PONV : Dispelling the Myth

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INTRODUCTION

Postoperative nausea and vomiting (PONV) has been variously described as, the big *little problem* [1], - the final therapeutic challenge to our speciality and the big, big problem of ambulatory surgery [2].
Despite several publications and editorials concerning PONV, as yet an optimal strategy for its prevention and management remains to be determined. To decrease the incidence of PONV, several antiemetic strategies are available - the newest of which are the Neurokinin antagonist. Much of this problem can be attributed to myths with regard to PONV that cloud our perceptions and hamper our pursuit of quality of care.

PONV – the consequences:-

PRACTICAL CONSEQUENCES

Little long term morbidity but critically determined by patient satisfaction. Distressing to patients, has been described as worse than postoperative pain (Macario et al., 1999).

ECONOMIC CONSEQUENCES

Prolonged recovery or hospital stays which increases medical care and costs.

MEDICAL CONSEQUENCES

- Aspiration of emesis
- Gastric bleeding
- Wound haematomas
- Amongst most common causes of hospital admission post ambulatory surgery

Routine administration of anti-emetics, however, increase costs and subjects all patients to potential side effects.
To that end, it is still controversial if the preferential use of the relatively new and more expensive like antiserotonin drugs for prophylaxis of PONV leads to increased effectiveness and benefits. [2]
Reliable preoperative predictions of PONV risk would enable anaesthesiologists to selectively apply antiemetic strategies. Predictions rest on the knowledge of the aetiology of PONV, which is multifactorial and includes patient related, anaesthetic and surgical factors.

DEFINITIONS [4] [8]

PONV encompasses three main symptoms that may occur separately or in combination after surgery.

- NAUSEA- described as an unpleasant sensation that immediately precedes vomiting but is not necessarily followed by vomiting (without muscular action). It is accompanied by hyper salivation and vasomotor changes.
- VOMITING- is the forceful expulsion of gastric contents from the mouth by powerful sustained expulsive muscular contractions. It is a reflex and not under voluntary control.
- RETCHING - usually follows nausea, involving laboured spasmodic movements against a closed glottis with contractions of abdominal muscles, chest wall and diaphragm without any expulsion of gastric contents.

PHYSIOLOGICAL MECHANISMS OF NAUSEA AND VOMITING [17]

Nausea and vomiting are two biologically different phenomena but often occur together and therefore highly correlated. [3]

As mentioned above, nausea is not always followed by retching or vomiting [3]. Nausea and vomiting can occur separately, nausea being more difficult to control pharmacological than emesis indicating that the neurobiological systems producing each, are partially different.

The neural systems responsible for the perception of nausea are largely unknown but likely require activation of cerebral cortex and other forebrain areas, possibly the amygdala.

The brainstem neural circuitry may provide the input to the forebrain to generate nausea as evidenced by the prodromal signs of nausea namely cold sweating, salivation, vasoconstriction, vasopressin release and gastric dysrhythmia. Some studies have identified differences in risk factors like a history of migraine being specific for nausea.

The vomiting response is produced by a central pattern generator (CPG) found in the lower brainstem - which is a collection of nuclei for generating cyclical output.

Four pathways so far identified, that are responsible for activation of CPG:

- Vagal: chemical or mechanical activation of the vagal afferent fibers innervating the gastrointestinal tract.
- CPG: direct chemical action on or near the brainstem CPG or closely associated nuclei, such as the area of postrema (AP).
- Vestibular: activation of the vestibular system by motion
- Forebrain: stimulation via descending pathways from the forebrain including the cerebral cortex. This last pathway is the least understood and likely plays an important role in the modulation of emesis by learning, e.g., anticipatory vomiting in cancer chemotherapy.

Although the inputs and outputs for emesis are well described, the CPG and more importantly the final common pathway for the emetic response are not. The nucleus of the solitary tract in the lower brainstem is a potential site for the common inputs from the vagus, vestibular system, AP and cerebral cortex. The chemical receptors involved in transduction of signals in the area of postrema and vomiting centre include dopaminergic, cholinergic, histaminergic, serotinergic and opioid. The Neurokinin -1 may represent the final common pathway in PONV.

INCIDENCE

The incidence is, despite modern anaesthetics and surgical techniques; still around 25-30%. This increases to as much as 70% in high risk patients.

CLASSIFICATION [4]

PONV may take place in single or multiple episodes, which may last minutes, hours, or even days. The lack of standardisation as to exact cut-off times between studies is important as early and late may have differing pathogenesis.

Early: occurring up to 2 to 6 hours after surgery -Volatile associated

Late: occurring up to 24 or 48 hours after surgery - Opioid induced symptoms and motion sickness in transportation either from recovery to ward or hospital to home.

Most episodes of PONV resolve within 24hours.

RISK FACTORS

Traditionally, investigations focused on a single potential causative factor with little attempt to control for other confounding variables [4]. This then lead to generation of endless risk factors that cloud our understanding of PONV.

With the advent of more sophisticated multivariable statistical analysis and stratification we have been able to identify the strongest risk factors for PONV. By using these few risk factors we are able to more accurately predict those at higher risk for PONV. This allows us to use prophylactic treatment in a rational and focused way.

Risk Factors for Postoperative Nausea and Vomiting (PONV) in Adults [5]

Patient-specific risk factors

- Female sex (IA)
- Non-smoking status (IVA)
- History of PONV/motion sickness (IVA)

Anaesthetic risk factors

- Use of volatile anaesthetics within 0 to 2 h (IA)
- Nitrous oxide (IIA)
- Use of intraoperative (IIA) and postoperative (IVA) opioids

Surgical risk factors

- Duration of surgery (each 30-min increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased by 16% after 30 min) (IVA)
- Type of surgery (laparoscopy, ear-nose-throat, neurosurgery, breast, strabismus, laparotomy, plastic surgery) (IVB)

Evidence Rating Scale [5]

- Level of evidence based on study design
  I Large randomized, controlled trial, *n* _100 per Group
  II Systematic review
  III Small randomized, controlled trial, *n* _100 per group
  IV Nonrandomized, controlled trial or case report
  V Expert opinion
- Strength of recommendation based on expert opinion
  A Good evidence to support the recommendation
  B Fair evidence to support the recommendation
  C Insufficient evidence to recommend for or against

