Paediatric Postoperative Vomiting

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KEY POINTS

- Postoperative nausea and vomiting (PONV) is distressing and increases postoperative morbidity.
- The vomiting centre coordinates the physiological reflex of vomiting, with central and peripheral inputs.
- PONV prevention requires identification of children at increased risk, utilising anaesthetic techniques that minimise PONV incidence, and implementing antiemetic prophylaxis adjusted for their level of risk.
- 5-HT3 antagonists and/or dexamethasone are the mainstay of prophylaxis. Evidence also exists for alternative pharmacologic and nonpharmacologic postoperative vomiting prophylaxis.
- Guidelines are likely to develop as more evidence is gathered regarding children in particular and as novel antiemetic agents emerge.

INTRODUCTION

Postoperative nausea and vomiting (PONV) and postoperative vomiting (POV) are nausea (the subjective feeling of sickness) and/or vomiting (the objective response of ejecting matter from the stomach) following anaesthesia or surgery. They are distressing symptoms that may adversely affect patient and carer satisfaction as well as increase the length of stay and readmission rates.[1] Prolonged POV may lead to other complications such as dehydration and electrolyte imbalance, wound breakdown or bleeding or aspiration pneumonitis,[1] making its prevention and management crucial to perioperative care. Given the difficulty that younger or preverbal children have in indicating the sensation of nausea, postoperative vomiting is considered a more appropriate measurable endpoint, and children are reported to have twice the incidence of POV (13% vs. 42%), compared to adults.[2]

This tutorial discusses paediatric POV and covers the physiologic mechanism of nausea and vomiting (due to the paucity of studies in children, this is based on adult studies), the assessment and mitigation of risk factors and the pharmacologic and nonpharmacologic options for the control of nausea and vomiting.

PHYSIOLOGIC PATHWAY OF VOMITING

The vomiting centre, located in the medulla, controls the act of vomiting. It receives signals from muscarinic acetylcholine (mACh) and neurokinin type 1 (NK1) receptors and integrates signals from the following sources via neural pathways[1,3] (Figure 1).

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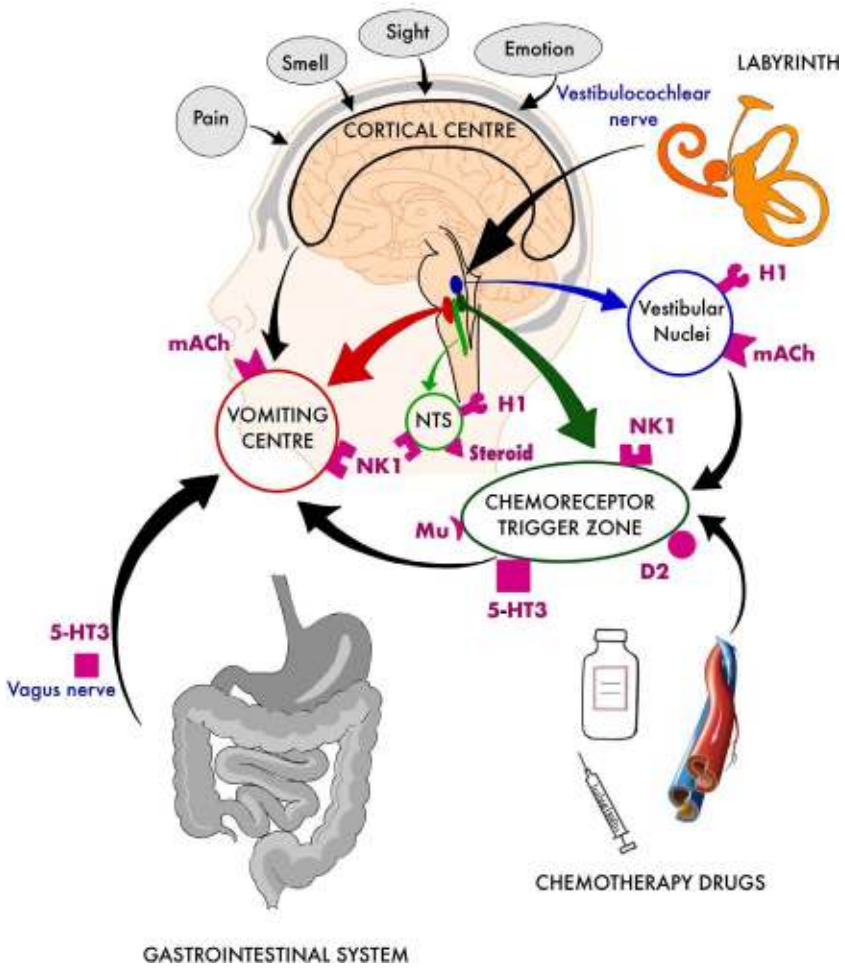

