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Antiemetic agents

G Manjooran

Department of Anaesthesia, School of Clinical Medicine, Faculty of Health Sciences, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: *grace.manjooran@wits.ac.za*

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Introduction

Emesis is defined as the forcible emptying of gastric and/or intestinal contents.[1] Nausea and vomiting have many causes, including drugs (nitrous oxide, chemotherapeutic agents, opioids, etc.), radiation therapy, pregnancy, motion sickness, postoperative, pain, etc.[2] Postoperative nausea and vomiting (PONV) occur immediately in the recovery area or up to 24 hours postoperatively.[2] The incidence varies between 30% and 80%, especially if no prophylaxis is given.[2,3]

PONV ranks high on the list of postoperative patient concerns.[2] It can result in wound dehiscence, aspiration, oesophageal rupture, dehydration, raised intracranial pressure, and pneumothorax due to the high pressures generated while retching.[2] The morbidity surrounding PONV itself is enough for anaesthesia to prevent its occurrence (prevention is better than cure). To adequately prevent and treat nausea and vomiting, it is essential to know the pathophysiology, receptors, and signalling molecules.

Definitions

These definitions are described within the realm of chemotherapy-induced nausea and vomiting (CINV) and are not always relevant to the anaesthetist.

Acute - nausea and vomiting within 24 hours of chemotherapy. PONV can be considered an acute form of nausea and vomiting as it is also defined within 24 hours.[1]

