Physiology and pharmacology of nausea and vomiting

Barbara J Pleuvry

Abstract

The physiology of nausea and vomiting is poorly understood. The initiation of vomiting varies and may be due to motion, pregnancy, chemotherapy, gastric irritation or postoperative causes. Once initiated, vomiting occurs in two stages, retching and expulsion. The muscles responsible for this sequence of events are controlled by either a vomiting centre or a central pattern generator, probably in the area postrema and the nearby nucleus tractus solitarius. Drugs which induce vomiting include ipecacuanha, a gastric irritant, and apomorphine, a dopamine-receptor agonist. Opioid drugs also induce vomiting, but opioid antagonists are not useful to treat nausea and vomiting. Anti-emetic drugs consist of a variety of neurotransmitter antagonists and may act in the periphery, the central nervous system or both sites. The most important drugs are antagonists at muscarinic, dopamine D_2, 5-HT_3, histamine H_1 and neurokinin NK_1 receptors. These drugs are discussed with particular attention to post-operative nausea and vomiting (PONV).

Keywords Anti-emetic drugs; emetic drugs; nausea and vomiting; post-operative nausea and vomiting (PONV)

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article you should be able to:

- list five pharmacological groups of anti-emetic drugs
- understand the mechanisms by which nausea and vomiting occur
- discuss the usefulness of various anti-emetic drugs in post-operative nausea and vomiting

Nausea

Nausea, a feeling of impending vomiting, can be studied only in humans and, since there are few volunteers who wish to experience this sensation, the mechanisms behind it have been little researched and so are obscure. However, the excessive salivation and swallowing associated with nausea indicate the involvement of the autonomic nervous system.

Vomiting

Vomiting consists of two phases, retching and expulsion. Expulsion does not occur without retching.

- During retching, the abdominal muscles and the diaphragm simultaneously contract and relax.
- Expulsion is characterized by a sustained contraction of the abdominal muscles, which is coordinated with the intercostal muscles and the muscles of the pharynx and larynx that close the glottis and elevate the soft palate. The external anal and urethral sphincter muscles are contracted, there is a retrograde contraction of the intestinal muscles, and the gastric fundus relaxes.

Other autonomic events include pallor, salivation, hypotension and sweating. The output neurons that govern these changes are scattered throughout the medulla oblongata and must be activated in the appropriate sequence. There is some controversy as to whether this sequence is controlled by a localized integrative site that generates vomiting (a vomiting centre), or whether a central pattern generator is involved, as has been described for locomotion and ventilation.

Causes of vomiting

Some of the factors that initiate vomiting are shown in Figure 1. The vomiting reflex protects the body from ingested toxins in food that have not been detected by sight, taste or smell. Irritation or distension of the upper gastrointestinal tract may also induce nausea and vomiting; distension of the duodenum is a particularly strong stimulus. Thus, vagal (and, to a lesser extent, sympathetic) afferent impulses travelling from the gastrointestinal tract to the hindbrain medulla can induce vomiting. Mechanoreceptors (which detect distension) or mucosal chemoreceptors (which detect acids, alkalis, irritants and probably bacterial toxins) initiate these afferent impulses, which stimulate neurons in the area postrema and the nearby nucleus tractus solitarius. Some authors site the vomiting centre in the nucleus tractus solitarius, but this is controversial. There is no anatomically distinct vomiting centre in this brain region.

Induction of vomiting, for example, with cytotoxic drugs, is associated with mucosal damage and the liberation of 5-hydroxytryptamine (5-HT) from the enterochromaffin cells. The released 5-HT probably stimulates the vagal afferent nerves by interaction with a 5-HT_3 receptor. Substance P, released from the gastric mucosa, acts on tachykinin NK_1 receptors and may function cooperatively with 5-HT (acting on 5-HT_3 receptors) in the upper gastrointestinal tract to induce vomiting. Agonists at NK_1 receptors also induce vomiting via a central mechanism.

Vomiting can also be induced by chemicals carried in the blood that are detected by the chemosensitive trigger zone (CTZ) in the area postrema on the caudal floor of the fourth ventricle (Figure 1). From a pharmacological point of view it is interesting and exploitable that the CTZ is functionally outside the blood–brain barrier. Animal studies have shown that the area postrema contains high concentrations of 5-HT_3, dopamine (D_2) and opioid receptors. In humans, drugs acting as agonists at these receptors cause nausea and vomiting. While antagonists at 5-HT_3 and D_2