Figure 1. Pathways involved in nausea and vomiting. 5-HT3, 5-hydroxytryptamine 3 receptor; D2, dopamine 2 receptor; H1, histamine 1 receptor;; mACh, muscarinic acetylcholine receptor; Mu, μ-opioid receptor; NK1, neurokinin type-1 receptor.

- Chemoreceptor trigger zone (CTZ): The CTZ is situated in the area postrema of the medulla, which is outside the blood-brain barrier; therefore, it is quicker to respond to emetogenic stimuli in blood than the vomiting centre. The CTZ also relays information from various other sources, such as the vestibular apparatus.
  Receptors: Dopamine 2 (D2), 5-hydroxytryptamine 3 receptor (5HT3), NK1 and μ-opioid receptors (Mu)
- Gastrointestinal (GI) tract: In response to infection, the enterochromaffin cells present in the GI tract release serotonin (5HT); the mechanoreceptors and chemoreceptors then relay the information to the vomiting centre via 5HT3 receptor activation of vagal afferents in the GI tract.
  Receptor: 5HT3 receptors
- The vestibular apparatus, located close to the vomiting centre, sends information regarding the position and head movement either directly to the vomiting centre or via the CTZ.
  Receptors: Histamine 1 (H1) and mACh
- Cortical higher centres: This area mediates aspects of pain, objectionable psychological factors, and unpleasant smells and sights.
- The nucleus tractus solitarius lies in the medulla close to the CTZ. It acts as a relay centre, gathering all visceral afferents (via cranial nerves IX and X) and is responsible for organisation of the final common pathway of vomiting.
  Receptors: H1, NK1 and corticosteroid

POV RISK FACTORS

To devise appropriate antiemetic prophylaxis and treatment, it is essential to estimate the child's risk of developing POV or PONV. The risk factors in the paediatric population can be categorised into pre-, intra- and postoperative,[4] summarised in Table 1.

Preoperative	Intraoperative	Postoperative
Age ≥3 y	Adenotonsillectomy	Long-acting opioids
Previous POV or PONV or motion sickness	Strabismus surgery	
Family history of POV or PONV	Otoplasty	
Postpubertal girls	Duration of surgery ≥30 min	
	Volatile anaesthetic agents	
	Anticholinesterases	
	Long-acting opioids*	

Table 1. Risk Factors for POV or PONV in the Paediatric Population.[4,5] POV indicates postoperative vomiting; PONV, postoperative nausea and vomiting. *Not incorporated as a risk factor per the guidelines[5] cited in Figure 4 .

Preoperative Factors

- Age: The risk of POV increases in individuals aged ≥3 years and continues to rise with increasing age.[5]
- Sex: Girls of postpubertal age are at a higher risk compared with their male counterparts; this is hypothesised to be related to the increase in sex hormone production.[5]
- History of POV, PONV or motion sickness: Previous and family history of POV or PONV are considered to be independent risk factors, and prior motion sickness is a specific risk factor in adults and children. [5]

Intraoperative Factors

- Type of surgery: Children undergoing adenotonsillectomy, strabismus surgery or otoplasty are at a higher risk of POV or PONV.[5]
- Volatile anaesthetic agents: the use of total intravenous anaesthesia and thus avoiding volatiles for maintenance has been shown to reduce the risk significantly.[4,5] There is still no clear consensus on whether nitrous oxide is a risk factor.[4,5]
- Duration of surgery ≥30 minutes: Longer operations require a longer duration of anaesthetic. With volatile agents, this is an established risk factor for vomiting in both adults and children.[4]
- Use of anticholinesterases: UK guidelines advise avoiding the use of neostigmine in children who are at high risk of vomiting.[5]
- Long-acting opioids: intraoperative administration of longer acting opioids can increase POV compared with short-acting opiates.[6]