Patient Related

1. Female gender – higher incidence and proved to be an independent predictor in multivariable analysis. Most studies have odds ratio ranging from 2-4 reflecting a two fold increase PONV risk for adolescent and adult female's. That prepubescent girls apparently lack increased likelihood of PONV could imply that the risk relates to hormonal factors. However, although initial studies, reported increased susceptibility to PONV during the first week of menstrual cycle, early stage of menstrual cycle has been disproved as a risk factor by a subsequent study and in a systematic review.(4)
2. Non smoking - Most anaesthesiologists are of the believe that smokers have a higher risk for PONV, due to the acute effect of the stimulant nicotine upon smoking their first cigarette when in fact non smokers more likely to have PONV, mechanism by which smoking reduces risk of PONV is unclear but a candidate theory is that chronic smokers maybe desensitized to noxious stimuli.(9)
   Cigarette smoking can result in as much as a 3-fold increase in CYP1A2 activity from induction by polyaromatic hydrocarbons(PAHs) - CYP1A2 being a major enzyme involved in metabolism of several drugs including those that are used by anaesthetists. Moreover, volatiles are metabolised via CYP2E1 and induction of these enzymes by nicotine and PAHs can account for any perceived differences in recovery that is a quicker and smoother recovery from anaesthesia(6).
3. Obesity- Has been disproved as a risk factor. Numerous multivariable analysis of large surveys were performed but only 1 survey identified BMI >25kg/m2 associated with a 5 fold risk, all others were unable to identify BMI as an independent risk factor. (9)
4. Age: Impact is not strong and fails to show statistical significance in some multivariable analyses (9). Children twice as likely as adults to experience PONV, lowest in children less than twelve and increases through age five (highest 6-16years).Elderly less frequent.

Surgery Related

1. Increased duration of surgery - shown to be independent risk factor by few well conducted studies in adults and children (4) (Each 30 minutes increase in duration increases the risk of PONV by – 60%)(Sinclair DR, Chung F, MeZeiG. Can PONV be predicted? Anaesthesiol 91: 109-118).
2. Type of surgery: Although incidences differ widely across various types of surgeries, recent multivariable analyses suggest strongly that this is mainly caused by the associated risk factor e.g. gynaecological surgeries performed in females. (7)

   Apfel et al found this not to be an independent risk factor, in considering a causal effect on PONV by type of operation could not be established in the study.(Commonly seen as risk factor but is controversial because some studies have shown significant results while others no significance on the same type.)
3. Other: Fluids - Less preoperative or intraoperative colloid compared to crystalloid administration.
   When a large volume of crystalloid is administered in prolonged surgery this may result in gastrointestinal tissue oedema leading to increased incidence of PONV. Is still controversial.

Anaesthesia related factors

1. Volatiles - Evidence has shown that the difference in early vomiting is clearly dose related with use of the volatile agent. (9)
   The choice amongst the volatile anaesthesia (isoflurane vs. sevoflurane vs.enflurane vs.desflurane) appears not to affect the incidence of PONV.
2. Intraoperative and postoperative opioids – Opoids given postoperatively are a major risk factor for PONV (Apfel et al, Anaesthesiology. 1999, Apfel and Roewer, Int Anaesthesiology Clin 2003).
   The data regarding intraoperative opioids are less. When given in low dose they do not appear to increase PONV. When given in higher doses, the emetogenic effect might be balanced out by the reduced need of volatile anaesthetics. Therefore intraoperative opioids should therefore not be considered as a risk factor for PONV (7)
3. Total Intravenous Anaesthesia (TIVA) – Using of propofol. The mechanism is unclear. A single induction dose does not appear to have any measurable effect but using propofol in a TIVA technique decreases the incidence of PONV. This may however be related to the avoidance of volatiles and not the propofol itself. The antiemetic effect of propofol is short-lived, it might be useful immediately post-operatively but it is not useful in the ward setting because of the marked sedation. It appears to have no value in relieving established PONV. (8)
4. Regional- avoiding opioids and volatiles
5. Large doses neostigimine (>2,5mg), still controversial
6. N2O - Although it has received considerable attention, in the literature, but in practice it is substantially less than that associated with volatile anaesthetics. More over the emetogenic effects of nitrous oxide and volatile anaesthetics are independent, - i.e. they are additive and not synergistic (9). The recommendation is to avoid its use.
7. Use of supplemental O2 has been disproved- it was thought that supplemental oxygen reduced PONV by ameliorating subtle ischemia,

thereby reducing the release of serotonin and other emetiogenic substances from the compromised bowel. Currently, standard oxygen (30%) is advised compared to high (50-80%). [4]

Limitations of current research into PONV risk factors and suggestion of future investigations. [4]

1. Although there has been improved knowledge of PONV risk factors, identification of these factors remains imperfect. There are substantial gaps in the potential risk factors. Studies are essentially epidemiological in approach focusing on readily discernible clinical factors. However, genetic and molecular biological patient characteristics have not been extensively examined and even certain clinical characteristics remain under investigated. In an editorial by Sweeney, potential PONV risk factors includes the degree of expression and activity of selected cytochrome P450 (CYP 450) hepatic cellular enzymes.

   CYP450 enzymes are responsible for metabolising a range of drugs including the anaesthetics, analgesics and antiemetic. The greater the expression and activity of these enzymes, the more rapid is the metabolism of substrate drugs. Individuals may thus be characterised as poor, intermediate, extensive or ultrarapid metabolizers of drugs. Furthermore, these enzymes synthesis maybe stimulated or suppressed by environmental influences (insecticides, petroleum products and solvents). Sweeney speculated that the protective effect of smoking in PONV may be related to inducers of CYP450 enzymes - of the polycyclic aromatic hydrocarbons, the component of the tar in portion in cigarette smoke

   Other clinical characteristics that affect CYP450 enzymes expression include alcohol consumption, commonly prescribed drugs like cimetidine and erythromycin or vegetables like cabbage, brussel sprouts should be investigated as possible PONV risk factors. Also, gender and racial differences have been documented in CYP450 enzyme. Of note, locally a study has been conducted titled “Non African ethnicity as a risk factor for PONV” that has shown statistical difference in the incidence of PONV between African and Non African [18].

2. Difficulty in controlling subtle clinical factors especially smaller or single centre studies like proficiency of particular anaesthetist or surgeon might mask the nature of a procedure that would be emetogenic in less skilled hands.

3. A third limitation of recent research with respect to PONV risk factors is variation in outcomes and data collection methods. Studies have considered nausea and vomiting separately, others combined although pathophysiological differences between the two. Although different risk factors can be identified between the two, it is rare to have postoperative vomiting without the symptom of nausea preceding. Further research is warranted to clarify the relation between the symptoms. In addition, defining PONV differs in studies, some either recorded or volunteered symptom, else in response to specific query while others relied on chart reviews. Direct and specific questioning captures a larger percentage of actual PONV incidences than spontaneous patient reporting.

4. Limited patient population studied, with minimal studies relating to children as well as outpatients. This raises queries of the general applicability of the findings that derive from adult patients.

5. There is difficulty in separating true from surrogate risk factors which stems from deficiencies in knowledge of PONV pathophysiology and the dangers in epidemiological research of confusing association and causality. For example certain types of surgery – gynaecological procedures maybe surrogate risk factors for the true risk factor of female gender.

