Nausea and vomiting after surgery

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Key points

5-Hydroxytrytamine type 3 (5-HT$_3$) receptor antagonists, and specifically ondansetron, are the most commonly used antiemetics for both prophylaxis and rescue treatment for PONV. Other first-line prophylactic antiemetics include dexamethasone, droperidol, and aprepitant for high-risk patients.

PONV still affects about one in three patients undergoing surgery with general anaesthesia.

The most reliable independent predictors of PONV are patient-specific (e.g. female gender) and anaesthesia-related (e.g. use of volatile anaesthetics).

Risk scores have been developed to predict the patient's risk of PONV. Choosing a prophylactic regimen based on the patient's risk score can reduce the incidence of PONV.

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Postoperative nausea and vomiting (PONV) is defined as any nausea, retching, or vomiting occurring during the first 24–48 h after surgery in inpatients. PONV is one of the most common causes of patient dissatisfaction after anaesthesia, with reported incidences of 30% in all post-surgical patients and up to 80% in high-risk patients. In addition, PONV is regularly rated in preoperative surveys, as the anaesthesia outcome the patient would most like to avoid. It is therefore not surprising that patients across Europe and North America express a high willingness-to-pay ($50–100) to avoid PONV. While suture dehiscence, aspiration of gastric contents, oesophageal rupture, and other serious complications associated with PONV are rare, nausea and vomiting is still an unpleasant and all-too-common postoperative morbidity that can delay patient discharge from the post-anaesthesia care unit and increase unanticipated hospital admissions in outpatients.

Physiology

The physiology of PONV is complex and not perfectly understood. According to our current model, the brain structures involved in the pathophysiology of vomiting are distributed throughout the medulla oblongata of the brainstem, not centralized in an anatomically defined 'vomiting centre'.[1] Such structures include the chemoreceptor trigger zone (CRTZ), located at the caudal end of the fourth ventricle in the area postrema, and the nucleus tractus solitarius (NTS), located in the area postrema and lower pons. The CRTZ receives input from vagal afferents in the gastrointestinal tract, and it can also detect emetogenic toxins, metabolites, and drugs circulating in the blood and cerebrospinal fluid due to its lack of the blood–brain barrier. The CRTZ projects neurones to the NTS, which receives input from vagal afferents and from the vestibular and limbic systems. The NTS triggers vomiting by stimulating the rostral nucleus, the nucleus ambiguous, the ventral respiratory group, and the dorsal motor nucleus of the vagus.

PONV can be triggered by several perioperative stimuli, including opioids, volatile anaesthetics, anxiety, adverse drug reactions, and motion. Multiple neurotransmitter pathways are implicated in the physiology of nausea and vomiting. Enterochromaffin cells in the gastrointestinal tract release serotonin, and the vagus nerve communicates with the CRTZ via 5-HT$_3$ receptors. The CRTZ communicates with the NTS primarily via dopamine-2 (D2) receptors. The vestibular system, which detects changes in equilibrium, communicates with the NTS via histamine-1 (H1) and acetylcholine (mACh). Anticipatory or anxiety-induced nausea and vomiting appears to originate in the cerebral cortex, which communicates directly with the NTS via several types of neuroreceptors. Therefore, antiemetic drugs have been developed that are effective against 5-HT3, D2, NK1, H1, and mACh receptors. However, no antiemetic can reduce the incidence of PONV to zero. In fact, only 20–30% of the patients will respond to any currently available antiemetic. Given that the panoply of available antiemetic drugs work on different receptor classes, multiple antiemetics can be safely and effectively combined to further reduce the risk of PONV in high-risk patients.