Postoperative Factors

Use of long-acting opioids: The use of long-acting opioids in the postoperative ward has been shown to increase the incidence of vomiting; hence, opiate-sparing techniques are recommended, especially for high-risk patients.[4]

Risk Stratification

The simplified risk score for POV in children (POVOC score) of Eberhart et al[7] demonstrates how accumulating risk factors is associated with an increase in the incidence of POV. This risk score incorporates duration of surgery ≥30 minutes, age ≥3 years, strabismus surgery and previous or family history of POV (Table 2). When 0, 1, 2, 3 or 4 of the depicted independent predictors are present, the corresponding risk for PONV is quoted as approximately 9%, 10%, 30%, 55% or 70%, respectively (Figure 2). Alternative methods of risk stratification have been incorporated in national POV prophylaxis guidelines[4,5] and are summarised (along with prophylaxis recommendations, which will be discussed later) in Figures 3 and 4.

Risk Factor	Score
Duration of surgery ≥30 min	1
Age of child ≥3 y	1
Strabismus surgery	1
History or family history of postoperative nausea and vomiting	1
Total points	0 to 4

Table 2. Simplified Risk Scoring System for Postoperative Vomiting in Children (POVOC Score) of Eberhart et al[7]

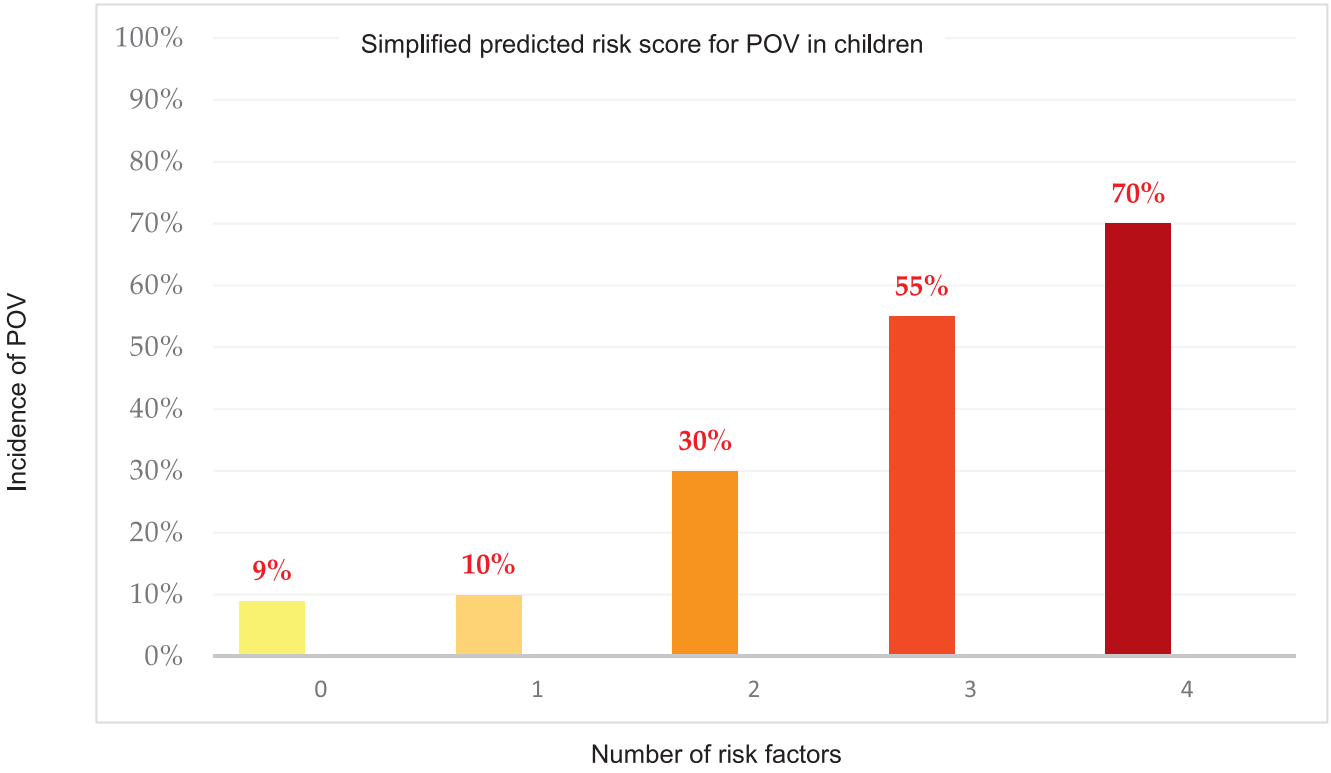

Figure 2. Simplified risk score for postoperative vomiting in children (POVOC score) of Eberhart et al[7].[7]

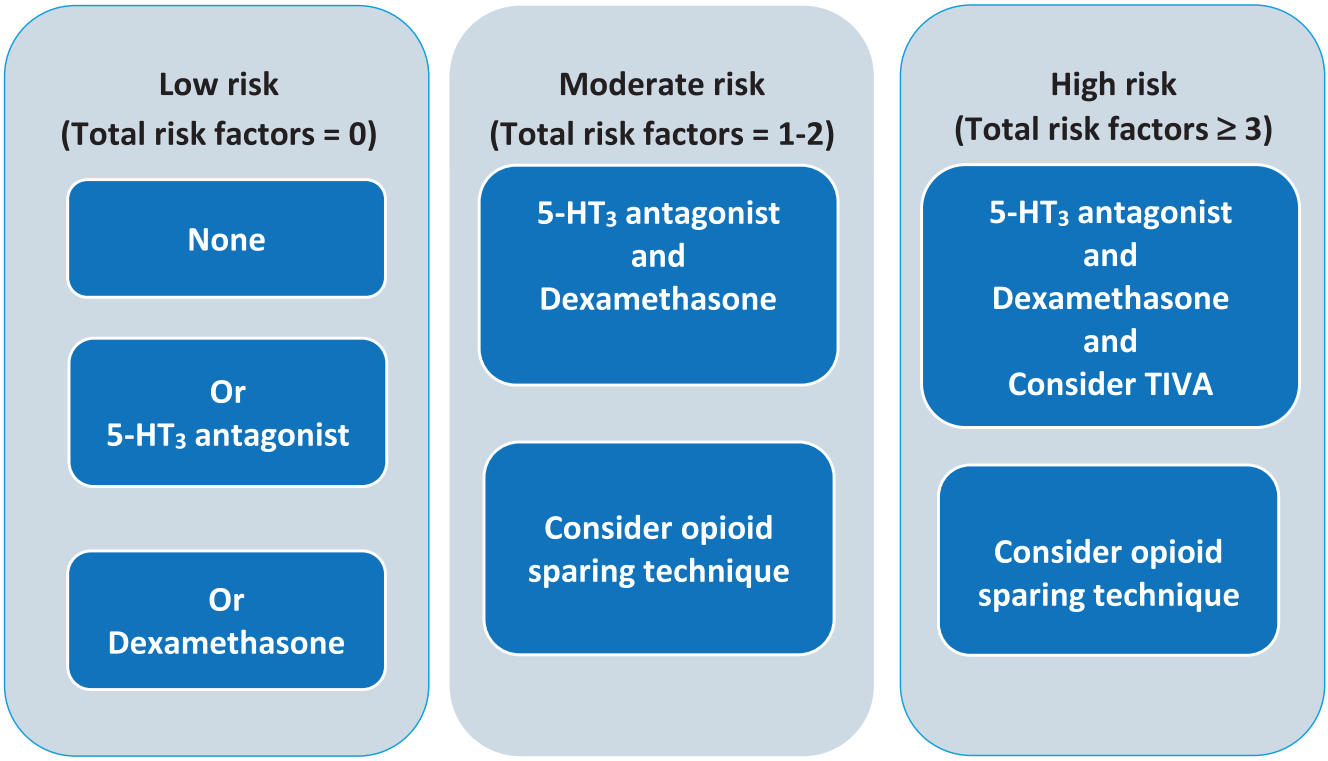

Figure 3. Example paediatric POV prophylaxis regimen.[4] For risk factors, see Table 1.

