to provide sedation the concentrations required for the treatment of PONV are well below these values and thus can be used in appropriately monitored settings.

There is much evidence in the literature that appropriate plasma concentrations of propofol are essential to demonstrate an antiemetic effect. Campbell et al[272] administered propofol 0.3 mg/kg at the completion of surgery and found that it had no effect in preventing PONV. Borgeat at al[235] found that the patient successfully treated with 10 mg bolus of propofol had relapse within 30 min after therapy. Simulation of 10 and 20 mg bolus dose of propofol revealed that the plasma concentration only remain above 300–500 ng/ml for 5-8 min after administration. However, a propofol loading dose of 10 mg followed by a continuous infusion of 10 µg/kg/min provides an immediate achievement and subsequent maintenance of an effective plasma concentration for the treatment of PONV. One patient in the present study did not achieve the required response and was considered treatment failure. This patient's highest plasma propofol concentration was 830 ng/ml. Hence it is important to note that high concentrations of propofol may not be effective in some patients in the treatment of PONV.

General anaesthetics maintained with propofol are associated with a lower

incidence of PONV compared to enflurane[240,242,243], isoflurane[288] or desflurane[249,250] based

anaesthetics. These findings only hold true when propofol is used throughout the procedure.

The protective effect of propofol against PONV seems to disappear when it is used as an

induction drug only. Although none of these studies measured the plasma concentrations of

propofol during the recovery period, the findings may not be surprising when one

considers that there is a therapeutic range of propofol to successfully prevent PONV.

The mechanism of action of propofol as an antiemetic is not known. It has been

postulated that propofol may act via an antidopaminergic pathway.[289] However, two recent

studies have not been able to substantiate this claim. Appadu and colleagues[290] showed that

propofol did not interact strongly with D_2 dopamine receptors. Hvarfner and associates,[291]

on the other hand, investigated subhypnotic doses of propofol infusion in healthy volunteers

after they were given apomorphine (acting on dopamine D_2 receptors in the chemoreceptor

trigger zone) to induce vomiting. They concluded that propofol given in a nonsedative dose

has no effect on apomorphine-induced vomiting. However, the total amount of apomorphine

given to induce vomiting was significantly larger during propofol sedation than during

saline infusion. They also did not measure blood concentrations of propofol. Several

mechanisms may be possible for propofol's antiemetic action. Propofol may have a direct

depressant effect on the chemoreceptor trigger zone, the vagal nuclei, and other centres

implicated in nausea and vomiting. Propofol also has been shown to decrease synaptic

transmission in the olfactory cortex, suggesting a decrease in the release of excitatory amino

acids such as glutamate and aspartate, which may be related to its antiemetic activity.[292]

Recently researchers showed that prolonged infusions of propofol (20 to 25 mg/kg/h for 6 h) cause decreased concentrations of serotonin in the area postrema,[293] and this may be mediated through gamma-aminobutyric acid$_A$ receptor mechanisms.[294]

One of the limitations of the study is the lack of a control group. The original plan was to include one. However, the institutional review board was adamant that it was unethical to include a placebo group as it was a PONV treatment study. Hence, the relief of PONV symptoms could have been due to some of the risk factors, e.g. inhalational agents and opioid's concentrations dissipating.

In summary we have defined the 50th percentiles for the plasma concentration of propofol associated with 50% reduction in nausea scores to be 343 ng/ml and the 10th to 90th percentile for similar outcome to be between 71 to 592 ng/ml. Based on simulation, the 50th percentile concentration can be achieved by a bolus dose of 10 mg followed by a continuous infusion of 10 μg/kg/min. This dose range does not cause significant sedation. Propofol as an antiemetic is associated with minimal side effects and a high degree of patient satisfaction.

CHAPTER 6

Comparison of Two Doses of Propofol vs. Placebo in Patient Controlled Nausea And Vomiting.

Abstract

Background

The role of propofol for the treatment of PONV is not well established. Empirical doses have previously been used to test the efficacy of propofol for treatment of PONV. We determined the plasma concentration of propofol for the effective treatment of PONV. Using this information, we designed this study to determine the efficacy and safety of two small doses of propofol administered by patient-controlled device for the treatment of established PONV.

Methods

Patients presenting for an ambulatory surgery under general anaesthesia were recruited. A standardized general anaesthetic regimen was prescribed. Those who experienced significant nausea and/or emesis in the recovery room were randomized to receive demand doses of propofol 20 mg (Group L), propofol 40 mg (Group H) or intralipid

(placebo-P). Study medications were prepared in equal volumes and were administered with a patient-controlled delivery device for 2 hours. The following parameters: nausea, vomiting, rescue antiemetic use, recovery profile, study drug administration history and satisfaction with treatment were assessed.

Results

Sixty-nine patients were enrolled in the study. Patient demographics were similar between the groups. The nausea score on average for a patient in groups L and H was 25% and 29% less than P ($p < 0.05$). This difference was apparent 15 min after initiation of therapy. More placebo patients vomited (L:12%, H:23% and P:56%; $p = 0.003$) and needed rescue antiemetics (L:17%, H:23% and P:70%; $p = 0.001$) compared with treatment groups. Placebo patients had a 9 and a 4 fold increase in risk of emesis and a 10 and an 8 fold increase in the likelihood of using a rescue antiemetic compared to groups L and H respectively. Sedation scores were similar between groups. Propofol treated patients had shorter PACU stay and higher satisfaction with their control of PONV than placebo ($p < 0.01$). There were 2 episodes of over sedation in the 40 mg propofol group but did not result in any adverse outcome.

Conclusions

Propofol appears to be safe and effective in treating PONV with great degree of patient satisfaction. A demand dose of 20 mg is recommended for treating PONV.

Introduction

The use of propofol as a maintenance anaesthetic agent intraoperatively is associated

with a reduced incidence of PONV.[227,237,270] However, the use of small doses of propofol as

a direct antiemetic has produced mixed results. Borgeat et al. demonstrated that propofol 10

mg were efficacious in treating PONV.[235] On the other hand, Zestos et al. found propofol in

small doses (0.2 mg/kg) were no difference in efficacy for the treatment of PONV compared

to placebo.[295] The use of subhypnotic doses of propofol infusion for the prevention of

PONV has also not been proven conclusively. Although Ewalenko et al. demonstrated the

efficacy of propofol when administered as an infusion postoperatively, other investigators

have not been able to produce similar results.[296,297,298]

Having defined the median concentration of propofol for 50% reduction in the

nausea scores[271], this study was designed to investigate the safety and efficacy of propofol

for the treatment of PONV, and the feasibility of its delivery by a patient-controlled device.

Methods

After Institutional Review Board approval and written informed patient consent,

ASA physical status I and II adult patients having day surgery with high emetogenic

potential under general anaesthesia were approached to participate in the study. Patients who

received an antiemetic on a regular basis or within 3 days of the study, who had symptoms

of nausea or/and vomiting within 24 hours, allergic to propofol, or not able to use a patient-

controlled analgesia (PCA) device were excluded from the study. A PCA machine (Lifecare™ PCA, Abbott Laboratory, Chicago, IL) was used to deliver the study solution. All patients were instructed on the use of the device during the pre-operative period. Patients received a standardized general anaesthetic which consisted of premedication with midazolam 1-2 mg, induction with fentanyl 2-3 μg/kg, thiopental 3-5 mg/kg and anaesthesia was maintained with fentanyl < 4 μg/kg/h, isoflurane 0.5-1.5%, N_2O 66% in O_2. Tracheal intubation and subsequent neuromuscular blockade were achieved with rocuronium or vecuronium. At the end of surgery, neuromuscular blockade was antagonized by glycopyrrolate 0.01 mg/kg and neostigmine 0.07 mg/kg.

In the postanaesthetic care unit (PACU), patients who experienced significant nausea (nausea score $\geq$ 5/10) and/or emesis, and requesting an antiemetic within 1 h of entry into the PACU, were enrolled. They were randomized to receive, in a double-blind fashion, propofol 20 mg (Group L), propofol 40 mg (Group H) or placebo (intralipid-Group P). The study drugs were prepared by the investigational drug pharmacy department in a 30 ml clear glass syringe with equal volume (4 ml) for each patient demand, and a lockout interval of 5 min with no maximum dose limit was prescribed. In group L, the volume of study solution was made up to 4 ml with 2 ml of intralipid and the placebo group received 4 ml of intralipid, to maintain complete blinding of the study solution. Rescue antiemetic (ondansetron 4mg i.v.) was administered when patient had nausea score > 4, two or more episodes of emesis or retching within 30 min or upon patient's request. The administration of propofol was discontinued after 2 hours. Patients were cared for in the PACU during the duration of the study.

The following variables were assessed prior to initiating treatment and at 15 and 30

min, 1, 1.5 and 2 h thereafter: nausea verbal rating scores (0-10), episodes of

vomiting/retching, rescue antiemetic use, sedation scores (Table 15), respiratory rate and

haemodynamics (heart rate, blood pressure and peripheral arterial oxygenation).

Table 15. Modified Observer's Assessment of Alertness/Sedation Scale

Response	Score level
Completely awake	5
Awake but lethargic response to name spoken in normal tone	4
Asleep but responds to loud verbal command	3
Asleep but responds to shaking	2
Does not respond to shaking	1
Does not respond to noxious stimulus	0

The time to readiness for PACU discharge was noted. Patients were discharged when

discharge criteria were met. Satisfaction with treatment (satisfied, neither satisfied nor

dissatisfied, dissatisfied) were assessed at the end of the study period. Data on patient's

study drug met and unmet demands, doses used were retrieved from the PCA machine.

Propofol utilization information were downloaded and the minimum effective plasma

propofol concentrations (concentrations at the point when patients self-administered a dose)

were simulated using a previously published propofol pharmacokinetic data set.[230] A

questionnaire on the incidence of post-discharge nausea, vomiting and satisfaction with

treatment were obtained at 24 h. Patients were asked to send back the questionnaire in a self-addressed envelope.

Sample size was estimated based on a two-tailed test of the difference between proportions in independent groups at alpha=0.05.[299] As there were no previous data on the efficacy of propofol for the treatment of PONV using this regimen, we based our power calculation on the incidence of nausea in patients having high risk surgery.[124] Considering nausea as the primary outcome, with a baseline (control) incidence of 60%, a sample size of 20 patients per group was found to provide 80% power to detect a difference of 30%. Mantel-Haenszel test, generalized estimating equations and logistic regression model, were used to analyze the data. A p value <0.05 was considered significant.

Results

A total of 200 patients were consented to participate in the study. Sixty nine patients met entry criteria and participated in the study. There were 24, 22 and 23 patients in the low dose propofol (Group L), high dose propofol (Group H) and the placebo (Group P) groups respectively. There were no significant differences among the groups with respect to age, weight, type of surgery, duration of anaesthesia, previous history of PONV or motion sickness, and use of intraoperative and postoperative fentanyl (Table 16).

Table 16. Patients' Demographics

	Low Dose	High Dose	Placebo
	n=24	n=22	n=23
M:F	3:21	5:17	2:21
Age	40 ± 13	40 ± 13	43 ± 11
Weight (kg)	81.2 ± 17.5	78.8 ± 24.4	81.6 ± 20.1
Type of surgery			
Gynaecology	7	8	5
Breast	7	6	4
ENT	5	5	9
General	5	3	5
Surgical duration (h)	2.3 ± 1.4	2.2 ± 1.4	2.2 ± 1.5
Intraoperative fentanyl use (µg)	429 ± 275	440 ± 379	380 ± 250
Postoperative fentanyl use (µg)	17 ± 34	23 ± 41	29 ± 48
Previous history of PONV/motion sickness	8/7	10/9	7/7

Values are numbers or mean ± SD

All three groups demonstrated decreasing severity of nausea over time (Figure 11).

Patients in the low dose group had a 25% less likelihood of being nauseous and patients in

the high dose group had a 29% less likelihood of being nauseous compared with the placebo

group (L vs. P: p=0.03, H vs. P: p=0.006). The difference in nausea scores between

treatment groups and placebo was apparent at 15 min after initiation of therapy and this

difference was seen throughout the study period. The complete response rate (no nausea,

vomiting or rescue antiemetic use) at 2 hours was significantly higher in the propofol treated

groups than placebo [L:19/24 (79%), H:16/22 (73%) and P: 5/23 (22%); p=0.01]. There

were significantly more patients in the placebo group who experienced vomiting [L:3/24

(12%), H:5/22 (23%) and P: 13/23 (56%); p=0.003] and the use of rescue antiemetic [L:4/24

(17%), H:5/22 (23%) and P: 16/23 (70%); p=0.001] compared with the L and H dose

propofol groups (Table 17). The odds ratio of emesis in the low and high dose propofol

groups were 0.11 (95% CI 0.02-0.43) and 0.23 (95% CI 0.06-0.78) compared with placebo

(The placebo group had a 9 and a 4 fold increase in risk of emesis compared to the low and

high dose groups). The odds ratio of rescue antiemetic use in the low and high dose groups

were 0.10 (CI 0.04-0.5) and 0.13 (CI 0.03-0.46) compared with placebo.