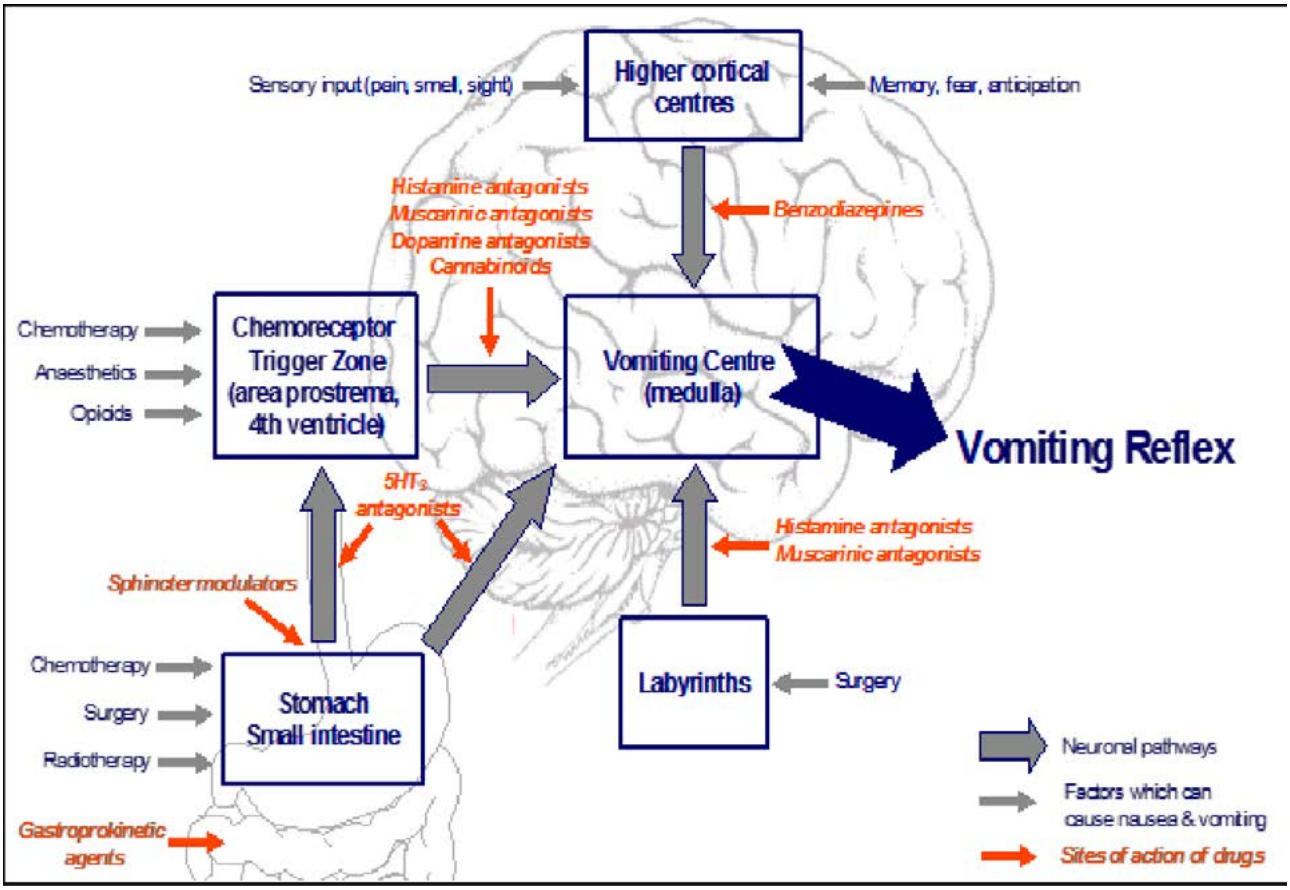

Figure 1: Pathophysiology of emesis[1]

Delayed - nausea and vomiting occurring 24 hours after chemotherapy administration.[1]

Anticipatory - this can be described as a conditioned response and can occur at any point before, during, and after chemotherapy is given. External stimuli can contribute to this type of nausea and vomiting. Anxiety-induced nausea and vomiting can be included in this definition.[1]

Breakthrough - nausea and vomiting that occurs during subsequent cycles of treatment despite prophylactic treatment and requires rescue antiemetics.[1]

Refractory - nausea and vomiting that occurs despite prophylactic and rescue antiemetics being administered.[1]

Postdischarge nausea and vomiting (PDNV) - nausea and vomiting that occurs after discharge for outpatient procedures; it can be acute or delayed in nature.[2]

Pathophysiology

Figure 1 shows the interaction of the various triggers, where they act, as well as the receptors involved in the process. This section should be revised before revising the relevant drugs to improve understanding.

The five receptors directly involved in emesis are muscarinic (M1), histamine (H1), dopamine (D2), serotonin (5-HT3), and neurokinin-1 (NK-1) receptors.[1,2]

Risk factors for PONV

Patient risk factors[2,4,5]

- Preoperative nausea and vomiting
- Female gender
- History of PONV or motion sickness
- Non-smoker
- Age
- CINV

Anaesthesia-related risk factors[2,4,5]

- Anaesthetic technique (general vs. regional)
- Volatile agents versus total intravenous anaesthesia (TIVA)
- Intravenous (IV) anaesthetics
- Nitrous oxide (N_2O) use
- Duration of anaesthesia
- Opioid use
- Neostigmine versus sugammadex for reversal
- Type of surgery: gynaecology, urology, cholecystectomy, laparoscopic procedures, strabismus repair, ear, nose, and throat procedures especially on the inner ear (tympanoplasty and adenotonsillectomy)
- Hydration status

Scoring systems

There are numerous scoring systems, but one of the more commonly used systems is the Apfel Simplified Risk Score for PONV.[5] It is used in adults and only constitutes four factors:[2,5]

1. Female gender
2. Non-smoker
3. History of PONV or motion sickness
4. Expected use of opioids intraoperatively

The presence of 0, 1, 2, 3, and 4 factors correspond to a risk for PONV of 10%, 20%, 40%, 60%, and 80%. Patients are classified into low, medium, or high risk depending on the number of factors present.[5]

Children are more difficult to assess and thus are only assessed for postoperative vomiting (POV).[2] A simplified scoring system by Eberhart et al.[6] is used, which is similar to the Apfel Score:

1. Surgery lasting ≥ 30 minutes
2. Age ≥ 3 years
3. Strabismus surgery
4. History of POV or family history of PONV

A score of 0, 1, 2, 3, and 4 positive factors correspond to a risk of POV of 10%, 10%, 30%, 50%, and 70%.[5,6] Like the Apfel scoring system for adults, risk categories are divided by the number of positive factors.[5]

Non-pharmacological methods to manage PONV[2]

- Acupuncture - P6 point
- Isopropyl alcohol

Pharmacological classification of antiemetics

There are five main classes of drugs, and these are based on the receptors involved in nausea and vomiting and their binding ligands.[2,4,5,7] Table I summarises the various agents that are currently available.