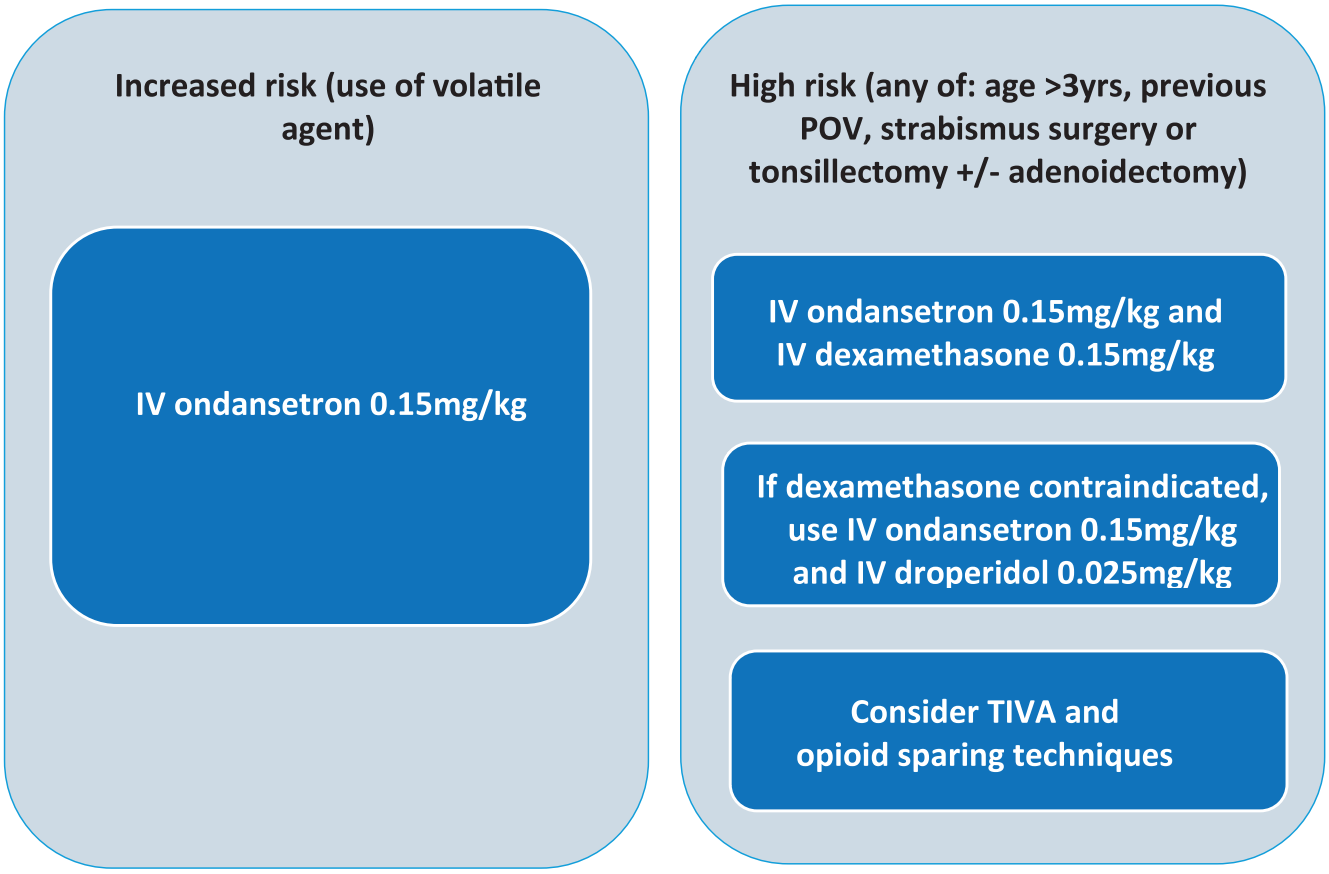

Figure 4. Example paediatric postoperative vomiting prophylaxis regimen.[5]