Risk factors

Although the available antiemetic drugs have been proven safe in clinical trials, no agent is without its side-effects. Side-effects of antiemetics range from mild (e.g. headache for ondansetron) to potentially severe (e.g. QT prolongation). To reduce the incidence of PONV without increasing the risk of unnecessary side-effects, antiemetic prophylactic regimens should be tailored to the patients most likely to experience PONV. To identify at-risk patients, it is critical to accurately identify strong and reliable independent risk factors using multivariable analysis, since patients cannot be randomized with respect to risk of PONV in clinical trials. Some risk factors, like gynaecological surgery, are associated with a high

incidence of PONV. However, this correlation is likely due to confounding factors inherent to the surgery type, like female gender. Thus, risk assessment based on the relative impact of 'true' (i.e. independent) risk factors is likely to be more robust.

Well-established risk factors

Patient-related

Female gender is consistently the strongest risk factor for PONV with an odds ratio (OR) of ∼3, which indicates that female patients are—on average—three times more likely than men to suffer from PONV.

Non-smoking status, with an OR of ∼2, roughly doubles the patient's risk of PONV. The specific mechanism underlying smoking's protective effect is unknown. One of the most commonly believed theories is that polycyclic aromatic hydrocarbons in cigarette smoke induce cytochrome P450 enzymes, thereby increasing the metabolism of emetogenic volatile anaesthetics. However, there is currently little evidence to support this theory.

A history of motion sickness, PONV, or both, also with an OR of ∼2, indicates a general susceptibility to PONV.

For adult patients, age is a statistically, though not clinically, relevant risk factor, with the incidence of PONV decreasing as patients age. For paediatric patients, however, age increases the risk of postoperative vomiting (POV), such that children older than 3 yr have been shown to have an increased risk of POV compared with children younger than 3.

Anaesthesia-related

The use of volatile anaesthetics is associated with a two-fold increase in the risk of PONV, with risk increasing in a dose-dependent manner, and no significant difference in incidence with different volatile anaesthetics. In fact, the use of volatile anaesthetics is the single most important factor for predicting emesis in the first 2 postoperative hours. Volatile anaesthesia may increase PONV by decreasing serum levels of anandamide, an endogenous cannabinoid neurotransmitter that acts on cannabinoid-1 and transient receptor potential vanilloid-1 receptors to suppress nausea and vomiting. Because replacing volatile anaesthetics with total i.v. anaesthesia with an agent like propofol reduces the incidence of PONV, some have suggested that propofol itself has antiemetic properties; however, there is little evidence to support this claim.

Nitrous oxide increases the relative risk of PONV by 1.4—less of an effect than previously believed.

Intraoperative and postoperative opioid use increases the risk of PONV in a dose-dependent manner. Opioids reduce muscle tone and peristaltic activity, thereby delaying gastric emptying, inducing distension, and triggering the vomiting reflex.

The duration of anaesthesia, which is closely linked to the duration of surgery, can help predict the patient's risk of PONV, since the duration of anaesthesia describes the patient's exposure to emetogenic stimuli like volatile anaesthetics and intraoperative opioids.

Potential risk factors

Patient-related

Low ASA physical status (I–II), history of migraine, and preoperative anxiety have all been associated with an increased risk of PONV, although the strength of association varies from study to study.

Anaesthesia-related

No randomized controlled trials and few multivariable analyses have investigated the effect of general *vs* locoregional anaesthesia on PONV, and ORs associated with general anaesthesia range from 1.3 to 10.6. It appears that locoregional anaesthesia is associated with less PONV.

The data concerning facemask ventilation are conflicting.

There is insufficient evidence to conclude that neostigmine increases the risk of PONV.

Surgery-related

There is much controversy over the impact of type of surgery on PONV. Some studies have shown that gynaecological, ophthalmological, otological, and thyroid surgery can each increase the risk of PONV. However, large prospective trials that used multivariable analysis to identify PONV risk factors found no such associations. Nevertheless, when categorized anatomically, type of surgery has been associated with need for early antiemetic rescue treatment in the post-anaesthesia care unit. In general, the type of surgery cannot provide reliable, reproducible, and clinically relevant information for assessing the patient's risk of PONV in adult patients. Conversely, in children, strabismus surgery was identified as an independent risk factor for POV.