Thus although multivariable analysis identifies an independent PONV predictor, potential underlying factors influencing that predictor must be borne in mind when applying the finding in clinical practice.

Clinical applicability of Risk factors [4]

There are 8 major PONV scoring systems which in addition to identifying independent PONV risk factors, developed formulas quantifying a given patients likelihood of suffering nausea, emetic events, or both. (see APPENDIX)
All include patient related factors with two formulas also showing surgery and anaesthesia related factors.

Seven of the eight were validated in additional populations, centres or both from those in which the formulas originally were developed.

Accuracy of scoring systems i.e. ability to correctly discriminate between patients who will or will not suffer PONV commonly tested through calculation of area under a given systems receiver operating characteristics (ROC)curves; displaying only poor to moderate accuracy ranging between 50-80% . That is a 12 -57% relative improvement over guess work, however despite these limitations in accuracy the scoring systems has shown to significantly reduce incidence of PONV in general and especially in high risk patients; while avoiding the expense and potential side effects of prophylactics.

There is ***no gold standard scoring system yet***, but based on main improvements, it is now more simplified and more user friendly. The simplified score eliminates laborious calculations and may reduce the required detailed history taking. The simplified score has demonstrated equivalent or superior discriminating power compared with more complex formulas.

Comparing the various systems

In adults, Koivuranta et al simplified system shown to have a statistically higher predictive value than the Palazzo and Evans non-simplified system(0,71 vs. 0,68 for postoperative nausea, P= 0,007 and 0,70 vs. 0,64 for postoperative vomiting; P< 0,05) and a numerically greater area under the ROC curve (0,66 vs. 0,63) than does the Apfel et al simplified system.

In children, Koivuranta et al simplified system had a significantly larger area under the ROC (0,61) than did the Palazzo and Evan system (0,56; P < 0,001) or the Apfel et al, simplified (0,58) or non simplified (0,59) systems (P < 0,003) for both Apfel et al systems.
In adults, Apfel et al simplified or original systems exhibited significantly greater accuracy than did the Palzazzo and Evans formula (0, 68 vs. 0, 64, P<0,005 for PONV and 0, 73 vs. 0, 68 for postoperative vomiting P=0,005 respectively). The Apfel simplified system also shows significantly greater accuracy in comparison to Sinclair's non-simplified formula in one adult study (0, 71 vs. 0, 64 P= 0,008), but Sinclair et al had significantly larger ROC curves than did either Apfel in a paediatric study (0, 65 vs. 0, 59 or 0, 58 P < 0,003).

In that paediatrics study, Sinclair et al. system also had significantly greater discriminating power than did Palzazzo and Evan formulae (0, 65 vs. 0, 56 P<0,001) but bear in mind Sinclair formula was developed in outpatients but all comparisons were inpatients!

As a whole the comparisons suggest that for inpatients Koivuranta et al, simplified system is perhaps the most accurate, but not vastly more accurate than the Apfel et al simplified or original or the Sinclair et al systems.

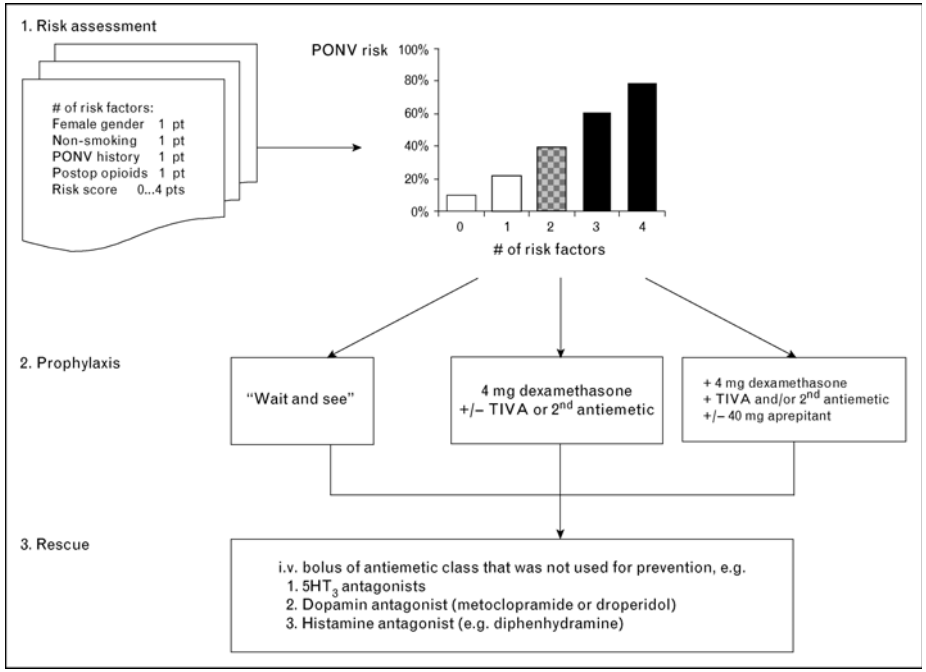
All four are superior to Palazzo and Evan formula. The comparisons also suggest that the use of different scoring systems for adults vs. paediatrics inpatients may increase accuracy.

Recommendations

Given the accuracy but relative simplicity - Koivuranta or an Apfel simplified are currently preferred choice for use in adults especially inpatients.
Eberhart simplified system is the choice for use in children especially inpatients but remembering only moderately accurate in predicting ability.
Apfel et al identified female gender, non-smoking, and history of PONV or motion sickness and postoperative use of opioids as risk factors. The presence of none, one, two, three or four factors were associated with a risk for PONV of 10, 21, 39, 61 and 79% respectively.

MANAGEMENT OF PONV

The Simplified Apfel et al score and suggested selection of anti-emetics can be titrated to clinical circumstances. [9]



Prophylaxis

In a study by Macario et al in which patients were ask to allocate $100 to avoid undesirable outcomes after surgery, PONV was allocated the largest amount and considered one of the most undesirable outcomes. It is unacceptable to neglect the prophylactic potential of anti-emetics to reduce the risks.

The avoidance of emetogenic factors during anaesthesia can reduce baseline risk of PONV. Strategies include TIVA instead of volatiles or regional, else optimise volatile administration via bispectral index (BIS) may decrease the incidence of PONV, and nitrogen instead of N2O.

Furthermore, the decision to provide anti-emetics as prophylaxis should be based on patient risk. Patients with 3 or 4 risk factors are considered high risk, and should receive prophylaxis.

MONOTHERAPY - has limited efficacy as is incapable of completely eliminating PONV when considering the different receptors involved and consequently higher failure rates resulting in increased cost to the institution.

COMBINATION THERAPY – a combination of anti-emetics drugs with differing sites of actions are thus more effective in successfully preventing PONV and decreases total cost incurred.