Figure 11. Nausea scores (VRS) versus time.

Nausea Scores vs. Time
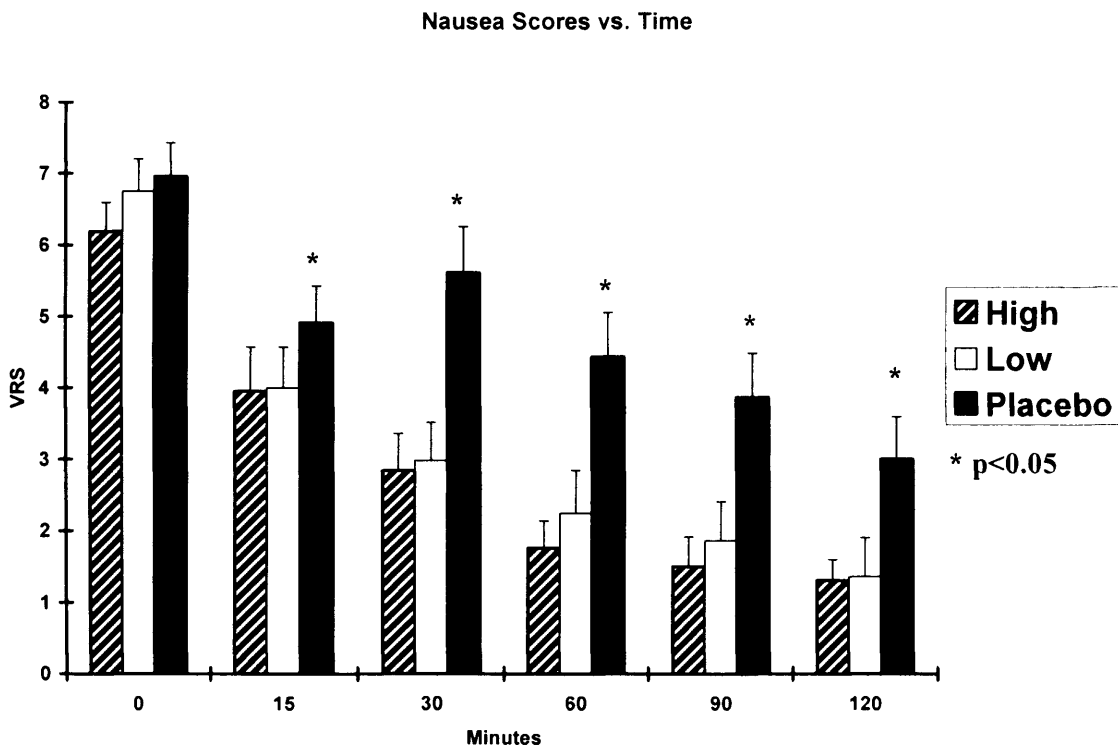
Values are mean and standard error bars.

Table 17. Patients' response, time to readiness for discharge and satisfaction with postoperative nausea and vomiting control in post anaesthetic care unit and at 24 hours.

	2 hours			24 hours		
	Low Dose n=24	High Dose n=22	Placebo n=23	Low Dose n=24	High Dose n=22	Placebo n=23
Complete response[#]	19 (79)	16 (73)	5 (22) *	12 (50)	12 (55)	8 (35)
Vomiting	3 (12)	5 (23)	13 (56) †	8(33)	8(36)	10(43)
Rescue antiemetic	4 (17)	5 (23)	16 (70) ‡			
PACU discharge readiness (min)	131 ± 35	141 ± 34	191 ± 92 §			
Patient Satisfaction						
Satisfied	23 (96)	21 (95)	10 (43)	22 (92)	16 (76)	12 (52)
Neither satisfied nor dissatisfied	1 (4)	1 (5)	3 (13)	2 (8)	2 (10)	4 (17)
Dissatisfied	0	0	10 (44)	0	3 (14)	7 (31)

Values are numbers (percentages) or mean ± SD
*p=0.01, †p=0.003, ‡p=0.001, §p=0.005; p values indicate placebo vs. propofol low and high dose groups.

PACU discharge criteria: haemodynamically stable, protective reflex present, operative pain controlled, absence of severe nausea or active vomiting, skin warm and dry, absence of bladder distention, oral temperature >35°C.

[#]Complete response rate at 24 hours was no nausea and vomiting.

The time to readiness for PACU discharge was significantly shorter in the low and high dose propofol groups compared to the placebo groups. (L: 131 ± 35 min, H: 141 ± 34 min, P: 191 ± 92 min; p=0.005). Two patients in the placebo group had to be admitted due to persistent and uncontrolled nausea and vomiting. There was no difference in sedation scores between the groups (Figure 12).

Figure 12. Sedation scores versus time.

Sedation Scores vs. Time
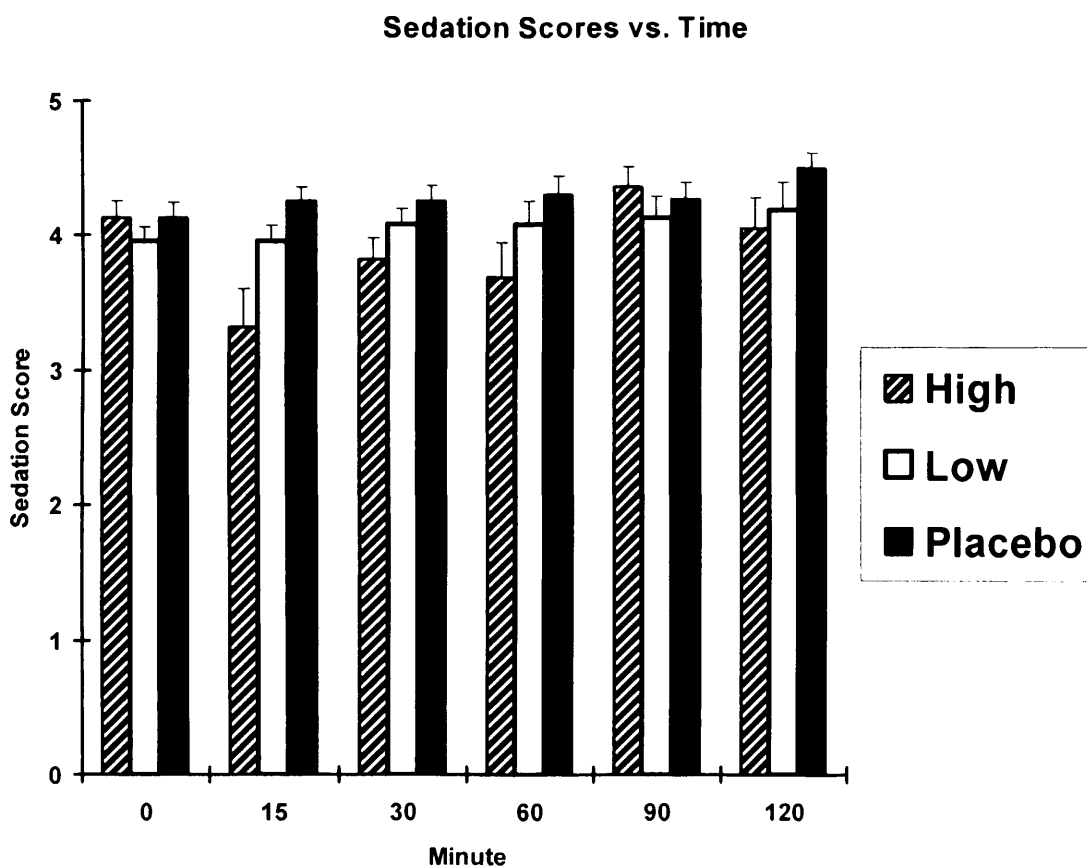
Values are mean and standard error bars.

However, 2 patients in the high dose propofol group experienced over-sedation; one patient had a sedation score of 3 (asleep but responds to loud verbal command), and another had a brief episode of apnoea with a sedation score of 1 (does not respond to shaking). No differences in pain scores, blood pressure, heart rate, respiratory rate, blood oxygen saturation were detected between the groups.

The propofol treated patients were also more satisfied with their control of PONV compared to placebo during their recovery room stay as well as at 24 h after discharge , p<0.05 (Table 18). Ninety six percent and 95% of the patients in the low and high dose propofol groups respectively were satisfied with the treatment compared to 43% in the placebo groups, p<0.05. Similar trends were observed at 24 hours.

Total propofol dose and patients' successful as well as unmet demands are presented in Table 18. There was a statistically significant difference in the unmet demands between the propofol treatment groups compared with placebo group. Figure 13 represents the individual patient data of the simulated minimum effective plasma propofol concentrations (MEC) for the two propofol treatment groups. The simulation was based on the timed doses administered by each patient via the patient-controlled device. The median (25-75th percentile) of the simulated MEC of propofol for the low and high dose groups were 174 ng/ml (170-297) and 296 ng/ml (240-437), respectively.

Table 18. The total dose of propofol administered, the number of successful deliveries and unmet patient demands.

	Low Dose (n=22)	High Dose (n=22)	Placebo (n=23)	p value
Total Propofol (mg)	100±60	200±80	0	
Successful Deliveries	5 ± 3 (5, 2-4)	5 ± 2 (5, 2-4)	8 ± 3 (7, 2-6)	0.0003
Unmet Demands	3 ± 4 (3, 2-6)	2 ± 4 (2, 1-5)	68 ± 136 12 (5-21)	0.0001

Values are mean ± SD, (median, interquartile range)

Figure 13. Simulated minimum plasma propofol concentrations in the high (40 mg) and low (20 mg) dose propofol treatment groups.

x = Propofol 20 mg group   o = Propofol 40 mg group
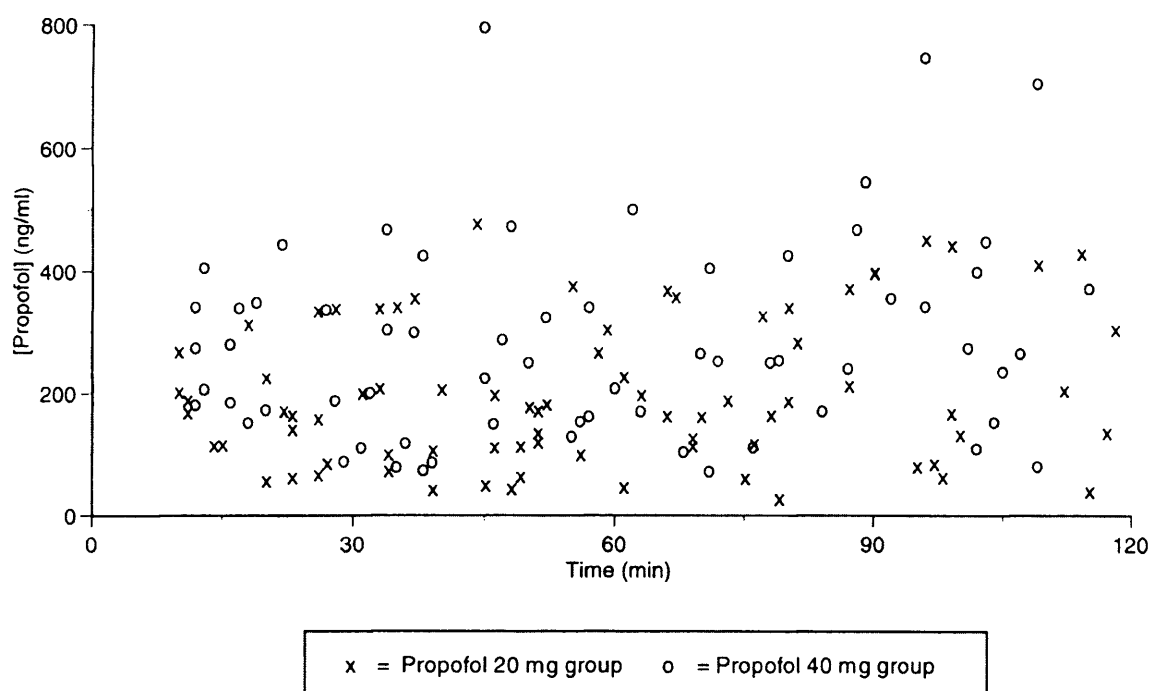
Discussions

Subhypnotic doses of propofol are efficacious for the treatment of PONV and are associated with an earlier readiness for PACU discharge and greater degree of patient satisfaction. A patient-controlled device may be used to deliver propofol in small boluses (20 mg) for this purpose and is safe in a PACU environment.