Disproved risk factors

Patient-related

Body mass index and menstrual cycle phase have no impact on the incidence of PONV.

Anaesthesia-related

According to a randomized controlled trial in over 5000 patients, the use of a short-acting opioid-like remifentanil instead of fentanyl does not decrease the incidence of PONV.[2]

The use of supplemental oxygen (F_{IO_2}: 80%) does not reduce the incidence of PONV.

While the use of nasogastric tubes may increase the incidence of nausea, gastric tube decompression has no effect on PONV.

Therefore, the major risk factors for PONV appear to be patient-specific and anaesthesia-related.

Risk scores for predicting PONV

To develop a predictive risk score for PONV, multivariable analysis is applied to an evaluation dataset to quantify the weight (i.e. OR) of each hypothesized risk factor as a coefficient. The

probability of PONV, given the presence of the relevant risk factors, is subsequently calculated in a validation dataset. By plotting sensitivity against the false-positive rate (1-specificity), the area under the receiver operating characteristic curve (AUC-ROC) can be calculated to describe the score's ability to discriminate between patients who will and will not experience PONV. An AUC-ROC of 1 represents perfect discrimination and an AUC-ROC of 0.5 denotes that the scoring system is no better than chance.

A risk score based on counting the number of risk factors present—which maintains the original score's predictive accuracy—will be easier to implement in clinical practice than one requiring the use of complex coefficients. Currently, there are two simplified PONV risk scores for adults and one simplified POV risk score for children.[3][4] Koivuranta et al.'s PONV risk score features five risk factors, namely female gender, non-smoking status, history of PONV, history of motion sickness, and duration of surgery >60 min. If 0, 1, 2, 3, 4, or 5 risk factors are present, the incidence of PONV is 17%, 18%, 42%, 54%, 74%, and 87%, respectively (ROC-AUC=0.71). Apfel et al. subsequently developed a simplified risk score based on data from Koivuranta et al.'s group and their own previous data that could be applied across centres and that reduced the number of risk factors in the model from five to four. The Apfel simplified score includes female gender, history of PONV and/or motion sickness, non-smoking status, and postoperative use of opioids. When 0, 1, 2, 3, or 4 factors are present, the risk of PONV is 10%, 20%, 40%, 60%, or 80%, respectively (ROC-AUC=0.69). Multifactorial scores are significantly more accurate at predicting the patient's risk of PONV than single risk factors like surgical site, history of PONV, or history of motion sickness (ROC-AUC=0.68, 0.53, and 0.58, respectively).

The POVOC score is the simplified risk score for predicting POV in children. The independent risk factors for POV are the duration of surgery ≥30 min, age ≥3 yr, strabismus surgery, and history of POV in the child or of PONV in his/her relatives. When 0, 1, 2, 3, or 4 risk factors are present, the incidence of POV is 9%, 10%, 30%, 55%, or 70%, respectively.

The ROC-AUC measures a risk score's validity for a specific population. Most scores have an ROC-AUC in the range of 0.65–0.80 due to the limited strength (OR=2–3) of individual predictors, which means that ∼70% of the patients can be correctly classified in terms of risk for PONV. The model's overall predictive capability cannot improve, even with the inclusion of additional predictors, unless predictors with higher ORs are discovered. In addition to the ROC-AUC, a more important measurement of the score is its utility, assessed using a calibration curve that compares predicted and observed PONV incidences in a population.

The three simplified risk scores showed favourable calibration curves and discrimination properties even in external validations of the models, which indicates that the scores can be clinically useful. Due to the models' inherent limitations in accuracy, however, prophylactic therapy should be administered to patients according to their predicted risk of PONV or the number of risk factors they have, as is done for the prevention of conditions like post-surgical venous thromboembolism (Fig. 1).