Key findings

Droperidol is more effective against nausea than vomiting. However, in comparison with ondansetron, droperidol is equivalent in prevention of vomiting. But ondansetron is superior in children and provides antiemetic control for up-to 24 hours. But droperidol is more cost effective. This puts forth the concept of balanced emesis, which is more efficacious and less toxic that is ondansetron which has better anti-vomiting efficacy can be combined with droperidol which has better anti-nausea efficacy but also provides protection against headache, which is a side effect of ondansetron. Their combination does not seem to increase the proarrhythmic risk of droperidol. [16]

The most effective anti-emetic combination regimen currently for prophylaxis is dexamethasone with a 5HT3 antagonist.

In the high risk combined pharmacological and non pharmacological (acupuncture or transcutaneous acupoint stimulation, acupoint stimulation and acupressure) has shown efficacy and is advantageous as no side effects as well as does not entail taking a pill. Furthermore, as many as three anti-emetics are justified in high risk of all different classes.

A multimodal approach will include :

- Preoperative anxiolysis
- Use of regional anaesthesia
- Use of propofol for induction and maintenance of anaesthesia - TIVA
- Avoidance of nitrous oxide
- Avoidance of volatile anaesthesia
- Minimization of intraoperative and postoperative opioids
- Minimization of neostigmine
- Prophylactic antiemetics (combination therapy)
- Non-pharmacological techniques - acupuncture

Rescue

Can be viewed as prophylaxis treatment failure or following no treatment

The treatment of established PONV has not been studied well.

Smaller doses may be required for rescue when compared to prophylaxis e.g. ondansetron 1mg in rescue was as effective as higher doses (2-4mg) when used in patients not receiving any prophylaxis. [9]

Treatment from another class is warranted following prophylactic failure. Either of the droperidol or 5HT3 can be used.
Do not repeat the dose of any prophylactic intervention if within 6 hours of initial administration.

DRUG EFFICACY and COST

Antiemetic efficacy and risk reduction

Drug -specific antiemetic potential is best described by changes in relative risk, which is a measure of drug efficacy independent of patient characteristics. In contrast, the effectiveness of a prophylactic intervention for a given population is probably best measured by the absolute risk reduction or number needed to treat (NNT), a measure specific to patients of a given group (high risk, moderate risk, low risk) [13].

Besides prophylactic treatment effectiveness, patient satisfaction and hospital stay or admission should also be used to gage true outcome measures.

The IMPACT trial developed to determine most efficient multimodal prophylactic regimen has shown that given prophylactic combinations of anti-emetics and anti-emetogenic anaesthetic techniques of ondansetron. dexamethasone, droperidol and TIVA reduced the risk of PONV by a quarter. Moreover, it demonstrated that all interventions acted independently of each other and that the action of the drugs was independent of the patients risk (each producing a relative risk reduction of 26% regardless of patients risk)[12].

In the paper by Gan, Consensus Guidelines for Management of PONV, the plane agreed that with respect to prophylaxis:

It was found that no difference exists amongst the 5HT3 antagonist with respect to efficacy when equivalent doses are used. When presented with a dose range, the smallest dose should be used. In addition, extra- pyramidal side effects and sedation seen with other medication (promethazine, prochloperazine, scopolamine, and propofol) are avoided. [8]. Limitations to their use are association with QT prolongation and decreased effectiveness in patients with increased CYP450 (2D6) activity (fast metabolizers) [13]

Dexamethasone at 8mg effectively prevents nausea and vomiting with NNT of approximately 4 and is described as being as effective as 5HT3 or droperidol. It should be administered prior to induction due to its slow onset of action.

Droperidols, efficacy is equivalent to that of ondansetron for prophylaxis, with NNT of 5 for prevention of both nausea and vomiting (0-24hr) and be given at end of procedure.

Metoclopramide is an alternative to droperidol. The dose that is similarly effective compared to other antiemetics is 25-50mg and not 10mg. Hypotension is most common side effect (secondary to peripheral D2 receptor blockade). Extrapyramidal symptoms and dystonia occur at an incidence of less than 1%.

Neurokinin – 1 antagonists are significantly more effective against vomiting (relative risk reduction with 40mg or 125mg apreptitant is between 70-80 %) than all currently available antiemetics, though antinausea are more likely clinically comparable to other treatment options. [13]

Cost efficiency implications:

Selection of appropriate anti-emetics will depend on the efficacy and safety profile but on their economic impact as well. There are only a few studies evaluating economic impacts per se. Limitations in the studies include differing doses and timing of administration making it difficult to define clear conclusions. Despite these limitations learning points that can be drawn include that 5HT3 antagonists are expensive but the literature shows that the dose determines the cost effectiveness not the choice of agent. Further, with the new Neurokinin -1 antagonist also being much more expensive, these should be reserved for high risk patients.

Alternative treatments options that are cost effective include dexamethasone combined with its safety profile making it a good first line option and droperidol.

Thus further high quality research is required for cost effectiveness evaluation of prophylaxis and treatment of PONV.

Ondansetron	4mg 8mg	R60 R90.92
Granisetron	3mg	R138
Palonosetron	250ug	R318
Droperidol	5mg	R3 per ampoule
Dexamethasone	4mg	R5 per ampoule

LOCAL PERCEPTIONS AND PRACTICES

Hospitals: KEH VIII, IALCH, RK KHAN, ADDINGTON, PMMH

An informal survey into preoperative identification of high risk patients at these hospitals revealed that mainly a history of PONV volunteered by the patient and procedure related were considered and as such was carried out at only 2 of the 5 hospitals.

Prophylaxis is practiced strongly at one institution only mainly using dexamethasone and droperidol in combination.

Drugs available for either prophylaxis or rescue at these hospitals:

- 5HT3 available at only 3 hospitals,
- dexamethasone, droperidol and maxalon are all available.

Perceptions of PONV included:

- Only if present in postoperative period treat
- Certain ethnic groups do not experience PONV
- Repeating dose of same agent is acceptable in rescue following prophylaxis
- Only one hospital is aware of current local studies into ethnical differences relating to PONV.
- None of the hospitals considered looking for PONV beyond the recovery room

PHARMACOLOGICAL CLASSIFICATION OF ANTIEMETICS [8]

CLASS	DRUGS
Anticholinergic	Hyosine (Scopolamine)
Antihistamine	Cyclizine(Valoid) Promethazine(Phenergan)
Dopamine antagonists	Metaclopramide(Maxalon) Droperidol (Inapsin) Prochlorperazine(Stemetil) Domperidone (Motilium
5HT3 Selective antagonist	Ondansetron (Zofran) Granisetron (Kytril) Topisetron (Novoban) Dolasetron (Zamanon)
Corticosteriod	Dexamethasone
Neurokinin-1 antagonist	Aprepitant
Cannobinoid	Nabilone
Other	Propofol, Acupuncture

Chart 1 – Drugs for prevention and treatment of postoperative nausea and vomiting