A number of investigators have demonstrated that intraoperative use of propofol for maintenance of anaesthesia is associated with a lower incidence of PONV compared to patients anaesthetized with inhalational agents.[240,242,249,288] More recently, propofol in subhypnotic doses have been used with success for the treatment of chemotherapy-induced emesis[234] as well as PONV.[235,283] The antiemetic action of propofol is not due to the intralipid emulsion in the formulation[282]. However, the efficacy of sub-hypnotic doses of propofol as a direct antiemetic has not been proven conclusively. In a relatively small study, Zestos et al. found that propofol 0.2 mg/kg was no more effective than placebo when administered for the treatment for PONV.[295]

The use of subhypnotic doses of propofol administered as an infusion for the prevention of PONV have also produced mixed results.[296,297,298] Although a number of studies have demonstrated efficacy when propofol was used as a low dose infusion (1-2 mg/kg/h) [283,296], others have failed to show such results using similar infusion regimen.[297,298] The dosing regimen employed in this study was based on our previous study where we defined the plasma concentrations of propofol for a 50% reduction in nausea scores to be

343 ng/ml.[271] Pharmacokinetic simulation suggested a bolus dose of 20-40 mg every 10 minutes would be required to achieve and maintain this concentration range. This study confirms that doses able to provide such concentration range are more effective than placebo in controlling PONV.

The concept of patient-controlled analgesia in the post-operative settings has been widely accepted and resulted in better pain relief and a great degree of patient satisfaction. [300,301] This is the first reported study where propofol was used as antiemetic delivered by a patient-controlled device. Patient-controlled delivery device is a convenient way of drug delivery, without involving the nurses in the recovery room who may have 3-4 patients to attend to at anytime. In addition, the pharmacokinetics of propofol makes it an ideal drug for patient-controlled delivery. This study demonstrated that patient-controlled antiemetic drug delivery is a feasible and safe technique. However, future studies are needed to compare the cost benefit ratio of this with other methods of deliveries, such as small dose continuous infusion or nurse administered propofol, and the use of other antiemetics.

Patients who received propofol also resulted in a shorter PACU stay and improved patient satisfaction. This may be related to the more rapid and successful control of PONV. Although placebo effect cannot be ruled out completely, however, we believe its effect is small and we were able to have effective blinding of the groups. The placebo group had poor control with symptoms of nausea and vomiting and more patients rated poor satisfaction with the treatment. The commonly held notion that nausea and vomiting in the immediate postoperative period are usually brief and get better without treatment is also untrue. As

demonstrated in this study, patients in the placebo group were more likely to have persistent

nausea and vomiting.

Based on the individual patient's dose and time of propofol administration, we

simulated the minimum effective propofol concentrations, i.e. the concentrations just before

each dose. This yielded a median simulated minimum effective plasma propofol

concentrations of 174 ng/ml (interquartile range 170-297 ng/ml) and 296 ng/ml (interquartile

range 240-437 ng/ml) for the low and high dose groups respectively. As these are the

simulated minimum effective concentrations, they are expectedly lower than the 343 ng/ml

reported for the median plasma propofol concentrations associated with successful control of

nausea. The simulated narrow interquartile range of propofol concentrations indicates that

inter-patient variability of the minimum effective antiemetic concentration of propofol is

small and well below that needed for sedation (900 – 1300 ng/ml)[302] and maintenance of

general anaesthesia (3000-10,000 ng/ml).[176]

A previous study compared the use of intraoperative propofol with ondansetron

administered at the beginning of an isoflurane maintained anaesthetic.[124] The group that had

propofol at induction as well as maintenance had significantly greater efficacy compared

with the ondansetron group. The incidence of emesis and rescue antiemetic use was lower in

the propofol group. However, the group where propofol was administered at induction and

towards the end of surgery (sandwich technique)[124] was not as protective against PONV.

Simulations of plasma propofol concentrations suggested that this group had subtherapeutic

drug levels.[124] Hence, it appears that propofol has a concentration response relationship for the prevention of PONV.

It was interesting to note that patients in the low dose propofol group had a lower risk of subsequent emesis and likelihood of using a rescue antiemetic compared with the high dose group. It appeared that propofol used as an antiemetic may have a ceiling effect at about 20 mg per dose. We do not have specific explanation for this phenomenon. It may be that patients in the high dose propofol group were more sedated and less clear headed, which could be more susceptible to emesis. Two patients in the high dose group experienced over sedation (OAA/S scores of 3 and 1 respectively). However, their peripheral oxygen saturations were above 96%. One of these patients had surgery lasting 3.5 hours and received 980 μg fentanyl intraoperatively. Hence, it is important to realize that high doses of propofol in combination with another sedative can result in increased sedation.

Patients' met and unmet demand data and their satisfaction with treatment provides the most compelling evidence that propofol possess antiemetic properties. Patients in the placebo group did not receive relief of their symptoms and hence continue to demand study medication during the lock-out intervals. These patients had higher incidence of vomiting, use of rescue antiemetic and also rated this modality of treatment poorly.

One of the limitations of the study was that we did not compare the propofol groups with a standard antiemetic group. Although additional information would have been helpful in clinical practice, this study design would also have required much larger sample size.

However, future studies should compared propofol used in this manner with another well established antiemetic.

In this study, we have demonstrated that propofol is safe and effective for the treatment of PONV and is associated with a shorter PACU stay and a high degree of patient satisfaction. The delivery of propofol by a patient-controlled device is a feasible and safe technique. As there was no difference between the low and high dose groups in efficacy and the potential of side effects with the high dose group, a 20 mg demand dose is recommended. Further studies are needed to compare the cost effectiveness of propofol patient-controlled antiemesis to other antiemetics, and the advantage of this drug delivery system over more conventional methods.

CHAPTER 7

Double-blind, Randomized Comparison of Ondansetron and Various Intraoperative Propofol Regimens for the Prevention of Postoperative Nausea and Vomiting

Abstract

Background

Propofol maintained anaesthetic is associated with a reduced incidence of PONV. Many practitioners utilize propofol in a "sandwich" technique (propofol for induction and towards the end of surgery) for its antiemetic effects. We therefore compare the efficacy of ondansetron and intraoperative propofol given in various regimens in a placebo controlled study.

Methods

Women patients scheduled for major breast surgery were approached for this study. Patients were randomly assigned to one of four groups. Group O received 4 mg ondansetron in 10 ml 0.9% saline and groups PI, PIP, and PP received 10 ml 0.9% saline before anaesthesia induction. Group O received thiopental, isoflurane, nitrous oxide-oxygen, and fentanyl for anaesthesia. Group PI received propofol, isoflurane, nitrous oxide-oxygen, and

fentanyl. Group PIP received propofol, isoflurane, nitrous oxide-oxygen, and fentanyl.

Thirty minutes before expected skin closure, isoflurane was discontinued and 50 to 150

mcg/kg/min propofol was given intravenously to maintain anaesthesia. Group PP received

propofol for induction and maintenance of anaesthesia, nitrous oxide-oxygen, and fentanyl.

Postoperative pain relief was provided with morphine administered by a patient-controlled

analgesia device. The incidence of nausea and vomiting, requests for rescue antiemetic and

sedation, pain scores, and haemodynamic data were recorded at various time intervals for 24

h.

Results

Within 6 h of surgery, groups O and PP had a lower incidence of nausea compared

with groups PI and PIP (P < 0.05). Fewer patients in group PP (19%) vomited during the 24-

h period compared with groups O (48%), PI (64%), and PIP (52%) (P < 0.05). The incidence

of antiemetic use was also less in group PP (P < 0.05). Patients in group PP had lower

sedation scores at 30 min and at 1 h (P < 0.05). There were no differences among the groups

in pain scores, blood pressure, heart rate, respiratory rate, and incidence of pruritus.

Conclusions

Propofol administered to induce and maintain anaesthesia is more effective than

ondansetron (with thiopental-isoflurane anaesthesia) in preventing PONV and is associated

with fewer requests for rescue antiemetic and sedation in the early phase of recovery. It is equally effective in preventing postoperative nausea as ondansetron in the first 6 h after operation. Propofol used only as an induction agent or for induction and at the end of surgery were not as protective against postoperative nausea and vomiting.

Introduction

Breast surgery is associated with a high incidence of PONV.[226] Propofol as an induction and maintenance agent has been associated with a lower incidence of PONV.[228,241,242,267,280] More recently, propofol in subhypnotic doses has been shown to be effective against chemotherapy-induced[236] nausea and vomiting and PONV.[235,283] Ondansetron is an effective antiemetic when compared with placebo,[50,303,304] metoclopramide,[305,306] and droperidol.[307,308]

Many clinicians utilize a propofol administration regimen, where propofol was used as an induction agent and the anaesthetic is then maintained with an inhalational agent. Towards the end of the surgery, the inhalational agent is replaced with a propofol infusion until wake-up. This is commonly known as the "sandwich" technique. It is generally believed that the patients would achieve a faster wake-up with a lower incidence of PONV. However, no study directly comparing propofol given in this fashion has been reported. We therefore conducted a double-blind, randomized study to compare the efficacy of ondansetron and intraoperative propofol administered in various regimens.

Methods

We enrolled 89 women classified as American Society of Anaesthesiologists physical status 1 or 2 who were 18 to 70 y old and scheduled for major breast surgery (mastectomy, breast reconstruction, and insertion of breast implants). We obtained institutional review board approval and patients gave their informed consent. Patients who had received drugs with an antiemetic effect within 24 h before initiation of anaesthesia, had received an investigational drug within the past 30 days, had vomited or retched within the preceding 24 h, or were twice their ideal body weight were excluded from the study. All patients received 1 to 2 mg midazolam as premedication. Patients were randomly assigned to one of four groups using computer-generated random numbers concealed in envelopes. Patients in group O received 4 mg ondansetron in 10 ml 0.9% saline, and groups PI, PIP, and PP received 10 ml 0.9% saline before induction of anaesthesia. Group O received 2 to 3 micro gram/kg fentanyl and 3 to 5 mg/kg thiopental intravenously, followed by 0.5% to 1.5% isoflurane and 66% nitrous oxide in oxygen. Group PI received 2 to 3 microgram/kg fentanyl and 2 mg/kg propofol intravenously, followed by 0.5% to 1.5% isoflurane and 66% nitrous oxide in oxygen. Group PIP received 2 to 3 microgram/kg fentanyl and 2 mg/kg propofol given intravenously, followed by 0.5% to 1.5% isoflurane and 66% nitrous oxide in oxygen. Thirty minutes before expected skin closure, isoflurane was discontinued and propofol 50 to 150 microgram/kg/min was administered intravenously to maintain anaesthesia until wake-up. Group PP received 2 to 3 micro gram/kg fentanyl and 2 mg/kg propofol intravenously, followed by propofol 50 to 150 microgram/kg/min intravenously and 66% nitrous oxide in oxygen. All patients received intravenous vecuronium to facilitate

tracheal intubation and subsequent neuromuscular blockade during surgery. Fentanyl up to a maximum intravenous dose of 5 microgram/kg/h was used during the procedure. At the end of surgery, 40 microgram/kg neostigmine and 8 microgram/kg glycopyrrolate were used to antagonize neuromuscular blockade.

Postoperative pain relief was provided by morphine (1 mg/ml) through the patient-controlled analgesia device (Life-care PCA, Abbott Laboratory, Chicago, IL) with standard settings (20 microgram/kg demand dose, 8-min lock-out intervals with maximum dose of 30 mg in 4 h). The incidence of nausea, retching, or vomiting and patient requests for rescue antiemetic (promethazine 12.5 mg i.v.) were recorded at 0.5, 1, 6, 12, 18, and 24 h by an independent observer blinded to the patients' treatment groups. Observer assessment of sedation scores[309] and patient assessment of pain scores (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = worst pain), incidence of pruritus and other adverse events, blood pressure, and heart and respiratory rates were also recorded at the same time periods.

Sample size calculation and statistics

Sample size was estimated based on a two-tailed test of the difference between proportions in independent groups at alpha 0.05.[299] Considering PONV as the primary outcome, with a baseline (control) incidence of about 65%, a sample size of 22 patients per group was found to provide 80% power to detect a difference of 30%; that is, a reduction

from 65% to 35% incidence. Based on the literature, a difference at least this large was expected between the control group (PI) and the treatment groups. Therefore, if either the propofol treatment group or the ondansetron group showed a greater reduction than placebo, the study would have at least 80% power to detect this difference. Categorical data were analyzed using the chi-squared test, and continuous data were analyzed by one-way analysis of variance. Post hoc analysis (Bonferroni adjustment) was performed to detect intergroup differences. A probability value less than 0.05 was declared statistically significant.