RISK REDUCTION

Choice of Anaesthetic Technique

The use of total intravenous anaesthesia (TIVA) has been shown to reduce paediatric POV; however, it is associated with an increased risk of bradycardia in particular during strabismus surgery secondary to the oculocardiac reflex.[4]

Opioid-Sparing Techniques

Evidence supports the use of opioid-sparing techniques in preventing paediatric POV.[5,6] This can be achieved by using nonopioid systemic analgesics (such as paracetamol and/or lidocaine) and regional anaesthetic procedures (eg, caudal, transversus abdominis plane or rectus sheath blocks, which are safe and efficacious).[4]

Fluid Administration

It has been suggested that prolonged fasting is associated with nausea and vomiting. A recent review recommends early and liberal resumption of oral fluid intake postoperatively as it is associated with reduced POV.[8]

Premedication

The concurrent use of $\alpha 2$ agonists such as intranasal dexmedetomidine or oral clonidine is associated with reduced rates of PONV in children compared with other premedication or placebos,[9,10] but further studies would be beneficial.

PHARMACOLOGICAL AGENTS FOR PROPHYLAXIS OR TREATMENT

The following are antiemetic medications as they relate to their receptors (Figure 5).

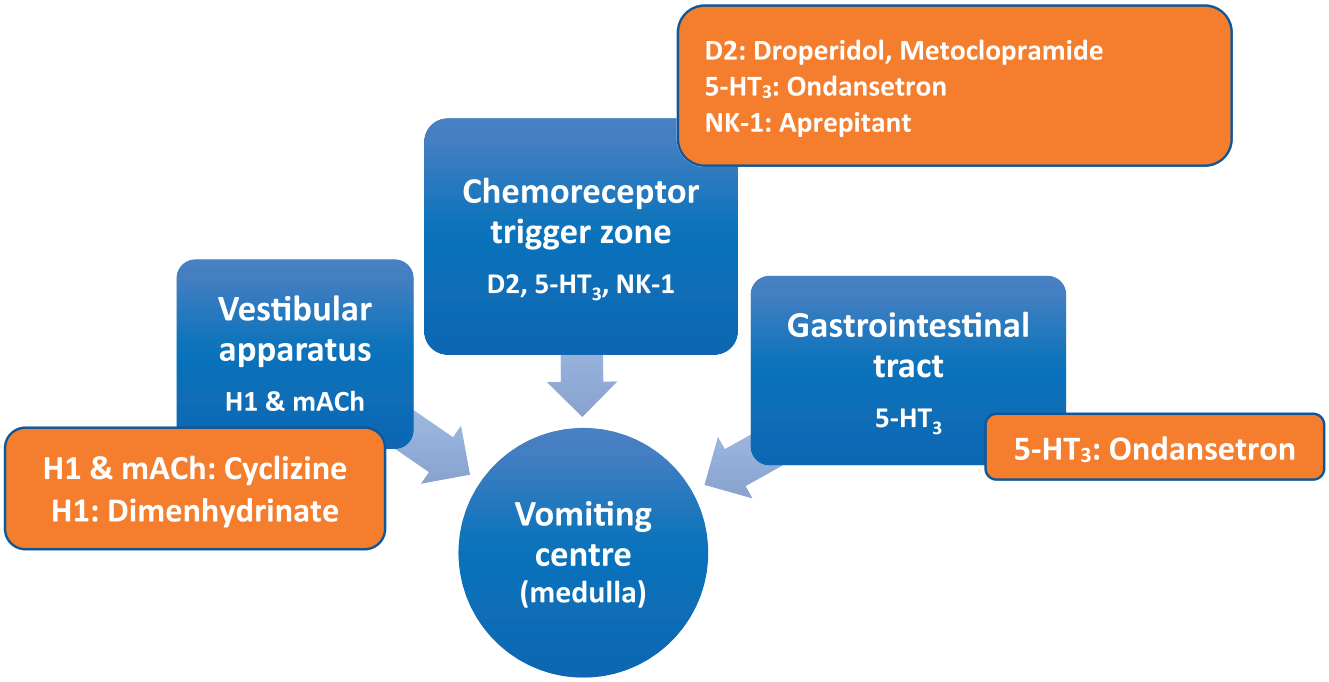

Figure 5. Summary of antiemetic sites of action. 5-HT3, 5-hydroxytryptamine 3 receptor; D2, dopamine 2 receptor; H1, histamine 1 receptor; mACh, muscarinic acetylcholine receptor; NK1, neurokinin type-1 receptor.