Drugs	Class	Dose for prophylaxis	Time of prophylaxis	Dose for treatment	Comments
Scopolamine	Anticolinergic	Transdermal patch	Up to 4 hours before end of surgery	Not indicated	Wash hands after handling patch
Dimnenhydrinate	Antihistamine	1-2 mg/kg or50-100 mg IV or IM	Before induction of anesthesia	50-100 mg IV	-
Promethazine	Phenothiazine	12.5-25mg IV. IM or trans-rectal	At end of surgery	12.5-25 mg	The 6.25 mg dose is advised for patients at risk due to sedation
Droperidol	Butyrophenones	0.625-1.25 mg IV	At end of surgery	1.25-2.5 mg IV	Electrocardiographic monitoring is needed due to risk of prolongation of QT and of *torsades de pointes*
Ondansetron	Antagonist of 5-HT3 receptors	4 mg IV	At end of surgery	4 mg IV	Risk of dose-dependent alterations
Dolasetron	Antagonist of 5-HT3 receptors	12.5 mg	At end of surgery	25-50 mg IV	Risk of dose-dependent alterations
Granisetron	Antagonist of 5-HT3 receptors	5 ug/kg or 1mg	At end of surgery	0.1 – 1 mg IV	Risk of dose-dependent alterations
Dexametasona	Corticosteroids	4-10 mg IV	Before induction of anesthesia	Not indicated	Well tolerated in single dose
Metoclopramide	Benzamides	10-20 mg IV	At end of surgery	10-20 mg IV	Indicated in case of NV induced by opioid , its use is not considered in PONV prophylaxis

IV - intravenous; IM - intramuscular; NV – nausea and vomiting; PONV – postoperative nausea and vomiting.

(http://www.scielo.br/scielo.php?pid=S0103-507X2009000100013&script=sci_arttext&tlng=en)

Anticholinergics e.g. scopolamine

These are potent inhibitors of muscurinic and cholinergic CNS emetic receptors in cerebral cortex and pons. Scopolamine blocks impulses from the vestibular nucleus to higher centres in CNS, reticular activating formation and vomiting centre. It also has peripheral effect causing a decrease in salivary and gastric secretions a well as an antispasmodic action. [8]

Use:

Treatment of motion sickness

Treatment of PONV – is as effective in preventing PONV as droperidol and ondansetron(13); effective in preventing PONV caused by opioids especially as premedication, but be aware that the duration of action of the opioid may outlast antiemetic effects of scopolamine and delayed PONV may result.

Dose:
Premed (IMI, IVI 0.2mg-0.65mg), 1.5mg transdermally placed behind ear the drug being effectively available from the patch for up to 72hrs. [13]

Side effects:
anticholinergic – sedation, blurred vision, mydriasis, dry mouth, memory loss, urinary retention, hallucinations and confusion and disorientation. Caution in elderly.

Antihistamine e.g. Cyclizine, promethazine [8]

These act by blocking acetylcholine receptors in the vestibular apparatus and histamine receptors in the nucleus of the solitary tract, with little effect on any receptors in the chemoreceptor trigger zone.[8]

Use:
Treatment in motion sickness and in the control of emesis following middle-ear surgery. Not first line agents in the prophylaxis and treatment of PONV.

Dose:
Cyclizine 50mg 8 hourly, orally, IMI, IVI (has moderate efficiency, low incidence of significant side effects and is cheap)
Promethazine 25mg IVI, IMI

Side Effects:
Dry mouth, tachycardia, sedation

Dopamine Antagonists [8]

Three main groups:

1. Phenothiazines: all have a common tricyclic nucleus; antiemetic efficacy is determined by the side chain on position 10 of the tricylic nucleus. This side chain radical group may be either aliphatic (promethazine, chlorpromazine) or heterocylic (prochlorperazine).
   The aliphatic phenothiazines have low antiemetic potency and are more sedating than the heterocyclic's.
   Phenothiazines are direct antagonists of dopamine (D2) receptors in the chemoreceptor trigger zone as well as moderate antihistamine and anticholinergic actions.

   Use: Major tranquilizers and sedatives mainly. Use in prevention and treatment of opioid induced PONV
   Dose: Prochlorperazine {Stemetil}) 12.5mg-25mg IMI, 5-20mg PO, 5mg sublingual.
   Side effects: Prochlorperazine provides good antiemesis but high incidence of extrapyramidal side effects (EPSE) including akathesia, acute dystonia (torticollis, opisthotonus and oculogyric crisis), pseudo – parkinsons and dyskinesia.
   Additional effects of prochlorperazine are anti-inflammatory, antipruritic, anticholinergic and antihistaminergic.

2. Benzamides: Metoclopramide acts on central dopaminergic receptors and on both central and peripheral 5HT3 receptors and on peripheral 5HT4 receptors. The anti-emetic effect is attributed to its affinity for D2 receptors. Also has prokinetic effects increasing lower oesophageal sphincter tone and enhancing gastric and small bowel motility via actions at 5HT4 receptors.
   Dose: low dose 0.1-0.2mg/kg I.V.I/ IMI/PO/ nasally. Studies have shown comparative with other antiemetics efficacy at a dose of 25-50mg not 10mg.
   Side effects: EPSE, sedation and hypotension

3. Butyrophenones e.g. Droperidol (Inapsin)
   Droperidol has been for years the foundation strategy against PONV, effective in small doses for prevention and treatment; often considered GOLD STANDARD in comparing efficacy and cost.

   NEWS FLASH
   2001 December the highest FDA warning applied to Droperidol the black box warning! The warning states that it may cause death or life threatening events associated with Qt prolongation and torsades de pointes.
   The proof - following 10 reported cases over the thirty year period that droperidol has been available.
   Droperidol has been found to be a potent blocker of rapid component of the delayed rectifier K current (Ikr) which is the main repolarizing channel in human heart, which is encoded by human ether a go-go related gene(HERG). Mutations of this gene are involved in congenital long QT syndrome. [10]

Moreover, all drugs inducing torsades pointes block Ikr and 5HT3 blocks Ikr and Na channels leading to lengthening of both depolarization and repolarisation.[10]

0,1mg/kg induces a dose dependent QTc interval prolongation (450ms males and 470ms in females) but the first line treatment 5HT3 (ondansetron, ganisetron,dolasetron) also prolongs QTc interval at high doses and has the possible risk of torsades de pointse. Moreover, there have been several cases of cardiac dysrthymias following administration of 5TH3 antagonist reported. So why is there no BLACK BOX warning for 5HT3 antagonists. [16]

In studies showing QTc interval changes associated with PONV treatment via droperidol and ondansetron –these induced similar clinically relevant Qtc interval prolongation! [15]

Hence the safety of 5HT3 may not be superior to that of low dose droperidol. [10]

Furthermore, description of life threatening polymorphic ventricular tachycardia – torsades de pointes can be caused by several drugs used during general anaesthesia induce lengthening of cardiac repolarisation (thiopental, suxamethonium, and all volatiles anaesthetics).