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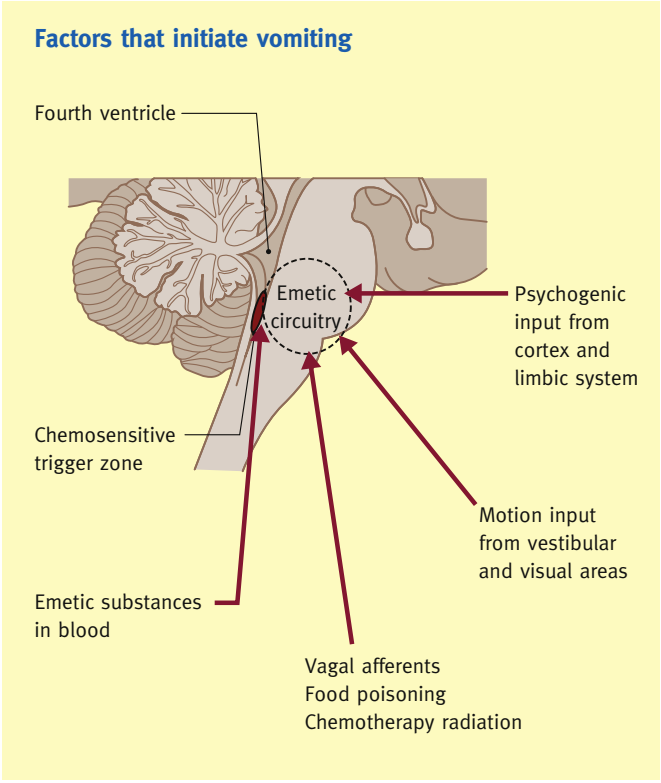

Figure 1

receptors are effective anti-emetic agents, opioid antagonists are not.

Motion sickness involves the vestibular system and is generally attributed to an abnormal balance between its inputs (angular accelerations and position with respect to a gravitational field) and that from the eyes. Such imbalances can be produced by the swell of the ocean, in zero gravity, reading in a moving car or train, or during rides in the fairground, for example. Labyrinthine stimulation enhances the emetic effects of many other vomiting triggers. Muscarinic cholinergic and histamine H_1-receptors are present in the vestibular nuclei. Both the vestibular system and the CTZ send impulses to the vomiting centre or central pattern generator, which initiate the sequence of smooth and skeletal muscle contraction associated with vomiting. Vomiting can also occur due to inputs from higher centres such as the limbic system, though the mechanisms behind this are uncertain. Table 1 describes the receptors involved in emesis and useful anti-emetic drugs.

Emetic drugs

Ingestion of a toxic substance can be treated by the use of drug-induced vomiting, provided that the patient is fully conscious and the ingested poison is not corrosive, a petroleum distillate, or a CNS stimulant. In the case of a CNS stimulant, the addition of an emetic drug may precipitate convulsions. Vomiting corrosive poisons can cause greater damage to the oesophagus and stomach, and petroleum distillates may be aspirated into the lung. Patients who are not fully conscious may have a reduced gag reflex and aspirate fluid into the lung.

Ipecacuanha is the emetic generally used. It is prepared from the root and rhizome of a South American plant. It has an irritant effect in the stomach due to the presence of two alkaloids (emetine and cephaeline). In lower doses, ipecacuanha has been used as an expectorant in the treatment of bronchitis and whooping cough. Emetine is used to treat amoebic dysentery. After oral administration, ipecacuanha takes 10–15 minutes to produce vomiting.

Vomiting can be induced more quickly (3–5 minutes) by a subcutaneous injection of apomorphine, a dopamine D_2-receptor agonist, which stimulates the CTZ. However, it also causes respiratory depression and a solution of the drug must be freshly prepared before administration, which limits its usefulness.

Anti-emetic drugs

Many drugs are used to treat nausea and vomiting, but this article concentrates on those used in anaesthesia for the treatment of postoperative nausea and vomiting (PONV).

The mechanism by which PONV occurs is unclear and probably multifactorial. It is more common in children than in adults and, after puberty, women are more susceptible to PONV than men, particularly if they are menstruating or pregnant. Stimulation of the CTZ by oestrogen during pregnancy is thought to be the cause of morning sickness. There is no animal model for PONV, therefore drug treatment has been restricted to trials of agents that are effective anti-emetics in other situations. A rational design of drugs based on an understanding of the condition has not been undertaken. Most studies have concentrated on the first 24 hours after surgery, but some patients experience late or post-discharge emetic symptoms which have been less well studied.[1,2]

Dopamine-receptor antagonists

Dopamine is involved in the production of emesis at the CTZ, and dopamine antagonists are effective anti-emetics. Most dopamine antagonists have no selectivity for the dopamine receptors in the CTZ and, by acting on dopaminergic systems in other part of the brain, they produce hyperprolactinaemia and extrapyramidal motor disturbances similar to Parkinson's disease.

Domperidone is less likely to cross the blood–brain barrier than other agents, and thus is less prone to, but not free from, extrapyramidal actions. However, there is debate about its effectiveness in PONV. There are also reports of severe cardiac arrhythmias after large doses, which resulted in the withdrawal of the parenteral preparation. These factors have caused a loss of interest in domperidone from an anaesthetic point of view. Until recently, despite its adverse effects, droperidol was the standard anti-emetic. However, following alerts of a prolonged QT-interval with chronic oral administration, the manufacturers decided to stop producing the parenteral product.