Results

A total of 89 patients completed the study. Groups O, PI, PIP, and PP consist of 21, 22, 25, and 21 patients, respectively. There were no significant differences among the groups with respect to age, weight, duration of anaesthesia, previous history of PONV or motion sickness, and use of intraoperative fentanyl and postoperative morphine (Table 19). No patient had a nasogastric tube inserted during the study period.

Table 19. Patient Demographic Data

	Group O (n=21)	Group PI (n=22)	Group PIP (n=25)	Group PP (n=21)	*P* Value
Age (yr)	45 ± 3	46 ± 12.5	46 ± 12.6	48 ± 14.2	NS
Weight (kg)	70 ± 16	72 ± 19	69 ± 17	70 ± 16	NS
Duration of anaesthesia (h)	2.6 ± 1.2	3.1 ± 1.5	2.8 ± 1.5	2.4 ± 1.3	NS
History of PONV/motion sickness (n)	5	6	7	5	NS
Intraoperative fentanyl (μg)	305 ± 150	312 ± 200	332 ± 218	310 ± 239	NS
Postoperative (24 h) morphine (mg)	10 ± 12	7 ± 6	10 ± 8	7 ± 8	NS

Values are mean ± SD.
NS = not statistically significant.

The overall incidence of PONV was 57%. The incidence of nausea in groups O and PP was less than in groups PI and PIP. This difference was statistically significant at 0.5, 1, and 6 h (P < 0.05). The incidence of postoperative vomiting and the use of rescue antiemetics within 24 h were significantly less in group PP compared with the other three groups (P < 0.05). Table 20 summarizes the incidence of nausea, vomiting, and use of rescue antiemetics among the groups.

Table 20. Cumulative Incidence of Postoperative Nausea, Vomiting and 24-Hour Request.

	Time (h)	Group O (n = 21) (%)	Group PI (n = 22) (%)	Group PIP (n = 25) (%)	Group PP (n = 21) (%)	_P_ Value
Nausea	0.5	3(14)	10(45)	9(36)	1(5)	<0.05
	1	4(19)	11(50)	9(36)	2(10)	<0.05
	6	5(24)	13(59)	11(44)	4(19)	<0.05
	12	9(43)	13(59)	12(48)	6(29)	NS
	18	13(62)	14(64)	14(56)	9(43)	NS
	24	13(62)	15(68)	14(56)	9(43)	NS
Vomiting	0.5	1(5)	3(14)	1(4)	0	NS
	1	2(10)	5(23)	3(12)	1(5)	NS
	6	4(19)	10(45)	8(32)	2(10)	<0.05
	12	8(38)	13(59)	10(40)	2(10)	<0.01
	18	8(38)	14(64)	12(48)	4(19)	<0.05
	24	10(48)	14(64)	13(52)	4(19)	<0.05
Request for rescue antiemetic	24	13(62)	15(68)	15(60)	6(29)	<0.05

Group PP patients consistently had lower sedation scores compared with the other groups (Figure 14). These differences reached statistical significance for group PP versus group O at 30 min and for group PP versus group PIP 1 h after the operation (P < 0.05 after

Bonferroni adjustment for post hoc comparison). There were no differences among the

groups in pain scores, blood pressure, heart and respiratory rates, and incidence of pruritus.

Figure 14. Sedation scores versus time (mean +/- SD). Group PP had lower sedation

scores compared to the other groups. * (p<0.05 Group PP vs. the other 3 groups)
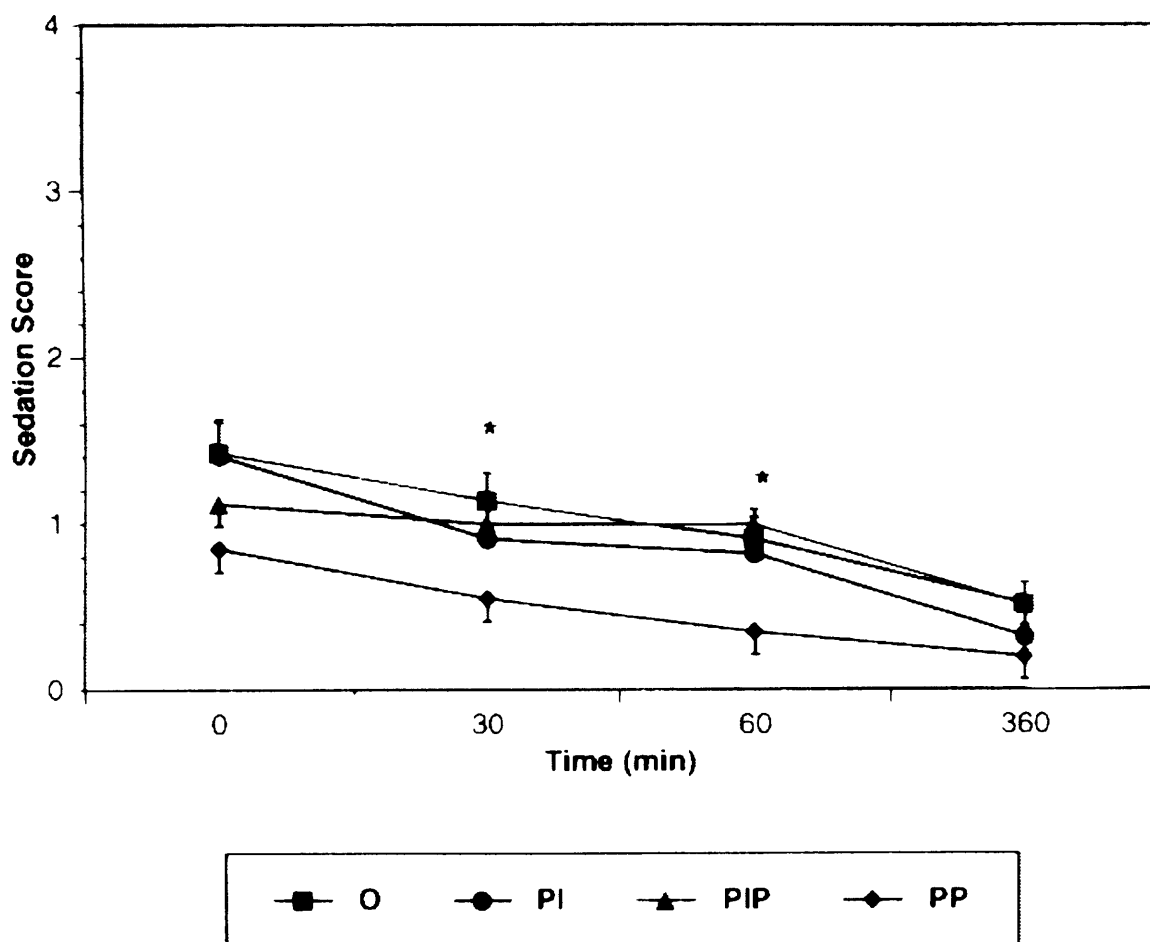
Discussions

The combined overall incidence of PONV in this population was 57% and was as

high as 68% in patients receiving propofol as an induction agent only followed by

maintenance of anaesthesia with isoflurane and nitrous oxide in oxygen. Major breast

surgery is associated with a high incidence of PONV. A previous study found the incidence

of nausea or vomiting to be as high as 60% and that most of these symptoms occur after

patients leave the postoperative care unit.[226] Recent reviews on PONV have not included

major breast surgery as a high-risk procedure,[1,16,104,310,311,312] probably because similar

studies in this patient category have been lacking. However, there are many common

denominators that may account for the very high incidence. Women have approximately two

to three times the incidence of PONV compared with men,[1,16,311,312,313] and the severity of

vomiting is also greater in women.[314] This may be due in part due to the difference between

men and women in levels of sex hormones.[315]

Ondansetron, a serotonin antagonist, is an effective antiemetic against PONV and

has minimal side effects[50,303,304] compared with other routinely used antiemetics. In

particular, when compared with droperidol, it is associated with less postoperative

drowsiness, restlessness, anxiety, or dizziness.[243] Although some data suggest that

ondansetron is superior to droperidol in the outpatient population,[308] the two drugs appear to

have similar efficacy in inpatient populations.[305,307]

Propofol was recently found to possess direct antiemetic properties,[235] and this

effect is not due to the intralipid emulsion in the formulation of propofol.[282] Propofol-based

anaesthetics have been associated with a lower incidence of PONV compared with

enflurane,[240,242,243] isoflurane,[288] or desflurane anaesthesia.[249,250] These studies found a low

incidence of PONV only when propofol was used throughout the procedure. The protective

effect of propofol against PONV seemed to disappear when it was used as an induction

agent only. We found that when propofol was used as an induction agent and anaesthesia

was maintained with isoflurane, nitrous oxide, and oxygen (group PI), it was not protective

against PONV. On the other hand, propofol used only as an induction agent has been

associated with a lower incidence of PONV in relatively short surgical procedures (less than

30 min).[245,266] Thus it is possible that a therapeutic range of plasma concentrations of

propofol, as has been shown in the previous chapter, is likely related to PONV protection.

We included group PIP (propofol as an induction agent and anaesthesia maintained

with isoflurane, nitrous oxide, and oxygen, followed by propofol substituted for isoflurane

30 min before the expected end of surgery) because many believe that propofol used in this

regimen might be associated with more rapid recovery and provide protection against PONV.

Our study, however, demonstrated that this technique, which is popular in clinical practice,

did not confer any advantage with respect to PONV or more rapid recovery as judged by

sedation scores. In contrast, the group receiving propofol for maintenance of anaesthesia did.

The plasma concentration of propofol for effective treatment of nausea was 350

ng/ml in our previous study.[271,283] This was much less than that needed for sedation (1,500 to

2,000 ng/ml) and maintenance of general anaesthesia (3,000 to 10,000 ng/ml). Borgeat and

associates[236] found an 85% to 90% success rate when propofol 17 microgram/kg/min was used to control chemotherapy-induced nausea and vomiting in a group of patients who did not respond to treatment with ondansetron and steroids during their previous chemotherapy cycle. We simulated their dosing regimen and showed that plasma concentrations of propofol lie between 300 and 500 ng/ml for the 24-h period. The simulation was based on the pharmacokinetic parameters for propofol reported by Gepts and colleagues.[230] (Appendix 2) In addition, the plasma concentrations of propofol associated with at least a 50% reduction of postoperative nausea is 405 +/- 59 ng/ml (mean +/- SEM) with 95% confidence intervals of 280 to 530 ng/ml. Using the data on propofol dosing regimens in patients in groups PI, PIP, and PP, we similarly simulated the plasma concentration of propofol in each of these patients for 6 h after the induction of anaesthesia. The results of the simulated data (Figure 15) showed that patients in group PP had higher plasma concentrations of propofol compared with those in groups PI and PIP (P < 0.01; analysis of variance) at all times during the 6-h recovery period. The simulated median plasma propofol concentration 1 h after termination of infusion was 424 ng/ml for group PP, 128 ng/ml for group PIP, and 41 ng/ml for group PI. This pharmacokinetic simulation may explain the difference in incidence of PONV among the three groups. Furthermore, the "sandwich technique" may have been protective against PONV for the first hour (36% vs. 50% for postoperative nausea and 12% vs. 23% for postoperative vomiting for group PIP vs. control, respectively) or after surgery of shorter duration, when the induction dose would contribute to the maintenance of therapeutic concentrations of propofol to prevent nausea and vomiting for a longer period.