At low doses (0,625mg-1,25mg) that are recommended for PONV, evidence of droperidol induced cardiac adverse events, in particular torsades de pointes is lacking.[16]

FDA recommends ECG be observed 2-3hours postoperatively following administration. For pre existing QT interval, the rationale for preoperative ECG and measuring QT prior to surgery is questionable and needs studies.

More recently, droperidol shown to be significantly more efficacious in decreasing PONV in the early than the late and similar efficacy against postoperative nausea and postoperative vomiting in a large multicentre trial except that it has a short duration of action (1/2 life = 2 hours). Hence should be administered at the end of procedure.

Dose: 0.25- 1.25mg IVI. The prophylactic dose of 0.625mg IVI is safe and effective .

Side effects: adverse effects seen when increasing doses, sedation, anxiety, restlessness, “locked in” syndrome. Hypotension is due to mild alpha blocking effects but not at PONV doses. [8]

Corticosteriod e.g. dexamethasone

The exact mechanism of action unknown, suggestions

Central or peripheral inhibition of the production or secretion of 5HT3 or central inhibition of the synthesis of prostaglandins or change in the permeability of the blood brain barrier to serum proteins.[8]

The onset of action is slow and hence needs to be given early, while its duration of action is 24 hours and with a single dose at induction is not associated with increased wound infection, is almost without adverse effects and is SAFE.

The efficacy in comparison to ondansetron has similar number needing to treat (NNTP) for PONV and satisfaction scores but is more cost effective. Best efficacy when dexamethasone is combined with 5HT3 [11].

A wide dose range for emesis due to chemotherapy 8-32mg, optimum dosing was found to be 8mg at induction for prevention of PONV. Unfortunately there is no place for steroids in established PONV!

Serotonin (5HT3) receptor antagonist [8] [19,20]

Although 5HT3s has revolutionized treatment of PONV they are not so innocent after all. The concerns surrounding their side effects had spurred the Canadian health authorities into issuing a black box warning for the dolasetron due to severe arrhythmias [12]. Remembering that majority of the drugs in this class are associated with QT prolongations. The only one not is palonosetron with a half life of 40 hours which has added benefit post anaesthetic recovery room discharge.

Studies suggestion equal efficacies amongst the drugs within the 5HT3 group but carriers of duplication of the CYP2D6 allele may alter this.

Genetic polymorphisms in drug metabolizing enzymes are a major cause of variability in drug metabolism that leads to the occurrence of adverse effects or lack of therapeutic efficacy.

CYP2D6 is the best characterized of these polymorphic CYP iso-enzymes, variants being due to point mutations, deletions or additions, gene rearrangements, and deletions or duplications of the either gene, and result in an increase, reduction, or complete loss of activity.

Metabolising about 25 % of all clinical used drugs in particular the 5HT3 antagonist, several studies have shown significantly that alternative

CYP2D6 phenotypes vary among the different ethnic groups and play a role in induction of adverse effects following administration of therapeutic agents, as well as drug -drug interactions.

CYP2D6 polymorphism can be classified according to Poor (PM), intermediate (IM), extensive (EM) and ultra rapid metabolizers(UM). This is seen with ondansetron and dolasetron which when present, the increased CYP450 2D6 activity are fast metabolisers.

Dolasetron, granisetron, ondansetron, palonosetron and topisetron have similar mechanisms of action but different pharmokinetic and pharmacodynamic properties (different chemical structure, and exhibit difference in receptor binding, dose response, and duration of effect.) Genetic polymorphism in the cytochrome P450 monooxgenase system, drug efflux transporter adenosine triphospate-binding cassette subfamily B member 1 and 5 hydroxytryptamine type 3 receptor subunits also contribute to the inter-individual variation in response to different 5 HT3 receptor antagonists. These differences account for differences in the duration of action and clinical efficacy of these agents. Understanding these differences allow anaesthesiologist to individualize antiemetic therapy in management of PONV.

CYP 2D6 - The highly genetically polymorphic 2D6 isoform of CYP (CYP2D6) is involved in the metabolism of ondansetron, tropisetron, palonosetron and dolasetron. In contrast the metabolism of granisetron involves the 3A4 isoform of CYP, which, although sensitive to inhibition and induction, has thus far not been associated with significant polymorphism of the CYP3A4 in the human population.

The 5HT3 antagonists are better antiemetic than antinausea drugs and their rapid metabolism was associated with the decrease in the frequency of vomiting, but not nausea episodes. [13]

Also duration of action is dependent on its affinity for 5TH3 receptor
Pharmocogenetics testing in patients may help differentiate responders to 5HT3 receptor antagonists from non responders and allow the anaesthesiologist to individualize emetic therapy. The cost-effectiveness of such screening in postoperative nausea and vomiting management has however, not been evaluated. Given the multifactorial nature of postoperative nausea and vomiting, a multimodal approach to reduce or eliminate risk factors will be most successful in its management.

5HT3 are highly specific and selective for nausea and vomiting blocking peripherally in the GIT and centrally at numerous sites including the CRTZ, the NTS and the cerebral cortex and the hippocampus.

Side effects headache, constipation dizziness and flushing. These drugs are metabolised by the liver and causes transient increase in liver enzymes. ECG abnormalities including QTc prolongation are well known.

Ondansetrons prophylactic dose is 4mg and treatment as low as 1mg, given at end of surgery due to short half life and can be repeated 8 hourly.

Ganisetron is more selective than the prototype, with elimination half time of 9h being 2.5 times longer than ondansetron with single dose being effective for 24 hours, dose in prevention is a single dose is 20-40ug/kg or 1mg. In addition is metabolised by the 3A4 isoform with less genetic polymorphism.

Dolasetron 12,5mg is as effective as Ondansetron 8mg but at a lower cost achieves same degree of patient satisfaction and oral use also available with 100mg being most effective.

Tropisetron (Navoban) is used in prophylaxis and treatment of PONV. Dosing is 2mg IVI shortly after induction of anaesthesia.