Antiemetic drugs

First-line antiemetic interventions

Three classes of antiemetic drugs,[5][6] serotonin antagonists (e.g. ondansetron), corticosteroids (e.g. dexamethasone), and dopamine antagonists (e.g. droperidol) have similar efficacy against PONV, with a relative risk reduction of ∼25%. Moreover, they act independently and, when used in combination, have additive effects (Table 1).[2]
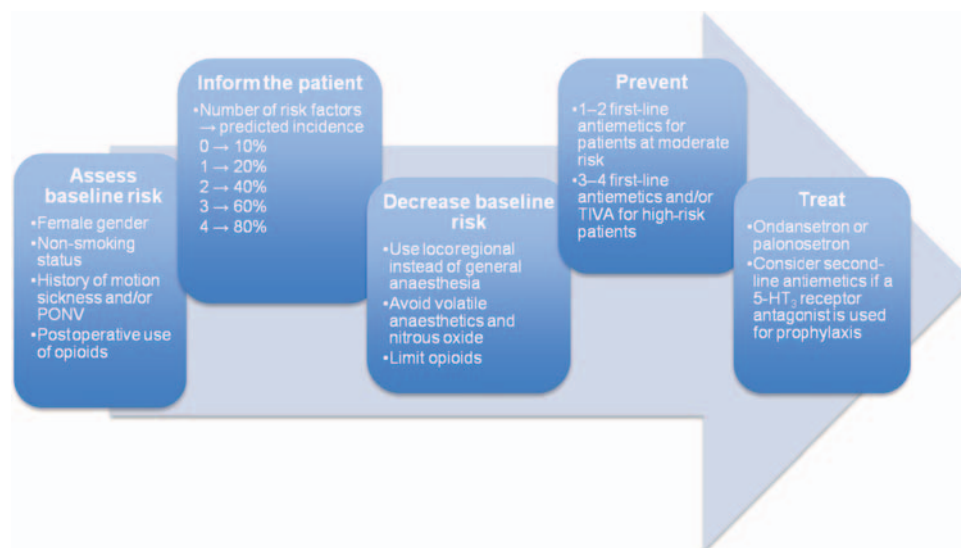

Fig 1 Management strategy of PONV in adults.

Table 1 Recommended dosages of antiemetic drugs for prophylaxis in adult patients

	Generic name	Mode of administration	Dose (mg)	Timing of administration
First class	Dexamethasone	I.V.	4–8	Induction
	Droperidol	I.V.	0.625–1.25	End of surgery
	Ondansetron	I.V.	4	Induction
	Palonosetron	I.V.	0.075	Induction
	Aprepitant	Oral	40	Before induction
Second class	Dimenhydrinate	I.V.	50	Induction
	Scopolamine	Transdermal	1	The night before/day of surgery
	Metoclopramide	I.V.	25–50	Induction

Three other serotonin antagonists, namely granisetron, dolasetron, and palonosetron, have a similar efficacy and side-effect profile (e.g. constipation, headache) to ondansetron. Like droperidol, ondansetron, granisetron, and dolasetron are associated with QTc prolongation, which increases the risk of torsades de pointes and must therefore be avoided when patients before operation exhibit QTc prolongation. The most recent serotonin antagonist, palonosetron, has no effect on the QTc interval and, furthermore, has a longer duration of action—up to 72 h—due to its unique 5-HT$_3$ receptor-binding properties. Therefore, palonosetron may be a particularly effective prophylaxis against PONV for ambulatory surgery.

The D2 receptor antagonist droperidol has a short plasma half-life and should therefore be given towards the end of surgery. Droperidol is associated with sedation and QTc prolongation and has even been issued a black-box warning from the US Food and Drug Administration following reports of severe cardiac arrhythmias, even though the black-box label is not for doses used in the perioperative period.

At low doses, dexamethasone is not only effective against PONV but also against post-surgical pain and fatigue.