Primary 5-HT3 Antagonist: Ondansetron

This class of medications has a large body of evidence supporting its use in preventing paediatric POV,[4] and the use of ondansetron is widespread. Ondansetron has been demonstrated to be effective at reducing POV in children in a dose-related manner, with the oral route (if tolerated) having similar efficacy to the intravenous route, and the timing of the dose (from preinduction to postoperative) having no bearing on effect.[5] It has been shown to be superior to both droperidol and metoclopramide[11] and is therefore recommended as first line for prevention of POV in the United Kingdom and United States.[4,5] Other 5-HT3 agonists such as tropisetron, granisetron, dolasetron, ramosetron and palonosetron have varying levels of evidence and are not all licensed for use in children.

Ondansetron is a carbazole derivative antagonising 5-HT3 receptors (hypothesised to have both central and peripheral effects[1]).

- Dose: 50–150 μg/kg up to 4 mg
- Side effects: headache, constipation, cardiac arrhythmias; it is contraindicated in long QT syndrome[12]

Dopamine Antagonists: Metoclopramide, Prochlorperazine, Droperidol

Due to a lack of evidence to support the use of metoclopramide in preventing paediatric POV, and an increased rate of extrapyramidal side effects in children compared with adults,[13] it is not recommended for this purpose in the United Kingdom.[5] However, in the United States, metoclopramide is considered an option for treatment of POV if other prophylactic agents have failed.[4] Prochlorperazine is not recommended to prevent POV in children as it has not been studied in this context and has a wide side effect profile.[5] The use of droperidol has been limited in practice due to potential extrapyramidal side effects or arrhythmias; however, UK guidelines recommend a low dose as second-line medication for prevention or treatment of POV, as it has been shown to be effective and safe unless contraindicated (eg, in patients with long QT syndrome).[5]

Metoclopramide

Metoclopramide is a benzamide derivative that acts as a dopamine antagonist and also acts directly on the GI tract.

- Dose: 100-150 μg/kg (maximum 10 mg)
- Side effects: extrapyramidal effects (eg, oculogyric crisis or tardive dyskinesia); it can cause neuroleptic malignant syndrome, as well as hypotension or arrhythmias[12]

Droperidol

Droperidol is a butyrophenone that antagonises D2 receptors at the CTZ and peripheral α-receptors.[1,3]

- Dose: 10-25 μg/kg up to 1.25 mg; owing to the potential for side effects, the lower dose of 10 μg/kg tends to be used in clinical practice
- Side effects: sedation, apprehension, hypotension, dose-related extrapyramidal side effects and neuroleptic malignant syndrome[12]

Anticholinergics: Scopolamine

Anticholinergics are selective antagonists at muscarinic receptors and thus have a wide side effect profile including sedation, dry mouth, urinary retention, blurred vision, restlessness and hallucinations. Transdermal scopolamine may have a role in safely ameliorating PONV in adolescents[14]; however, a meta-analysis recommended against its use for younger paediatric patients.[15]

Antihistamines: Cyclizine, Dimenhydrinate

Studies on cyclizine for prevention of paediatric POV are lacking; however, what evidence there is indicates that it is ineffective and therefore not recommended in the United Kingdom.[5] UK guidelines also state that, although there is literature substantiating the use of dimenhydrinate to reduce paediatric POV, this protective effect may not extend to tonsillectomies.[5]

Cyclizine

Cyclizine is a H1 antagonist with combined anticholinergic properties. It is used as an antiemetic in motion sickness, radiotherapy and opioid-induced emesis in adults.