Neurokinin Antagonist [13]

Despite selective 5HT3 receptor antagonists representing major advancement in control of PONV, further improvement is warranted. An alluring strategy to blocking emesis, irrespective of the initiating stimulus would be to treat patients with a pharmacological agent that is able to depress activity of neurones within the medullary emetic circuitry. In the quest to discover a highly effective broad spectrum antiemetic neuroscientists focused on the role of other neurotransmitter systems than the serotergenic system. Their attention was drawn to the role of tachykinins since these have immunohistologically identified in the dorsal vagal complex of the ferret, an area essential in evoking vomiting. The emetic action of the tachykinin, substance P within the medullary emetic circuitry was demonstrated using resinferatoxin – an ultra potent capsaicin analogue that exhibits anti-emetic properties in the ferret against both centrally and peripherally acting agents. Andrews and Bhandari suggested that resinferatoxin exerts its antiemetic activity by depleting substance P at

a central site in the emetic pathway. Upon these results, potent and highly selective non peptide NK1 receptor antagonists that cross the blood brain barrier and antagonize the central effects of substance P were developed as tools for investigation of physiological role of Substance P in emesis. (14)

Tachykinins are part of the group of neuropeptides with the ability to promote a contractile action in smooth muscles and sharing the common C-terminal sequence Phe-Xaa-Gly-Leu-MetNh2. These compounds include substance P (for pain) and Neurokinin A and B (NKA and NKB). They exert their biological activity through 3 G –protein coupled receptor subtypes, identified as NK1, NK2, and NK3. According to the Montreal nomenclature, NK 1 receptor is defined as the mediator of the biological activity encoded by the C – terminal sequence of tachykinins, for which substance P is more potent agonist than NKA or NKB. Since substance P is believed to exert a key role within the central emetic circuitry, selective NK1 receptor antagonists were expected to express potent antiemetic activity.

The nucleus tractus solitary lying ventrally to the area postrema in the so called subnucleus gelatinosus is a good candidate for the site of action of NK1 receptor antagonists. Extensive substance P like immunoreactivity has been identified in this region and the tachykinins have been proposed as transmitters in vagal afferents.

NK antagonist's role in the maze of options is unique due to its central role on a potential final common pathway, presenting the prospect of a broader spectrum antiemetic activity than the 5HT3 receptor antagonists, dopamine receptor antagonists, anticholinergic agents and corticosteroids. However, like in pain management efficacy of NK 1 receptor antagonists in treatment of nausea and vomiting is enhanced in combination with other anti-emetics from different classes.

The investigational NK1 receptor antagonists studied include GR205171 (vofopitant, GlaxoSmithKline), CP 122721 (Pfizer), CJ 11974 (Pfizer), L754030 (fosaprepitant).
Numerous compounds are under investigation, including casopitant (GlaxoSmithKline), maropitant(Pfizer), netupitant (Helsinn), rolapitant or SCH 619734 (Schering Plough), T 2328 (Mitsubishe Tanabe Pharma), and vestipitant (GlaxoSmithKline).

The currently available and approved NK1 receptor antagonist is oral aprepitant for PONV prophylaxis at a dose of 40mg, being superior in that

offers a more complete response in the first 24hrs post operatively against nausea and vomiting as shown in a randomized, multicentre, double-blind phase III trial of 922 patients undergoing open abdominal surgery which were allocated randomly to receive one of the three antiemetic treatments prior to operation – oral aprepitant 40mg, oral aprepitant 125mg or IV ondansetron 4mg or matching placebos for prevention of PONV.

Other specific advantages include:
- Its oral formulation.
- Being easily administered with premedication.
- The option of IV form (fasaprepitant) for rescue in established PONV.
- Possibility of sparing other validated anti-emetics as rescue drugs as recommended in failure of prophylaxis and
- Long lasting effect of the drug.

Safety of this new kid on the block has never been a concern, with all investigational drugs being well tolerated and no drug related toxicity. Moreover, NK1 receptor antagonists have no impact on the QTc interval.

Limitations noted to be:
- Their poor solubility
- The influence on CYP3A4 metabolism – which may be specific for aprepitant, hopefully the other NK1 receptor antagonist will address these issues.

In terms of cost, is more expensive than generics and likely to be reserved for high risk patients.

Cannabinoids e.g. Nabilone and Dronabinol (8)
Used in prevention of chemotherapy induced nausea and vomiting but has not been compared to 5HT3 antagonists
Dose :4-8mg per day in divided doses
Side effects: high incidence of drowsiness, dizziness and lethargy

ETHICS

Ethical dilemmas can arise in any anaesthetic practise. Ethical teaching requires that patients interest take priority over others interest.
Our responsibility: To assess each patients underlying risk and to then select the appropriate measure.
Medico legally should we be held liable for inappropriate or omission of this responsibility?

FUTURE

The research efforts have mainly been in two directions: one is to elucidate risk factors for the individual case using results from epidemiological studies. The other is to look for therapeutic and prophylactic agents using molecular engineering based on 10- to 20-year-old knowledge of the emetogenic receptors in the midbrain and then go for testing in prospective studies.

However, if we use all our skills and present knowledge in predicting PONV, we know that within a group of patients with an identical risk profile, some will get symptoms and others will not. Further, we know that no single drug is more than 25—30% effective in preventing or treating PONV, and even with a multimodal drug combination approach there will be failures.

Thus, there is a need to work further on identifying basic, cellular and biochemical mechanisms of PONV and to bridge such knowledge into improved prediction of PONV risk and better prevention and treatment strategies. Potential areas of interest could be genetic markers of PONV and better understanding of the micro milieu in the nausea-vomiting centre.

CONCLUSION

Anaesthesiologists can best serve patients in this era of limited resources by making choices based on evidence of drug effectiveness, side effect profile, patient preferences and associated decrease in total costs. [(2)]

Prophylactic anti-emetics benefit select patients, but the routine use of expensive 5HT3 antagonists or NK-1 can't be justified on the basis of available evidence [(2)].

The rule of three can summarize this large body of evidence.

1. identify the at risk patients
2. try to keep baseline risk low like TIVA with propofol and avoiding emetogenic drugs (N2O) in part of the multimodal approach.
3. when you decided to give an antiemetic give it rationally, combining most effective and bearing in mind the cost. [(21)]

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APPENDIX. PONV Risk Scoring System