Figure 15. Simulated plasma propofol concentrations for groups PI, PIP, and PP 6 h after completion of surgery. Bold lines indicate the median concentrations for each group. The upper bold line represents the median concentrations for Group PP, middle bold line represents Group PIP and the bottom bold line represents Group
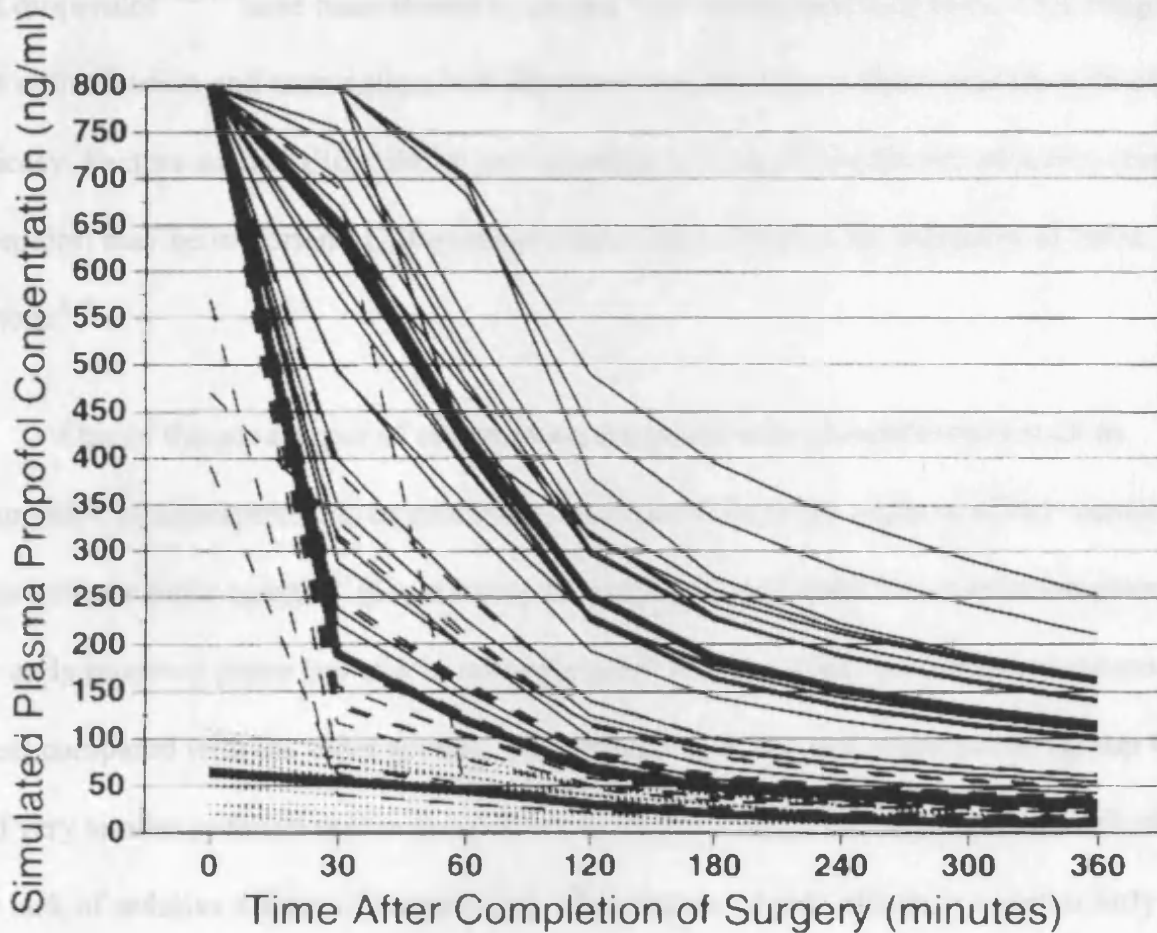
PI.

In this study, the antiemetic effects of propofol and ondansetron persisted through 6 h. Paxton and coworkers[308] found that the lower visual analogue score for postoperative nausea associated with ondansetron when compared with other antiemetics disappeared after

4 h. Ondansetron has a relatively short half-life of 2.8 +/- 0.6 h after a single 8-mg

intravenous dose.[316] Most of the parent drug is metabolized by hydroxylation and excreted

in the urine. Although the metabolites have some 5HT3-antagonist activity, they do not

contribute significantly to the therapeutic effect. However, the efficacy of ondansetron[317]

and droperidol[318,319] have been shown to exceed their elimination half-lives. This suggests

that redistribution and termination half-life alone may not have a direct relation with clinical

efficacy. Factors such as diffusibility and retention of drug within the site of action (central

receptors) may be important. Unfortunately there are no data on the influence of these

factors.[318]

One of the advantages of ondansetron compared with phenothiazines such as

droperidol, prochlorperazine, or promethazine is that it lacks the sedative effect commonly

seen with the latter agent.[320] In our study, we noted a significantly lower sedation score in

the early recovery phase (up to 1 h) when propofol was the induction and the maintenance

agent compared with the other groups. The patients who received ondansetron (group O)

had very similar sedation scores compared with those in the placebo group (PI), indicating

the lack of sedative effects of ondansetron. The absence of side effects is a particularly

desirable characteristic of any drug considered for antiemesis against PONV. Propofol, used

for induction and maintenance, was effective in preventing PONV, was associated with

early postoperative patient recovery, and did not cause other side effects.

In summary, propofol (when used to induce and maintain anaesthesia) and

ondansetron are equally effective for prophylaxis against postoperative nausea in the first 6

h. Propofol used in this manner was more effective than ondansetron in decreasing the

incidence of vomiting and the use of rescue antiemetics and sedation in the early recovery

period. Propofol used only as an induction agent (group PI) or for induction and at the end

of surgery (group PIP) were not as protective against PONV.

CHAPTER 8

A Randomized Comparison of Propofol versus Inhalational Based Anaesthetic Multimodal Management Strategy for the Prevention of Postoperative Nausea and Vomiting.

Abstract:

Background

Multimodal PONV prophylaxis management strategy appears to be superior to single agent prophylaxis. Propofol when given as the anaesthetic maintenance agent has been shown to reduce PONV. We tested the hypothesis that a multimodal PONV prophylaxis regimen incorporating total intravenous anaesthesia (TIVA) with propofol, and a combination of ondansetron and droperidol, is more effective than a combination of the same antiemetics in the presence of inhalational based anaesthetic or propofol alone.

Methods

Ninety patients undergoing laparoscopic cholecystectomy were randomized to one of three groups. Group 1 (multimodal group) received TIVA with propofol, droperidol and ondansetron. Group 2 (combination group) received droperidol and ondansetron with isoflurane and nitrous oxide for maintenance of anaesthesia. Group 3 (TIVA group) received

propofol for induction and maintenance of anaesthesia. PONV outcome variables including complete response (no PONV and no rescue antiemetic), incidence of nausea and vomiting and patient satisfaction on PONV control were assessed up to 24 hours.

Results

Complete response at 2 hours postoperatively, was 90 %, 63% and 66% in Groups 1, 2 and 3, respectively (p<0.05 Group 1 vs. 2). At 24 hours, the complete response was 80 %, 63% and 43% in Groups 1, 2 and 3, respectively (p<0.05 Groups 1 vs. 3). Patient satisfaction was also greater in the multimodal group compared to the other two groups in PACU (p<0.05).

Conclusions

The multimodal management strategy for PONV was associated with a higher complete response rate and greater patient satisfaction when compared to similar antiemetic prophylaxis with inhalational based anaesthetic or TIVA with propofol.

Introduction

Laparoscopic surgery is increasingly replacing open abdominal procedures.

Postoperative nausea and vomiting (PONV) are common after laparoscopic cholecystectomy

with a reported incidence from 53-72 %.[57,65,321,322] As the aetiology of PONV is often

multifactorial, there has been increasing interest in using a combination of antiemetics from

different classes for PONV prophylaxis for more effective management. Total intravenous

anaesthesia (TIVA) with propofol has been shown to be associated with less PONV

compared with inhalational agents, especially in the early postoperative period.[240,249,288] The

use of a multimodal approach incorporating both TIVA and a combination of antiemetic

agents was reported to be associated with an incidence of PONV below 10%. Published

studies to date investigating a multimodal approach for PONV prophylaxis have compared

the multimodal regimen to standard balanced anaesthesia using a volatile agent with or

without a single agent antiemetic prophylaxis.[167,169] It is unclear if the combination of two

antiemetics in the presence of TIVA with propofol is superior to combination antiemetic

regimen with volatile anaesthetic.

From our previous work, we demonstrated that propofol administered as the sole

anaesthetic conferred efficacy in reducing the incidence of PONV. Therefore this

prospective double-blind randomized controlled trial was designed to test the hypothesis that

a multimodal PONV prophylaxis regimen incorporating TIVA with propofol, and a

combination of ondansetron and droperidol, is more effective than a combination of the

same antiemetics in the presence of isoflurane/ nitrous oxide based anaesthetic, or TIVA

with propofol in ambulatory patients undergoing laparoscopic cholecystectomy.

Methods

Patients scheduled for laparoscopic cholecystectomy were enrolled after obtaining

IRB approval and written informed patient consent. Exclusion criteria were ASA physical

status IV or V, antiemetic or glucocortiocosteroids use within 24 hours of surgery , allergy

to ondansetron, droperidol or propofol, pregnancy, breast feeding, obesity (BMI>34), mental

retardation, or psychiatric illness. For women of childbearing potential, a negative serum β-

hCG test was confirmed before enrolment.

Anaesthetic technique was standardized. All patients received midazolam up to 2 mg

IV and fentanyl up to 100 mcg as premedication. Patients were randomly assigned to one of

three treatment groups. Randomization was achieved using a sealed envelope technique and

was prepared by an independent personnel not associated with the study. In group 1

(multimodal group), propofol 1.5-2.5 mg/kg was used for induction and 50-150 mcg/kg/min

for maintenance of anaesthesia with 50 % oxygen in air (no nitrous oxide). Droperidol 0.625

mg was given intravenously at induction of anaesthesia and ondansetron 4 mg was given

intravenously at the end of surgery. In group 2 (combination group), propofol 1.5-2.5 mg/kg

was used for induction of anaesthesia followed by maintenance with 0.5 –2.5 % inspired

isoflurane and 50 % nitrous oxide in oxygen. Droperidol 0.625 mg was given intravenously

at induction of anaesthesia and ondansetron 4 mg was given intravenously at the end of

surgery. Patients in group 3 (TIVA group) received propofol 1.5-2.5 mg/kg for induction and 50-150 mcg/kg/min for maintenance of anaesthesia with 50 % oxygen in air (no nitrous oxide). The patients' tracheas were intubated using a muscle relaxant of the anaesthestist's choice. An orogastric tube was inserted for suction of gastric contents following induction of anaesthesia and was removed at the end of surgery. Intraoperative analgesia was provided by fentanyl up to 5 mcg/kg/h. Ketorolac 30 mg i.v. was also given at the end of surgery. Local infiltration with 10 ml bupivacaine 0.5 % was administered around the trocar incision sites. Muscle relaxation was reversed with neostigmine 70 mcg/kg and glycopyrrolate 10 mcg/kg.

Data were collected by an independent research nurse unaware of the patients' randomization. The duration of surgery and anaesthesia, as well as the length of PACU stay were recorded. Postoperative assessments were made at 0, 30, 60, 90,120 min in PACU and at 24 h by telephone interview with a trained interviewer blinded to the patients' group. Nausea, emetic episodes, nausea score (11-point, linear numeric scale 0–10, where "0" represents no nausea and "10" represents worst nausea (the concept was explained to patients preoperatively), sedation scores (0-5) (modified observer's assessment of alertness/sedation scale – Table 15)[323], and rescue antiemetic use were recorded during these time intervals. The time to readiness for PACU discharge, when patients were fully awake, and oriented, with stable vital signs, minimal pain (<3 on a 0-10 scale) and were able to ambulate and not experiencing any side effects, were recorded. Patients rated their satisfaction with the control of PONV using a 5-point scale, ranging from 1 (very satisfied) to 5 (very dissatisfied) just before discharge from the hospital and at 24 hours.

Nausea was defined as a feeling of the urge to vomit, as solicited by the investigators during assessments. Vomiting was defined as expulsion of stomach contents through the mouth. Retching was defined as an attempt to vomit, not productive of stomach contents. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. A complete response was defined as no PONV and no need for rescue antiemetics. In the PACU, ondansetron 4 mg was used as the initial rescue medication for PONV. This was given if nausea was intractable and lasted for at least 15 minutes, if three emetic episodes occurred within 15 minutes, or at any time at the patient's request. Postoperative pain in the PACU was treated with fentanyl i.v. doses of 25-50 mcg.

Sample size calculation and statistics

Previous studies performed by our group demonstrated an incidence of nausea and or vomiting of 65% in this population under general anaesthesia without a prophylactic antiemetic. A sample size of 30 patients per group was determined to be adequate to demonstrate a 30% reduction in the incidence of PONV (from 65% to 35%) with $\alpha= 0.05$ and $\beta= 0.8$. Descriptive statistics was used to summarize the demographic characteristics of patients. Because subjects will be randomly assigned to treatment, no differences in these variables are expected across the treatment groups at baseline. Fisher's exact test and chi-squared procedures for categorical data, and Wilcoxon rank sum test and the Kruskal-Wallis test for continuous variables were performed for comparisons among the treatment groups.

Three treatment group comparisons were performed: the multimodal group versus the

combination and the TIVA groups. P< 0.05 was accepted as statistically significant.

Results

Ninety patients were enrolled in the study. The three groups were similar with

respect to age, weight, height, gender, ASA status, race, history of PONV or motion

sickness, duration of surgery, the amount of midazolam used pre-operatively, and the

amount of fentanyl used intraoperatively and in PACU (Table 21).