Neurokinin-1 receptor antagonists are a promising new class of antiemetics that were originally developed and approved for chemotherapy-induced nausea and vomiting. Administrated orally before surgery, aprepitant has similar efficacy against nausea and greater efficacy against vomiting compared with other commonly used antiemetics. In fact, in two randomized controlled trials, aprepitant decreased the incidence of vomiting by 70–80%. Aprepitant is not associated with QTc prolongation or sedative effects, but its high cost limits its use to high-risk patients.

Second-line antiemetic interventions

The following drugs are characterized by less favourable side-effect profiles or limited evidence of efficacy.

Metoclopramide is a widely used D2 antagonist. Contrary to popular belief, the 10 mg dose has no effect on PONV, but 25–50 mg has similar efficacy compared with other antiemetics. Metoclopramide use has been associated with extrapyramidal and sedative side-effects.

Haloperidol is a butyrophenone similar to droperidol. Nonetheless, precise data on optimal dosage, timing, and safety are lacking. I.V.

injection is now off-label in the USA due to reports of cardiac arrhythmias and death associated with its use.

Dimenhydrinate is an antihistamine like promethazine and cyclizine. There are few randomized controlled trials investigating its use for PONV, and the drug is associated with a significant rate of side-effects like sedation, dry mouth, visual disturbance, and urinary retention.

Transdermal scopolamine is a cholinergic antagonist typically used to treat motion sickness. A recent meta-analysis showed a 40% risk reduction in PONV, but a three-fold increase in visual disturbance, compared with placebo when transdermal scopolamine is administered the night before or the day of surgery.

An alternative to pharmacological treatment may be acustimulation of P6, which has demonstrated some efficacy in reducing PONV without major side-effects.[7] Some uncertainties remain regarding the type of stimulation to apply, the timing, and the target population.

Preventive and therapeutic strategies

Decrease the baseline risk

First, the patient's baseline risk should be calculated using the Apfel simplified risk score for adults or the POVOC score for children.

If possible, use loco-regional anaesthesia instead of general anaesthesia. If general anaesthesia is required, total i.v. anaesthesia with propofol and nitrogen reduces the incidence of PONV by 30%, making this intervention as effective as an antiemetic drug.

Limiting the perioperative administration of opioids decreases not only the risk of PONV but also hyperalgesia.

Combine effective antiemetics

As previously mentioned, antiemetic drugs like ondansetron, dexamethasone, and droperidol are similarly effective, each reducing the patient's risk by 25%.[2] Because they work on different receptor classes, their effects are additive.[2] Thus, patients at low-to-moderate risk can be given one or two interventions (e.g. TIVA, antiemetic drugs), whereas patients at high risk can receive three or four interventions. Using the patient's risk to tailor antiemetic prophylaxis has been shown to be effective and is thus recommended in expert guidelines.[8 9] In doing so, it is important to consider both the patient's risk and the safety and relative efficacy of

the available interventions. But even more important is implementing an institutional protocol to prevent and treat PONV. It may be reasonable to take more aggressive steps to prevent PONV in outpatients, such as using long-acting agents like transdermal scopolamine or palonosetron.

Treat patient

Despite implementation of and adherence to consensus guidelines, a significant number of patients still suffer from PONV in the post-anaesthesia care unit, in the hospital, and at home.

Ondansetron is the most commonly used drug for rescue treatment. However, ondansetron is no more effective than placebo for rescue treatment if the patient received a 5-HT$_3$ receptor antagonist intraoperatively as prophylaxis. Therefore, antiemetics administered as rescue treatment for PONV should be of a different class than the drug administered as prophylaxis.[9]

Outpatients should be offered rescue treatment that can be administered orally or in a patch application (e.g. transdermal scopolamine).

Conclusions

Practitioners should systematically implement prophylactic and therapeutic antiemetic strategies based on randomized controlled trials, meta-analyses, and evidence-based consensus guidelines to reduce the institutional rate of PONV. Assessing and informing the patient of his/her baseline risk, providing adequate prophylaxis, and treating established PONV with rescue antiemetics of a different class are the foundations of successful management of this distressing postoperative outcome.

Declaration of interest

None declared.

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