1. M1 receptor antagonists
2. H1 receptor antagonists
3. D2 receptor antagonists
4. 5-HT3 receptor antagonists
5. NK-1 receptor antagonists
6. Adjuvants

M1 receptor antagonists

These agents primarily antagonise the M1 receptors. These drugs are mainly used in the management of nausea and vomiting caused by motion sickness.[1] The most common drug is scopolamine, also known as hyoscine hydrobromide. This drug should not be confused with hyoscine butylbromide (Buscopan), which we commonly see in our theatre drug drawers for IV use. Cyclizine has antagonistic effects on both M1 and H1 receptors and is used for motion sickness. Cinnarizine is indicated for

motion sickness and inner ear diseases causing nausea and vomiting.[1]

H1 receptor antagonists

These drugs are H1 receptor blockers.[1,2] They act centrally and are mainly used as antiemetic agents for motion sickness.[7,8] They are not given routinely as agents for PONV but can be prescribed to offset the extrapyramidal side effect of metoclopramide while complementing its antiemetic effect.[2,9] Examples of drugs within this class are diphenhydramine, dimenhydrinate, and meclizine. Promethazine has antihistamine effects and is sometimes also classified under this group. Common side effects include sedation, dizziness, confusion, dry mouth, and urinary retention.[8,9]

D2 receptor antagonists

Centrally positioned D2 receptors are blocked by this class.[1] There are three divisions of antiemetic drugs within this class, namely phenothiazines, butyrophenones, and benzamides.[4,7]

Prochlorperazine, promethazine, and chlorpromazine fall under phenothiazines and are mainly used for allergies (H1 receptor antagonist), but can be used to treat PONV. Their main side effect is excessive sedation. Less commonly occurring side effects are extrapyramidal effects (dystonia, tardive dyskinesia), hypotension, jaundice, and agranulocytosis. Chlorpromazine is mainly used for motion sickness, after failing to manage symptoms with M1 or H1 receptor blockers.[1,4,7]

Butyrophenones include droperidol, haloperidol, and amisulpride. These drugs potentiate the effects of opioids and tranquillisers.[2] Major side effects are like those for the phenothiazines, but also include a dose dependent interval prolongation on an electrocardiogram (ECG) that can present as QTc prolongation or torsades de pointes.[4,7,8] Droperidol has fallen out of favour due to the QTc prolongation and easy availability of other drugs.

Metoclopramide and domperidone are examples of benzamides. They both have multiple sites of action, both peripherally and centrally. Metoclopramide acts on M1 and 5-HT4 receptors peripherally and on D2 and 5-HT3 receptors centrally.[1,4,8] Domperidone does not cross the blood-brain barrier (BBB), it acts on the chemoreceptor trigger zone (CTZ) by inhibiting D2 receptors and peripherally by inhibiting M1 receptors.[1,7] Side effects are similar to the phenothiazines.[4,8] It is important to note that domperidone cannot cause extrapyramidal effects as it does not cross the BBB.

5-HT3 receptor antagonists

These agents block 5-HT3 receptors both peripherally and centrally. Peripherally, they block 5-HT3 receptors in the gastrointestinal tract (GIT) at vagal nerve terminals. Centrally, they block 5-HT3 receptors within the CTZ.[1] Ondansetron and granisetron are the commonly known agents within this class. Other agents include dolasetron and tropisetron. The most recent additions are the second-generation drugs, palonosetron and ramosetron. Both are long-acting (3–5 days duration of action) and have a higher affinity for the 5-HT3 receptor than first-generation drugs. A single dose of either is sufficient for PONV.[2,7]

Common side effects with this class include headache, dry mouth, fever, malaise/fatigue, and constipation.[7,8] Serotonin syndrome has also been reported as a complication with this class of drugs, but it mainly occurs when used concomitantly with other serotonergic drugs.[7,8,10]

ECG interval prolongation is another serious complication associated with high morbidity.[10] The most well-described example is QTc prolongation associated with ondansetron.[10,11] Other arrhythmias have also been reported; these are usually dose dependent, occurring after IV use and happen more frequently when there is concomitant use of other interval-prolonging drugs.[11]

NK-1 receptor antagonists

This class is unique for having anxiolytic, antidepressant, and antiemetic effects.[12] These drugs cross the BBB and their antiemetic effects are due to substance P regulation via inhibition of NK-1 receptors centrally.[1] Examples include aprepitant, fosaprepitant, rolapitant, and netupitant. This class is best suited for use in delayed onset nausea and vomiting. Common side effects include sleepiness, GIT disturbances, fever, and itching.[2,8,12] More serious side effects include hives/rash and Steven-Johnson syndrome.[7,8,12] Many potential drug interactions can occur with concomitant use, therefore taking a thorough history of medications the patient is currently using is of utmost importance.