There was a significant difference between the groups in the complete response rate

at 2 hours and 24 hours postoperatively (p<0.05). Before discharge from the hospital, there

was also a significant difference between the groups in the number of patients who were

very satisfied with PONV management. The complete response rate in the multimodal group

(90 %) was significantly higher compared to the combination group (63 %) (p=0.03) but was

not statistically different compared to the TIVA group (66 %) (p=0.057). During the first 2-h

postoperatively, the average nausea score and the need for rescue antiemetic use were

significantly lower in the multimodal group compared with the combination and the TIVA

groups (p<0.05). There was no difference in sedation scores, incidence of vomiting and the

duration of PACU stay (Tables 21 and 22).

Table 21. Patient demographics

	Multimodal	Combination	TIVA
Number, n	30	30	30
Age, yr	45 ± 12	42 ± 15	45 ± 15
Weight, kg	81 ± 19	88 ± 24	84 ± 13
Height, cm	168 ± 9	162 ± 21	164 ± 20
Sex (male/female), n	9/21	3/27	8/22
ASA status (I,II,III), n	7/22/1	5/22/3	7/21/2
Race (A/AA/C)	1/4/25	0/5/25	0/6/24
History of PONV or motion sickness (yes/no), n	7/23	8/22	5/25
Duration of surgery, min	83 ± 23	95 ± 21	94 ± 32
Midazolam dose, mg	1.87 ± 0.33	1.85 ± 0.67	1.78 ± 0.08
Fentanyl dose, mcg	200 ± 76	188 ± 55	187 ± 56
Duration of PACU stay, min	171 ± 81	179 ± 98	181 ± 100

Values are mean ± SD or n.

TIVA= total intravenous anaesthesia, PONV= postoperative nausea and vomiting, PACU= post-anaesthesia care unit, A= Asian, AA= African American, C= Caucasian.

Table 22. Incidence of complete response, nausea, vomiting, degree of nausea, sedation scores, use of rescue antiemetics, and patients' satisfaction with PONV management.

	Multimodal	Combination	TIVA	P value
Complete response (0-2 h)	27 (90) †	19 (63)	20 (66)	0.03
Complete response (0-24 h)	24 (80) *	19 (63)	13 (43)	0.02
Average nausea score (0-2 h)	0 (0-1)* †	0 (0-4)	0 (0-1.5)	0.057
Average sedation score (0-2 h)	4.5 (2.7-5)	4.2 (0.7 – 5)	4.4 (3.3 – 5)	0.1
Incidence of nausea (0-2 h)	2 (7) * †	9 (30)	10 (33)	0.02
Incidence of nausea (0-24 h)	6 (20)*	11 (37)	17 (57)	0.02
Incidence of emesis (0-2 h)	0 (0)	3 (10)	2 (7)	0.36
Incidence of emesis (0-24 h)	1(3)	5 (17)	6 (20)	0.13
Need for rescue antiemetic (0-2 h)	2 (7)* †	9 (30)	10 (33)	0.02
Number of very satisfied patients (2 h)	29 (97)*†	21 (70)	21 (70)	0.03
Number of very satisfied patients (24 h)	29 (97) *	25 (83)	22 (73)	0.14

Values are median (range), or numbers (%).
* p <0.05 compared with the TIVA group.
† p <0.05 compared with the combination group.

At 24 h postoperatively, the number of patients who experienced a complete response was significantly higher in the multimodal group (80 %) compared with the TIVA group (43 %) (p=0.007), but was not different compared to the combination group (63 %) (p=0.25).

The number of patients who were very satisfied with PONV management before discharge from the hospital was significantly higher in the multimodal group (97 %) compared to both the combination and the TIVA groups (70 %) (p=0.01). At 24 h, the number of patients who were very satisfied with PONV management was significantly higher in the multimodal group (97 %) compared to the TIVA (73 %) (p=0.025) but not to the combination group (83 %) (Table 22).

Discussions

We have demonstrated that a multimodal management strategy for the prevention of PONV incorporating TIVA with propofol and a combination of two antiemetics was superior to the use of similar combination in the presence of inhalational anaesthetic or TIVA with propofol alone. In patients with high risk for developing PONV, routine prophylaxis has been shown to be efficacious in reducing the incidence.[35,324] This approach has been found to be more cost-effective and associated with a higher degree of patient satisfaction compared with treatment of established symptoms.[325] However, the optimal prophylactic antiemetic regimen has not yet been established. A combination of antiemetic agents acting at different receptor sites was found to be more efficacious compared with prophylaxis using a single agent.[160] The use of a multimodal approach was also found to have improved efficacy and has been advocated for patients at high risk for PONV.[128] This technique involves a combination of antiemetics, use of less emetogenic anaesthesia techniques, adequate intravenous hydration, and effective pain control.[326] We have adopted this technique in our multimodal group.

A technique incorporating TIVA with propofol, a combination of antiemetics acting at different receptors, avoiding nitrous oxide and high-inspired oxygen concentrations was described in two previous studies. In the first, Scuderi et al compared the multimodal approach to standard out-patient anaesthesia with or without ondansetron 4 mg in females undergoing outpatient laparoscopy. The multimodal group received TIVA with propofol and remifentanil, triple antiemetic combination with droperidol 0.625 mg, dexamethasone 10 mg and ondansetron 1 mg, adequate hydration, no nitrous oxide, 80 % oxygen, and no neuromuscular blockade. The other two groups received sevoflurane, nitrous oxide, and muscle relaxation with reversal at the end of the procedure. Patients in one group received antiemetic prophylaxis with ondansetron 4 mg while patients in the other group received placebo. The multimodal management resulted in a complete response rate of 98 % in PACU, compared to 76 % in the ondansetron group and 59 % in the placebo group.[167]

In the second study in females undergoing gynaecological and breast surgery, Eberhart and colleagues also found that a multimodal approach consisting of TIVA with propofol, no nitrous oxide, 80 % oxygen, dexamethasone 8 mg, haloperidol 10 mcg/kg, and tropisetron 2 mg, was associated with a 7 % incidence of PONV over 24 hours, compared with 41 % in the control group (desflurane, nitrous oxide, no antiemetic prophylaxis).[169]

While these two studies demonstrated the excellent efficacy of the multimodal approach for PONV management, the contribution of TIVA and avoidance of volatile agents and nitrous oxide to the success of the technique could not be evaluated because there was

no TIVA only group. Furthermore, these studies compared the multimodal approach to an inhalational technique with or without antiemetic prophylaxis using a single agent. Improved PONV prophylaxis using a combination of different antiemetics compared to prophylaxis using a single agent has previously been shown.[128]

In this study, we found that a multimodal approach consisting of TIVA with propofol, a combination of ondansetron and droperidol, and avoiding nitrous oxide, was associated with a higher complete response rate during the first two postoperative hours, compared with isoflurane/ nitrous oxide based anaesthetic with similar antiemetic combination. Patient satisfaction was also higher in the multimodal group. There was, however, no difference between the two groups in the duration of PACU stay. At 24 hours, there was also no difference between these two groups in both the complete response rate and in patients' satisfaction. This finding confirms that the antiemetic effect of propofol is short lived, since the improved PONV prophylaxis in the multimodal group did not extend into the post-discharge period. The limitation of the antiemetic effect of propofol to the early postoperative period has been shown in previous chapters[124] and other study.[163]

When compared to the TIVA group, patients in the multimodal group had a significantly lower incidence of nausea, lower nausea scores, required fewer rescues and were more satisfied with PONV management during the first 2 hours postoperatively. This superiority of the multimodal group also extended into the post-discharge period with a significantly higher complete response rate and greater patient satisfaction at the 24 hours assessment.

In a meta-analysis, Tramer reported that omitting nitrous oxide from general anaesthesia decreases postoperative vomiting significantly if the baseline risk of vomiting is high.[131] In this study, however, there was no difference in the incidence of emesis between patients who received nitrous oxide (the combination group) and those who did not receive nitrous oxide (the multimodal and the TIVA groups). This might be due to the administration of a combination of two antiemetics to patients who are receiving nitrous oxide and suggests that omitting nitrous oxide might not confer any additional benefit in patients receiving prophylaxis with a combination of antiemetic agents. However, such conclusion cannot be drawn from our study, since there was no control group receiving the inhalational technique without nitrous oxide. Apfel and colleagues showed that the exclusion of nitrous oxide only reduce the risk for developing PONV by 12%.[130]

This study has some limitations. Although it was powered to detect an overall difference between the groups in the incidence of PONV, it was not adequately powered for intergroup comparisons. We therefore failed to achieve statistical significance for some of the comparisons. We did not collect data about the smoking status of the patients. Non-smoking status is now considered a risk factor for PONV since it was included in Apfel's simplified risk scoring system.[108] Our study started before the publication of this scoring system, and therefore we did not collect information about the smoking status of the enrolled patients. Another criticism might be the absence of a placebo group in our study. However, since laparoscopic cholecystectomy is associated with a high risk of PONV in these ambulatory patients, we felt that it was ethically inappropriate to include a placebo group.

Another concern might relate to the Food and Drug Administration "Black Box" warning

regarding the use of droperidol for antiemetic prophylaxis. However, this warning has been

challenged by many anaesthesiologists.[37,40,41] Most experts in the field would agree that low

dose droperidol has been proven to be a safe and cost-effective antiemetic for over 30

years.[327]

In summary, we found that, in patients undergoing laparoscopic cholecystectomy, a

multimodal approach incorporating TIVA with propofol, a combination of ondansetron and

droperidol, and omitting nitrous oxide, was associated with a higher complete response rate

and greater patient satisfaction in the PACU, compared to similar antiemetic prophylaxis

with isoflurane/nitrous oxide based anaesthetic. The multimodal group also had a

significantly lower incidence of PONV and greater patient satisfaction when compared to

TIVA group at 24 hours postoperatively.

CHAPTER 9

A Randomized Comparison of Propofol and Isoflurane based Anaesthetics in Reducing Postoperative Nausea and Vomiting in Children and Adolescents

Abstract

Background

In children radiofrequency catheter ablation (RFCA) is typically performed under general anaesthesia. With the use of volatile agents in these patients postoperative nausea and vomiting (PONV) is common with an incidence of emesis as high as 60%, and the prophylactic administration of antiemetic drugs was reported to be ineffective. We have previously demonstrated the antiemetic effects of propfol when administered as the sole anaesthetic. In this study, we tested the hypothesis that a propofol based anaesthetic would have a lower incidence of PONV than an isoflurane based anaesthetic in children.

Methods

Children or adolescent were randomly assigned to receive either an isoflurane or propofol based anaesthetic. Prophylactic ondansetron was given to all patients and droperidol

was used as a rescue antiemetic postoperatively while PONV was monitored in the postoperative period. Incidence of nausea, vomiting, use of rescue antiemetic, sedation scores were recorded. The costs for the anaesthetic were also calculated.

Results

Fifty-six subjects were included in this study. The cumulative incidence of PONV was significantly higher in isoflurane group (nausea 63% and emesis 55%) compared with the propofol group (nausea 21% and emesis 6%). Rescue with droperidol was more effective in the propofol group compared with the isoflurane group. 70% of patients in the isoflurane group developed further vomiting compared with 0% after rescue with droperidol.

Conclusions

RFCA under isoflurane based anaesthetic was associated with a higher incidence of PONV compared with propofol based anaesthetic. Rescue antiemetic with droperidol was ineffective following isoflurane based anaesthetic. In contrast a propofol based anaesthesia is an effective strategy to prevent PONV in children undergoing RFCA.

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Introduction

In children radiofrequency catheter ablation (RFCA) is a highly effective treatment for supraventricular tachycardia (SVT).[328,329] General anaesthesia is often required to ensure comfort during the prolonged procedure and to assure immobility in order to facilitate accurate mapping and subsequent ablation of the accessory pathway and/or arrhythmogenic focus. However, PONV is a common problem in children and adolescents undergoing RFCA under volatile anaesthetics; an incidence of emesis as high as 60% has previously been reported.[330] Moreover, the intraoperative administration of prophylactic antiemetics (ondansetron, droperidol, and metoclopramide) was reported to be ineffective.[330] We hypothesize that the administration of a propofol based anaesthetic could effectively reduce PONV in this population as has been previously shown in other adult groups at high risk for developing PONV.[124] Therefore, we performed a randomized trial to test the hypothesis that a propofol based anaesthetic would have a lower incidence of PONV than an isoflurane based anaesthetic.

Materials and Methods

After IRB approval and written informed consent from the parent and, when appropriate, the participant's assent was also obtained, children from 4–18 yr admitted to undergo RFCA were enrolled in the study. Subjects with contraindications to the use of either propofol or isoflurane were excluded. Patients were randomly allocated to receive

propofol or isoflurane. Blocked randomization was generated using a computer random number. All patients included in the present study were part of a study evaluating electrophysiologic effects of propofol and isoflurane where sustained SVT was induced successful with the initially assigned drug.