- Dose: 0.5-1 mg/kg up to 50 mg
- Side effects: tachycardia with intravenous injection, pain on injection, extrapyramidal symptoms[12]

Dimenhydrinate

Dimenhydrinate has antiemetic properties attributed to competitive H1 antagonism in the vestibular system

- Dose: 0.5 mg/kg up to 25 mg
- Side effects: antimuscarinic symptoms such as sedation or dry mouth[5]

NK1 Antagonists: Aprepitant, Fosaprepitant

These newer agents are emerging as potentially efficacious. In ongoing pharmaceutical trials, aprepitant appears to be safe and to have similar efficacy to ondansetron in preventing POV in adults.[16] A clinical trial is also underway for paediatric patients.[17] Fosaprepitant is the intravenous prodrug of aprepitant.[18]

Aprepitant acts as a central NK1 receptor antagonist to prevent the binding of substance P to these receptors and the resulting emetic effects.[18]

- Dose: 3 mg/kg up to 125 mg[4]
- Side effects: fatigue, headache, reduced appetite, constipation, dyspepsia, hiccups, flushing[12]

Corticosteroids: Dexamethasone

Multiple studies have shown dexamethasone to reduce paediatric POV compared with placebo, with a low side effect profile.[4,5] Suggested mechanisms of action are reduction of either prostaglandins or 5-HT release.[19]

- Dose: 0.15 mg/kg up to 6.6 mg
- Side effects: administered awake, it can cause perineal warmth. Other adverse effects include hyperglycaemia, mood disturbance and thromboembolism.[12] Dexamethasone may precipitate tumour lysis syndrome in patients with large, high-grade tumours (eg, lymphoma or leukaemia).[5]

Combination Therapies

Used in combination, these agents can have synergistic effects. Evidence shows that ondansetron and dexamethasone used together are more effective at reducing paediatric POV than either agent alone and that ondansetron and droperidol in combination is more effective than ondansetron alone.[5]

NONPHARMACOLOGIC MANAGEMENT

Acustimulation (Including Acupressure and Acupuncture)

Several randomised controlled trials and meta-analyses in children suggest that acupoint stimulation of various modalities at different areas (but in particular the Pericardium 6 [PC6] acupuncture point) is as efficacious at reducing POV as antiemetic drug prophylaxis.[5] The PC6 point lies between the tendons of the palmaris longus and flexor carpi radialis muscles, 4 cm proximal to the wrist crease.

Other Nonpharmacologic Treatment

The uses of ginger, chewing gum and carbohydrate loading need more valid studies to claim importance.

EXAMPLES OF POV PREVENTION AND TREATMENT STRATEGIES

Paediatric POV risk stratification and prophylaxis recommendations from a recent US consensus statement[4] are summarised in Figure 3. For rescue therapy of POV, it is recommended that an alternative agent from a different class be added (eg, droperidol, dimenhydrinate or metoclopramide) or to consider acustimulation.

UK guidelines[5] categorise POV risk slightly differently but suggest similar prophylaxis regimens with doses (see Figure 4). For rescue therapy, ondansetron is recommended if not already given; otherwise, an antiemetic from a different class (eg, dexamethasone or droperidol) is suggested.

SUMMARY

PONV in children is unpleasant for both children and their carers and can lead to serious complications. Therefore, it is important to predict who is at risk and manage them accordingly. This tutorial has explored the physiology of vomiting, highlighted risk factors predisposing to paediatric POV and looked at the evidence base for pharmacologic and nonpharmacologic prophylactic antiemetic therapies. There are various guidelines for how to stratify risk and which specific agents to use, examples of which are presented in this tutorial. The common themes for preventing POV in children at higher risk include a combination of a 5-HT3 antagonist such as ondansetron with dexamethasone due to their synergistic effect, along with consideration of TIVA and/or opiate-sparing techniques. There is a lack of research into paediatric POV specifically, and identifying nausea in younger children can be challenging, adding further complexity to the issue. As more studies are conducted, and newer therapies (such as 5-HT3 antagonists not yet licensed for children or NK1 antagonists) continue to be investigated, the optimal management strategies will also evolve.

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