Scoring system (reference[s])	Formula	Accuracy: area under the receive operating characteristic curve [95% CI] (reference[s])*	Comments
Simplified (Unweighted Scoring Systems			
Apfel et al. (29)	(gender: male = 0, female = 1) + (history of PONV or motion sickness: no = 0, yes = 1) + (smoking status: no = 0, yes = 1) + anticipated use of postoperative opioids: no = 0, yes = 1)	0.58 [0.54–0.62] in children (48) 0.63 [0.60–0.66] (81) 0.679 [0.634–0.724] (20) 0.68 [0.66–0.72] (28) 0.71 [not reported] (31)	Range of possible scores: 0–4. Risk of PONV by score (29): 0, 10% 1, 21% 2, 39% 3, 61% 4, 79%
Eberhart et al. (36)	(duration of surgery ≥30 min: no = 0, yes = 1) + (age ≥3 yr: no = 0, yes = 1) + (strabismus surgery: no = 0, yes = 1) + (history of PV in child or of PV/PONV in a parent or sibling: no = 0, yes = 1)	0.72 (0.68–0.77) (36)	Range of possible scores: 0–4. Only scoring system developed for children. Developed for vomiting only. Risk of PV by score (36): 0, 9% 1, 10% 2, 30% 3, 55% 4, 70%
Koivuranta et al. (19)	(gender: male = 0, female = 1) + (history of PONV: no = 0, yes = 1) + (duration of surgery >60 min: no = 0, yes = 1) + (smoking: no = 0, yes = 1) + (history of motion sickness: no = 0, yes = 1)	0.61 [0.58–0.65] in children (48) 0.66 [0.63–0.69] for PONV, 0.66 [0.63–0.69] for nausea, 0.65 [0.62–0.68] for vomiting (81) 0.692 [0.648–0.736] (29) 0.71 [0.69–0.73] (1) 0.719 for nausea, 0.695 for vomiting [95% CIs not reported] (19)	Range of possible scores: 0–5 Risk of PO nausea, vomiting, respectively, by score (19): 0, 17%, 7% 1, 18%, 7% 2, 42%, 17% 3, 54%, 25% 4, 47%, 38% 5, 87%, 61%
"Semi-Simplified Scoring System": requiring a nomogram			
Van den Bosch et al. (26)	= sex (male = 0, female = 6) + history of PONV or motion sickness (no = 0, yes = 10) +smoking status (no = 8, yes = 0) +surgery type (lower abdominal or middle ear = 8, other = 0) +anesthetic technique (propofol = 0, isoflurane = 9) +age (15–19 yr = 20, 20–24 yrs = 19, 25–29 yr = 17, 30–34 yr = 16, 35–39 yr = 14, 40–44 yr = 13, 45–49 yr = 11, 50–54 yr = 10, 55–59 yr = 9, 60–64 yr = 7, 65–69 yr = 6, 70–74 yr = 4, 75–79 yr = 3, 80–84 yr = 1, ≥85 yr = 0)	0.72 [0.70–0.74] (26) 0.70 [0.68–0.72] (predicted for other inpatient populations) (26)‡	Range of possible scores: 0–61. Risk of PONV by point score 2, 10% 12, 20% 19, 30% 25, 40% 31, 50% 31, 50% 36, 60% 42, 70% 49, 80% 59, 90%
Weighted Scoring Systems: predicted risk = $e/1\text{-}e^z$ when:			
Apfel et al. (27)	−0.92 +1.28 x (gender: male = 0, female 1) −0.029 x (age in yr) −0.74 x (smoking status: no = 0, yes = 1) +0.63 x (history of PONV or motion sickness: no = 0, yes = 1) +0.26 x (duration of anesthesia in hours)	0.59 [0.56–0.63] for vomiting in children (48) 0.62 [not reportd] (81) 0.698 [0654–0.742] (29) 0.70 [0.67–0.72] (1) 0.77 [not reported] for vomiting (27)	Developed for vomiting only.
Koivuranta et al. (19)	−2.21† +0.93 x (gender: male = 0, female = 1) +0.82 x (history of PONV: no = 0, yes = 1) +0.75 x (duration of surgery >60 min: no = 0, yes = 1) +0.61 x (smoking status: no = 1, yes = 0) + 0.59 x (history of motion sickness: no = 0, yes = 1) −0.92	0.689 [0.645–0.733] (29) 0.66 [not reported] (81) 0.695 for vomiting, 0.719 for nausea [95% CI is not reported] (19)	

APPENDIX. PONV Risk Scoring System *continued…*

Scoring system (reference[s])	Formula	Accuracy: area under the recei operating characteristic curv [95% CI] (reference[s])*	Comments
Palazzo and Evans (21)	−5.03 +2.34 x (postoperative opioids: no = 0, yes = 1) +3.97 x (history of PONV: no = 0, yes = 1) +2.4 x (gender: male = 0, female = 1) +078 x (history of motion sickness: no = 0, yes = 1) −3.2 (female with previous PONV: no = 0, yes = 1)	0.56 [0.52–0.60] in children (48) 0.62 for vomiting, 0.682 for nausea [95% CIs not reported] (19) 0.64 [0.62–0.67] (28) 0.68 [0.65–0.70] (1) 71% [not reported] § (32)	
Sinclair et al. (17)	−5.97 −0.14 x (age in yr/10) −1.03 x gender (gender: female = 0, male = 1) −0.42 x (smoking status: no = 0, yes = 1) +1.14 x (history of PONV: no = 0, yes = 1) +0.46 x (duration of surgery in 30-min increments) +2.36 x (general anesthesia; no = 0, yes = 1) +1.48 x (ENT surgery: no = 0, yes = 1) 1.77 x (ophthalmological surgery: no = 0, yes = 1) +1.90 x (plastic surgery: no = 0, yes = 1) +1.2 x (gynecological surgery except dilatation and curettage: no = 0, yes = 1) +1.04 x (orthopedic surgery on knee: no = 0, yes = 1) +1.78 x (orthopedic surgery on shoulder: no = 0, yes = 1) +094 x (orthopedic surgery elsewhere: no = 0, yes = 1)	0.65 [0.61–0.69] in children (48) 0.64 [not reported in inpatients (31) 0.68 [0.66–0.71[in inpatients (2 0.785 [0.774–0.796] in original outpatient population (17)	Only scoring system developed in outpatients.

CI = confidence interval; ENT = ear, nose and throat; PO = postoperative; PONV = postoperative nausea and vomiting; PV = postoperative vomiting.
*All values are for PONV in adults unless indicated otherwise; †Published in (26); ‡Estimated by using bootstrapping techniques, adjusted for over-optimism (26); § This figure represents the overall correct prediction rate of the Palazzo and Evans scoring system in a second patient population rather than the area under the receiver-operating characteristics curve.

Table 4. Overview of Risk Factors Use in Risk Scoring Systems

	Adults, simplified or semisimplified systems			Adults, nonsimplified systems				Children, simplified system	Number of systems in which risk factor is used
Risk Factor*	Apfel et al. (29)	Koivuranta et al. (19)	Van den Bosch et al. (26)	Apfel et al. (27)	Koivuranta et al. (19)	Palazzo and Evans (21)	Sinclair et al. (17)	Eberhart et al. (36)	
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
Anesthesia-related									
Duration of anesthesia				X					1/8
Anesthetic 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 = anesthesia-related; D&C = dilation and curettage; ENT = ear nose and throat; GYN = gynecologic; OPHTH = ophthalmologic; ORTHO = orthopedic; PONV = postoperative nausea and vomiting; PR = patient-related; SR = surgery-related, X = used in the particular risk scoring system.
* For specific permutations of these risk factors in the different scoring systems, the reader is referred to Appendix, Table A1.
† Simplified scoring systems omit constants and coefficients derived from logistic reression modeling in favor of binary, yes/no scoring for each item in the system. The semi-simplified system of Van den Bosch et al. (26) also omits constants and coefficients. However, instead of using binary scoring for its items, the Van den Bosch system assigns different point values to particular alternative variables for each, so that a nomogram is required to use the system.