Premedication consisted of midazolam given either orally (0.5 mg/kg up to a maximum of 10 mg) or intravenously (2 mg) when intravenous access was established prior to induction of anaesthesia. Routine monitoring included electrocardiography, noninvasive blood pressure measurement and pulse oximetry. In all patients, anaesthesia was induced by inhaling sevoflurane via a face mask. Pancuronium (0.1 mg/kg) was used to facilitate endotracheal intubation and fentanyl (2-4 µg/kg) was administered prior to laryngoscopy. After tracheal intubation sevoflurane was discontinued. Thereafter, anaesthesia was maintained with the assigned study drug, propofol or isoflurane, in a 66% nitrous oxide and 33% oxygen mixture. Real-time bispectral (BIS) data were obtained via electroencephalogram electrodes through a fronto-temporal montage (BIS™ sensor, Aspect Medical Systems, Newton, MA) and the EEG activity was recorded using an Aspect 1050, version 3.3 (Aspect Medical Systems, Newton, MA). Dosage of the study drugs was adjusted to maintain the BIS within a range of 50-60. Pancuronium was used as the neuromuscular agent during the intraoperative period.

RFCA procedures

Details of the electrophysiologic (EP) procedure in these patients have been reported

elsewhere.[331] Briefly, a diagnostic EP study was performed to identify the tachycardia and to

map the critical substrate. After conclusion of the diagnostic study, ablation of the

pathological substrate(s) was performed using radiofrequency energy. Then a final

diagnostic electrophysiologic study was performed. All patients received isoproterenol

(0.03-0.07 µg/kg/min) al least once during the procedure.

Approximately 30 min before the conclusion of the procedure all patients received

ondansetron (0.1 mg/kg up to 4 mg), ketorolac (0.5 mg/kg up to 30 mg), followed later by

neostigmine (40 µg/kg) and glycopyrrolate (8 µg/kg) to antagonize neuromuscular blockade.

Stomach contents were suctioned with an orogastric tube in all patients.

Patients were transferred to the recovery room following awakening from anaesthesia.

The incidences of postoperative nausea, and retching or vomiting were recorded by an

independent observer unaware of the patient's treatment group at the following time intervals:

(0 - 0.5, 2, and 18 h). Droperidol (20 µg/kg) was used as rescue anti-emetic in patients who

vomited, rectched, or at patient's request. Haemodynamic variables (arterial blood pressure,

heart rate, respiratory rate) and observer assessment of sedation scores (Table 15)[323] were

recorded at 0, 15, 30, 60, and 90 min after patient admission to the post anaesthesia care unit.

Patients were ready for discharge from the post anaesthesia care unit when the following

criteria were met: aerodynamically stable; protective reflex present; patient fully conscious and

able to protect own airway; pain adequately controlled; absence of severe nausea or active

vomiting; skin warm and dry. All patients were then admitted to the ward and discharged from the hospital the next day.

Cost were calculated as follows: isoflurane according to the formula by Dion[332] at a price of \$19.74 (£14) / 100 ml, propofol in 200 mg steps at a price of \$10.24 (£6) / 200 mg.

Statistical Analyses

A sample size of 28 patients in each group would have adequate power of 85% to detect a PONV-risk reduction of 50% between the two treatments: this would be a reduction from 60% (expected in the isoflurane group[330]) to 30% (expected in the propofol group[124]). Continuous data were analyzed by Student's *t*-test and categorical data were analyzed using Fisher's exact test. Repeated measurements (haemodynamic parameters and sedation scores during the stay in the post anaesthesia unit) were analyzed using mixed models (SAS-System 6.12, SAS Institute, Cary, NC, USA). A probability value less than 0.05 was considered statistically significant.

Results

Fifty-six subjects were included in the study. Demographic data are shown in Table 23. The patient characteristics were similar with a predominance of males in both groups.

Total anaesthesia time was not different between the two groups (317 ± 88 min. vs. 319 ± 97

min in the isoflurane and propofol groups, respectively).

Table 23. Demographic data.

	Isoflurane	Propofol
Age (years)	13.1 (9.5 , 16.3)	12.9 (8.1 , 16.3)
Gender (% female / % male)	48 / 52 *	31 / 69 *
Height (cm)	153 (137 , 170)	153 (128 , 176)
Weight (kg)	53 (31 , 68)	56 (34 , 81)
Administered Drugs		
Fentanyl (mcg)	168 (100 , 250)	171 (125 , 250)
Pancuronium (mg)	8.6 (6 , 10)	10.3 (7 , 14)
Propofol (mg)		1600 (1088 , 1820)
Isoflurane (MAC·h)	3.8 (2.8 , 4.9)	

Values are mean and $(25^{th}, 75^{th}$ percentile) or * = %

The incidence of postoperative nausea at 0.5, 2, and 18 h and the incidence of

vomiting was statistically significantly lower in the propofol group compared with the

isoflurane group (Tables 24 & 25). The isoflurane patients had an early onset of PONV

during the first 2 hours after termination of the anaesthesia and no patient suffered from a

new onset of PONV after 2 hours. In contrast the onset of PONV in the propofol group was

delayed. The use of a rescue antiemetic drug was significantly greater in isoflurane group

(Table 25). After the use of the rescue antiemetic drug in the isoflurane group, 10 of 14

patients vs. 0 of 5 patients in the propofol group had at least one further episode of vomiting.

The time until readiness for discharge from the PACU was not different between the groups

(propofol 106 ± 44 min *vs.* isoflurane 114 ± 40 min). However, the cost for administered

propofol ($87 ± 38) was significantly higher compared with isoflurane ($4 ± 1, p=0.001).

There were no statistically significant differences among the groups in postoperative

sedation score (Figure 16).

Table 24. Incidence of postoperative nausea and vomiting at different time intervals

Interval Time (h)	Nausea ISO	Nausea PRO	p Value	Vomiting ISO	Vomiting PRO	p Value
0 – 0.5	41%	7%	<0.005	26 %	0 %	<0.005
2	41%	10%	<0.02	41%	0 %	<0.001
18	33%	10%	<0.05	33 %	6 %	<0.02

ISO = isoflurane, PRO = propofol, p value Fisher's exact test.

Table 25. Cumulative incidence of postoperative nausea, vomiting and use of rescue antiemetic

Time (h)	Nausea ISO	Nausea PRO	p Value	Vomiting ISO	Vomiting PRO	p Value	Rescue antiemetic ISO	Rescue antiemetic PRO	p Value
0.5	41%	7%	<0.005	26%	0%	<0.005	33%	0%	<0.001
2	63%	10%	<0.001	48%	0%	<0.001	55%	14%	<0.002
18	63%	21%	<0.005	55%	6%	<0.001	55%	17%	<0.005

ISO = isoflurane, PRO = propofol, p value Fisher's exact test.

Figure 16. Sedation scores in post anaesthesia care unit
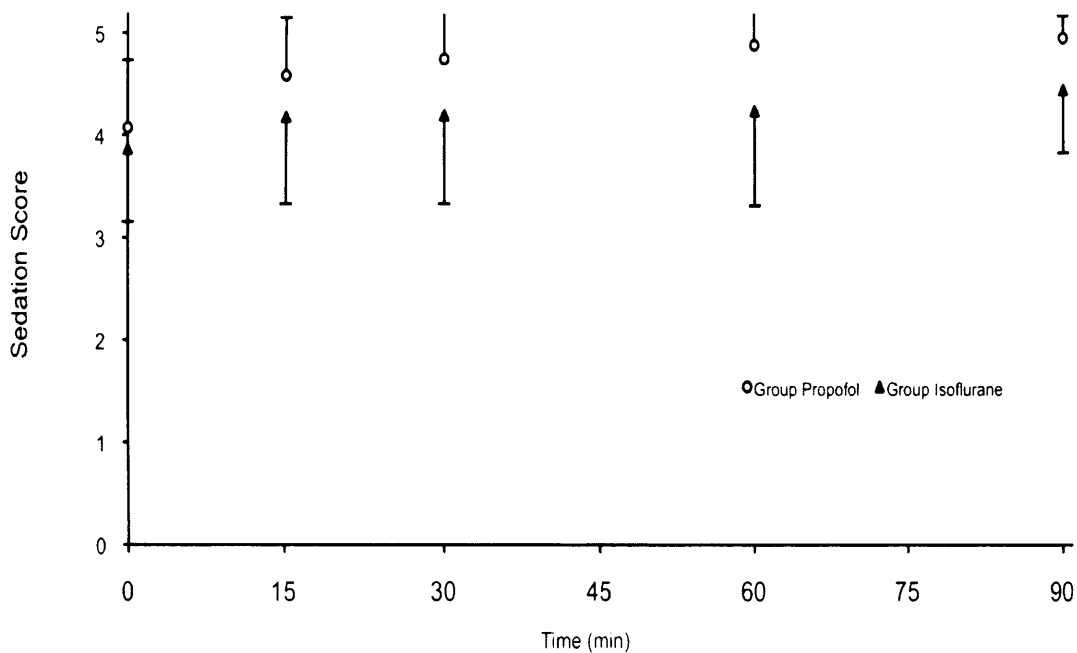
Mean ± SD.

Discussions

The results from this study confirmed that children and adolescents undergoing

RFCA under anaesthesia with isoflurane are at a high risk for developing PONV. The

prophylactic use of ondansetron and the antiemetic therapy with droperidol were not very

effective in this population undergoing isoflurane based anaesthesia. However, propofol

based anaesthesia was associated with a lower risk for developing PONV.

In the present study, the incidence of PONV in patients receiving isoflurane was 63% despite prophylaxis with ondansetron 30 min before the end of anaesthesia. In addition, after the use of droperidol, when administered as a rescue antiemetic, recurrent vomiting was observed in 70% of patients receiving isoflurane based anaesthesia, suggesting that PONV prophylaxis with ondansetron and PONV treatment with droperidol might not be effective in this population. These observations were in line with results previously reported in patients undergoing RFCA under volatile anaesthetics; neither the prophylactic use of ondansetron nor droperidol decreased the incidence of emesis in a placebo controlled study.[330]

Propofol-based anaesthetics have been associated with a lower incidence of PONV.[124,288] In a pharmacokinetic propofol simulation in the postoperative period[124], we showed that in patients where propofol was used throughout the procedure (duration 2.4 ± 1.3 h), the calculated average concentration was in a range known to reduce PONV effectively up to 6 h.[271] Thus, the postoperative antiemetic effect lasting up to 18 h in the propofol group in the present study might be attributed to the effect of combination antiemetic with ondansetron and propofol enhancing the antiemetic effects.[124] In a more recent study, Apfel et al[130] demonstrated an additive effect of propofol and ondansetron when administered in combination. When combining preventive ondansetron with propofol in children undergoing tonsillectomy, Barst and coworkers found a very low emesis incidence of 7% in the 24-h period following surgery, which contrasted with an incidence of 22% when propofol was given alone.[333] Nevertheless, whether the similarly low incidence

of PONV achieved in our study in the propofol group was the result of the combination of these two antiemetic drugs or related to the long lasting administration of propofol alone is less certain. However, there are numerous studies demonstrating increased efficacy for the prevention of PONV when combination antiemetics versus single agent were used.[21]

Patients undergoing RFCA under general anaesthesia represent a unique population in several perspectives. RFCA is not a painful procedure; in this study fentanyl was given in small doses predominantly at induction of anaesthesia and NSAIDS were given at the end of the procedure and in the postoperative period. Thus opioids did not play a significant role in provoking PONV in this setting. All patients included in this study were kept immobile in bed after the procedure until the next morning, reducing the effects of motion induced sickness . Hence, we speculate that the high incidence of PONV in patients receiving isoflurane was primarily related to the long duration combined application of the volatile anaesthetics and nitrous oxide, though the contribution of nitrous oxide is likely to be smaller.[130]

The lower incidence of PONV with propofol came with an additional costs. Given there are no clinically relevant differences regarding the electrophysiolgic properties between these drugs in patients undergoing RFCA[331], the favourable outcome regarding PONV arguably might justify the use of propofol. However this cost must be put into perspective: first, costs associated with episodes of emesis were not assessed in this study; and second, patients and parents' satisfaction with the perioperative course were not assessed. A recent study in adults demonstrated that patients are willing to pay an extra

median amount of US$56-$100 out of their own expense to avoid PONV.[5,334] Another study

evaluating parents' willingness to pay extra for reducing the incidence of postoperative

emesis in their children found the median amount to be £50 (US$75) [95% confidence

interval: £20-80]. [335] At the time this study was conducted, propofol was still under patent.