Adjuvants

Corticosteroids

Dexamethasone is the most researched drug among the corticosteroids. The mechanism of action is not well understood. Possible mechanisms are:[1,2,4,7,8]

- Changes in the BBB changing permeability to emetogenic substances
- Decreasing brainstem encephalin release
- Inhibiting central prostaglandin synthesis
- Decreasing serotonin synthesis and release
- Depletes gamma-aminobutyric acid (GABA) stores

Only minor side effects have been reported with short-term use, including insomnia and mood changes.[2,4,7,8] Studies have shown that single doses of dexamethasone do not increase surgical site infection rates or result in prolonged raised glucose levels.[2]

Table I: Antiemetic drugs and dosages[2,4,5]

Drug	Dosing
Anticholinergic agents (M1)	
Scopolamine	Transdermal patch applied either the evening before (or at least 4 hours before) surgery or after surgery; 1 patch (1 mg) replaced every 72 hours
Cyclizine (Valoid)	50 mg IV at end of surgery 50 mg p.o. 8 hourly
Histamine receptor antagonists (H1)	
Diphenhydramine (Benadryl)	25–50 mg p.o. 6 hourly 10–50 mg IV 6 hourly (max 400 mg/day) 10–50 mg, up to 100 mg if needed intramuscular (IM) 6 hourly
Dimenhydrinate	1 mg IV at induction 50 mg p.o. 4 hourly
Meclizine	25 mg p.o. 6 hourly
Dopamine receptor antagonists (D2)	
Phenothiazines	
• Prochlorperazine (Stemetil)	5–10 mg IV/IM at end of surgery
• Promethazine (Phenergan)	6.25–12.5 mg IV at induction
Butyrophenones	
• Droperidol (Inapsine)	0.625–1.25 mg IV at induction
• Haloperidol	1 mg IV/IM at end of surgery
• Amisulpride	5 mg IV at induction over 1–2 minutes
Benzamides	
• Metoclopramide (Maxolon)	10 mg IV at induction
• Domperidone	
Serotonin receptor antagonists (5-HT3)	
Ondansetron (Zofran)	4 mg IV at end of surgery 8 mg p.o. 1 hour before induction, then 8 hourly
Granisetron (Kytril)	0.35–3 mg IV at end of surgery, then 12 hourly
Palonosetron (Onicit)	0.075 mg IV as a single dose just before induction
Neurokinin-1 receptor antagonists (NK-1)	
Aprepitant	40 mg p.o. preoperatively; 32 mg IV over 30 seconds preoperatively
Fosaprepitant	150 mg IV preoperatively
Rolapitant	90 mg p.o. preoperatively
Adjuvants	
Corticosteroids	
• Dexamethasone (Decadron)	4–8 mg IV at induction
Cannabinoids	
• Nabilone	1–2 mg p.o. 6–8 hourly
• Dronabinol	5–10 mg p.o. 12 hourly

Cannabinoids

These drugs are currently not indicated for PONV but are included for completeness. The antiemetic effects are via central CB1 and CB2 receptor inhibition.[1] Currently, available drugs are oral nabilone and dronabinol; there are no IV formulations available. They are currently approved for use related to CINV.[1,2,13] Common side effects include vertigo, hypotension, dysphoria, xerostomia, and sedation.[1,13]

Other

Other drugs such as propofol, midazolam, and olanzapine have been used for PONV. Propofol at induction, TIVA maintenance, and sub-hypnotic doses have been shown to have antiemetic effects.[2] Midazolam has been used to prevent anticipatory nausea and vomiting in patients receiving chemotherapy or radiotherapy. Midazolam has no antiemetic effect but causes sedation, which can blunt physiological responses.[2] Olanzapine is a second-generation antipsychotic agent with antiemetic properties via D2 and 5-HT2 receptors. It has highly sedating properties and should be used with caution.[2]

ORCID

G Manjooran https://orcid.org/0000-0002-9838-4676

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