In today's generic cost of propofol, there would be less difference between the propofol and

isoflurane.

Several limitations must be noted. First, assessment of nausea is difficult in children.

Since only one subject was a preschool-aged child we consider the information gathered

accurately reflect the presence or absence of nausea. Second, no placebo control is available

in this study. Therefore, the potential effect of the prophylactic use of ondansetron in this

population remains unknown. Third, an inhalational induction with sevoflurane was used in

all patients in this study. However, the short lasting use of this agent at the beginning of the

procedure most likely did not confound the findings in our study.

In conclusion, children and adolescents undergoing RFCA under general anaesthesia

with isoflurane were associated with a high incidence of PONV. The use of propofol based

anaesthetic reduced the incidence to very low levels, with some increase in costs.

CHAPTER 10

Conclusions

In these series of clinical investigations we have systematically determined the antiemetic effects of propofol and recommend how propofol should be used in clinical practice to have this effect.

Our work has generated the following new scientific knowledge. First, we found a high percentage of US anaesthesiologists use propofol for its antiemetic effects. We also learned the various regimens that propofol has been used to achieve this beneficial effect. Next, we defined the dose response of propofol which are associated with an antiemetic effect. We then utilised this information to provide the explanation for the antiemetic effects of propofol when administered in various regimens and helped determine the appropriate dose to be used for the treatment of established PONV. The propofol was delivered using a patient-controlled delivery system, which has not been previously described. We found this delivery system safe and efficacious in the PACU environment. However, given the practice pattern may be different in different hospitals and different countries, caution should be exercised when using propofol outside the theatre environment. Continuous monitoring of patients should be adopted when propofol is used in this fashion.

We also explored the various regimens of propofol for prophylactic prevention of PONV and presented evidence why TIVA with propofol was more effective in preventing

PONV than propofol administered either as an induction agent only or in a "sandwich"

technique, a regimen commonly practised before these data were published. We

demonstrated that multimodal management strategy incorporating propofol and other

combination antiemetic was the most efficacious especially in patients at high risk for

developing PONV. These findings are in keeping with other work published on the use of

combination antiemetic and multimodal approach for the management of PONV. Indeed

Apfel et al confirmed that propofol, along with other commonly used antiemetics such as

ondansetron, droperidol and dexamethasone has similar degree of risk reduction and the

combination of these drugs appear to be additive in their efficacy. Lastly, we demonstrated

that propofol anaesthetic is more effective in preventing PONV than inhalational anaesthetic

in children.

The original hypothesis of this thesis was that propofol has antiemetic properties and

this property is concentration dependant. The above studies were conducted between 1994

and 2000. Since then, numerous studies comparing propofol and inhalational agent based

anaesthetic have been published and have confirmed our findings, namely propofol based

anaesthetic is associated with a lower incidence of PONV compared with inhalational based

anaesthetic and the use of propofol as an induction agent only does not confer meaningful

antiemetic effect. As propofol is no longer patented, the use of propofol as a continuous

infusion for maintenance of anaesthesia is widespread in the US and even more so in UK

and Europe. The availability of target-controlled infusion (TCI) automated pump has largely

facilitated its popularity in these countries.

Retrospectively, some of the experiments could have been improved with a more robust protocol and methodology. For example, a larger sample size and a greater variety of background and location among the anaesthesiologists surveyed could have yielded a more representative results (Chapter 4); the inclusion of a placebo group in determining the plasma propofol concentrations for its antiemetic effects (Chapter 5); the inclusion of a standard antiemetic regimen group (e.g. ondansetron) would have enabled efficacy comparison between propofol and ondansetron for the treatment of established PONV (Chapter 6).

Some exciting new knowledge has emerged since the conduct of these studies. These new information advanced our knowledge on the mechanism of propofol as an antiemetic. Appadu et al[290] and Hvarfner et al[291] have previously reported that propofol does not possess significant antidopaminergic properties. Cechetto et al[294], in an elegant rat model, demonstrated a lower level of serotonin and its metabolites, 5-hydroxy indole acetic acid (HIAA) in animals that received a propofol infusion compared to controls which received intralipid. They concluded that the reduced levels of serotonin in the area postrema (AP) and the CSF could explain the antiemetic property of propofol. In addition, propofol may also directly act on AP neurons via a $GABA_A$ receptor to reduce their activity. More recently, Barann and colleagues[336] examined the kinetics of the action of propofol and its lesser hydrophobic derivatives 2-isopropylphenol and phenol on human 5-HT3A receptors. They found that propofol, as well as its derivatives, appear to have an inhibitory effect on the serotonin receptors and the underlying mechanisms appear to involve the phenolic hydroxyl group, hydrophobic interactions and steric restrictions. This add further evidence that

propofol exert its antiemetic properties, at least in part via the serotonergic pathway.

However, PONV are multifactorial and other receptors, e.g. cholinergic, histaminergic and

neurokininergic receptors, have been shown to be also important in the mechanism of

PONV. Furthermore sedatives such as midazolam[79,166] and dexmedetomidine[337,338] also

appear to have some antiemetic effect. Hence, the potential of propofol acting as a sedative

and other receptor based mechanisms could not be excluded.

These future directions of research in this area should focus on other potential

mechanisms of propofol induced antiemesis effect and if the concentrations of propofol at

the effect-site are related to the severity of nausea and vomiting. In addition, further research

is needed to develop a practical and safe delivery system for administering propofol as well

as a user-friendly patient-controlled delivery system.

I believe these series of clinical investigations presented in my MD thesis have

helped us improve the understanding of propofol for the management of PONV and provide

a useful background knowledge for further development of propofol as an antiemetic.

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Appendix 1

1.   Do you use Propofol in an effort to reduce post-operative nausea and vomiting (PONV) following general anaesthesia?
      O Yes (Go to #2)O No (Thank you for your time!)

2.   How do you use Propofol as described in #1? (Please answer all that apply)
      Percent of Use

      _____%At Induction only

      _____%At Induction and Emergence only (sandwich technique)

      _____% as primarily Propofol based anaesthetic (Induction, Maintenance, and
                    Emergence)

3.   If you use Propofol only at induction, do you: (Check all that apply)
      O Use for cases less than 60 minutes?

      O Use for cases longer than 60 minutes?   (Please go to #4 or #7, as applicable)

4.   If you use Propofol only at induction and emergence, do you: (Check all that apply)
      O Use for cases less than 60 minutes?

      O Use for cases longer than 60 minutes?   (Please go to #5 or #7, as applicable)

5.If you use a Propofol based anaesthetic, do you:(Check all that apply)

O Use for cases less than 60 minutes?

O Use for cases longer than 60 minutes?

6.   Please explain your dosing technique for a **TYPICAL** patient: (Check all that apply)
      A. Maintenance (during a Propofol based anaesthetic):
      Boluses (if used): O 10 mgO 20 mgO 30 mgO 40 mgO>40mg
      Doses given every: O OnceO 1-4 MinO 5-10 MinO 11-15 MinO>15Min

      Infusion:O 10-40 mcg/kg/minO 50-90 mcg/kg/minO 100-150 mcg/kg/min
      O 160-200+ mcg/kg/min

B. Emergence:
Boluses (*if used*): O 10 mgO 20 mgO 30 mgO 40 mgO>40mg

Doses given every: O OnceO 1-4 MinO 5-10 MinO 11-15 MinO>15Min

Time before end of case that you begin Propofol dosing:

O 1-5 MinO 6-10 MinO 11-15 MinO16-30 MinO 31-45 MinO>45Min

7.Do you <u>usually</u> combine Propofol with:

O DroperidolO OndansetronO ProchlorperazineO Promethazine

O MetoclopramideO Other_____

When do you give the above?: O Near beginning of caseO End of case/ PACU
O Other_____

8.Do you think Propofol has acceptable efficacy in the treatment of PONV?

    O Yes:O As the sole anti-emetic agent

    O Only in combination with drugs in #7

    O Only when used as primarily Propofol based anaesthetic

    O No

Thank you.

Appendix 2. Pharmacokinetic variables of propofol administered as constant rate intravenous infusions in humans.[176]

Table 2. Propofol Pharmacokinetic Parameters Derived from Compartmental (c) and from Noncompartmental (nc) Data Analysis

Parameters	Propofol rate (mg·kg⁻¹·hr⁻¹)			
	3 (n = 6)	6 (n = 6)	9 (n = 6)	Mean (n = 18)
$t_{1/2\alpha}$ (c) (min)	3.1 ± 1.1	3.2 ± 1.1	2.3 ± 1.3	2.8 ± 1.2
$t_{1/2\beta}$ (c) (min)	32.1 ± 15.2	37.5 ± 14.3	24.6 ± 14.2	31.4 ± 14.7
$t_{1/2\gamma}$ (c) (min)	402.7 ± 254.4	385.5 ± 282.2	277.0 ± 138.5	355.0 ± 226.6
MRT (nc) (min)	203.6 ± 155.4	208.5 ± 199.2	117.2 ± 43.4	176.4 ± 145.6
C_{ss} (c) (μg·ml⁻¹)	2.060 ± 0.432ᵇ	3.573 ± 0.748ᶜ	5.885 ± 0.762ᵇ	
(nc) (μg·ml⁻¹)	2.032 ± 0.450ᶜ	3.544 ± 0.756ᶜ	6.000 ± 0.799ᵈ	
V_c (c) (L)	21.350 ± 9.502	16.408 ± 4.350	13.013 ± 3.633	16.924 ± 6.957
V_{ss} (c) (L)	348.333 ± 249.794	331.500 ± 256.932	181.667 ± 73.677	287.167 ± 212.855
(nc) (L)	349.167 ± 203.673	348.333 ± 257.970	175.500 ± 51.177ᶜ	
Vd_β (c) (L)	1007.667 ± 451.195	973.333 ± 498.481	598.333 ± 244.213	859.778 ± 432.314
Cl_B (c) (L·min⁻¹)	1.883 ± 0.414	1.864 ± 0.269	1.563 ± 0.181	1.770 ± 0.322
(nc) (L·min⁻¹)	1.927 ± 0.512	1.892 ± 0.298	1.532 ± 0.134	1.781 ± 0.374

Table 3. Propofol Transfer Rate Constants between Compartments Assuming a Three-Compartment Open Model with Central Elimination

Rate constants	Propofol rate (mg·kg⁻¹·hr⁻¹)			
	3 (n = 5)	6 (n = 6)	9 (n = 6)	Mean (n = 17)
K_{10} (min⁻¹)	0.0966 ± 0.0292ᵃ	0.1212 ± 0.0359	0.1288 ± 0.0431	0.1190 ± 0.0351
K_{12} (min⁻¹)	0.0961 ± 0.0909	0.0696 ± 0.0465	0.1733 ± 0.1404	0.1140 ± 0.1051
K_{13} (min⁻¹)	0.0380 ± 0.0075	0.0455 ± 0.0196	0.0415 ± 0.0177	0.0419 ± 0.0155
K_{21} (min⁻¹)	0.0375 ± 0.0257	0.0330 ± 0.0216	0.0915 ± 0.0806	0.0550 ± 0.0558
K_{31} (min⁻¹)	0.0027 ± 0.0012	0.0032 ± 0.0012	0.0039 ± 0.0014	0.0033 ± 0.0013

Fraction of drug in the central compartment during terminal phase

Fc	0.0189 ± 0.0088	0.0190 ± 0.0070	0.0232 ± 0.0082	0.0204 ± 0.0077

Fraction of drug eliminated during the terminal phase

	(n = 6)	(n = 6)	(n = 6)	(n = 18)
F_{el}	0.297 ± 0.069	0.298 ± 0.087	0.265 ± 0.070	0.286 ± 0.073

Appendix 3.

Equipment.

Plasma propofol was measured by high-performance liquid chromatography with fluorescence detection. The separation and quantification procedures were conducted with a C-18, 15-cm × 4.6-mm column (Supelcosil LC-18; Supelco, Bellefonte, PA). The excitation and emission wavelengths were 275 and 310 nm, respectively, and both monochromator slit widths were 10 nm.

Procedure

Plasma was prepared for chromatography by precipitation of plasma proteins with acetonitrile. Propofol was detected by a fluorescent detector at an excitation wavelength of 275 nm and an emission wavelength of 310 nm. The minimum detectable concentration of plasma propofol was estimated as 0.1 pg/mL. The intraassay coefficients of variation determined by replicate analysis of quality control specimens at three different concentrations (0.63, 2.5 and 10 pg/mL) were 2.5%, 2.0%, and 2.0%, respectively. The interassay coefficients of variation for propofol were 3.6% at 0.63 Fg/mL, 3.1% at 2.5 Fg/mL, and 2.2% at 10 pg/mL.