Metoclopramide and domperidone have additional prokinetic activity (enhanced gastric and upper intestinal motility), which may contribute to their anti-emetic effects. The prokinetic action has been attributed to an agonist action of metoclopramide on 5-HT_4 receptors. Metoclopramide also has some 5-HT_3 antagonistic effects at higher doses. The dopamine antagonists that are still available as anti-emetics are shown in Table 2.

Muscarinic cholinoceptor antagonists

In the treatment of PONV, the muscarinic receptors present in the hindbrain medulla are important targets. The two muscarinic

Neurotransmitters involved in nausea and vomiting

Vomiting trigger	Neurotransmitter	Receptors involved	Anti-emetic drugs
Irritation and/or distension of the gastrointestinal tract	5-HT	5-HT_3	Ondansetron, granisetron, palonosetron
	Substance P	NK1	Aprepitant
Toxins and chemicals acting on the chemosensitive trigger zone	Dopamine	D_2	Domperidone, prochlorperazine, perphenazine, metoclopramide
	5-HT	5-HT_3	Ondansetron, granisetron, palonosetron
Motion on vestibular nuclei	Acetylcholine	Muscarinic	Hyoscine, atropine
	Histamine	H_1	Cyclizine, promethazine
Input directly to vomiting centre	Acetylcholine	Muscarinic	Hyoscine, atropine
	Histamine	H_1	Cyclizine, promethazine
	Substance P	NK_1	Aprepitant

5-HT, 5-hydroxytryptamine; D, dopamine; H, histamine.

Table 1

antagonists used as anti-emetics in anaesthesia are hyoscine and atropine. Both are lipid soluble and penetrate the brain to reach the vomiting centre. Intramuscular administration of hyoscine is generally more effective as an anti-emetic than intramuscular atropine but was associated with increased drowsiness and delayed recovery from anaesthesia. To increase its duration of action, hyoscine has also been used as a transdermal preparation. The patch needs to be applied several hours before the emetic stimulus to enable an adequate plasma concentration to be obtained. Several authors have demonstrated the efficacy of transdermal hyoscine in PONV, but others have failed to detect a significant difference from placebo. Negative results were more likely when the duration of patch application before the stimulus was short or additional premedication drug administration was uncontrolled.

Muscarinic receptors are found in the periphery, associated with the effector organs of the parasympathetic nervous system. Thus, typical antimuscarinic adverse effects such as dry mouth and blurred vision are common, though not usually serious.

Histamine H_1-receptor antagonists

Both histamine H_1 and muscarinic receptors are present in the vomiting centre and the vestibular nucleus. The antihistamine drugs that are used to treat nausea and vomiting also have antimuscarinic activity; therefore it is unclear which property is more important for their anti-emetic action. Cyclizine has been used extensively to treat PONV and most reports demonstrate efficacy with few side effects such as sedation. Promethazine is a markedly sedative drug and has been used by anaesthetists to premedicate children, but whether its efficacy is due to its sedative or anti-emetic effect is debatable. Oral dimenhydrinate given at least 1 hour before surgery has also been used to prevent PONV. Second-generation antihistamines (e.g. terfenadine, astemizole) are not effective anti-emetics because they do not cross the blood–brain barrier.

5-HT_3-receptor antagonists

5-HT is released by cytotoxic agents and contributes to nausea and vomiting by actions in the gastrointestinal tract and the brain. In addition, dopamine antagonists may be ineffective in severe chemotherapy-induced emesis. These observations prompted the successful trial of 5-HT_3 antagonists (e.g. ondansetron) in chemotherapy-induced emesis. Subsequently, oral ondansetron was found to be effective in PONV, a finding that has been confirmed, using both the oral and intravenous routes, in many postoperative situations. Generally, the adverse effects of ondansetron were mild and no signs of the extrapyramidal symptoms or dry mouth seen with alternative anti-emetics were reported.

Granisetron and palonosetron[3] are also effective in PONV. Other 5-HT_3 antagonists, such as dolasetron and tropisetron, have been used in only a few trials of PONV, in which they were

Dopamine antagonists used to treat postoperative nausea and vomiting

Drug	Route	Elimination half-time (hours)	Side effects	Comments
Perphenazine	IV	9.4	Extrapyramidal disorders	Not recommended for children Delayed recovery
Prochlorperazine	IV, IM	6.8	Extrapyramidal disorders Delayed recovery	Fewer adverse effects than perphenazine?
Metoclopramide	Oral, IV, IM	4.0	Extrapyramidal disorders Restlessness	Poor brain penetration so fewer adverse effects than others except domperidone
Domperidone	Oral, rectal	4.0–5.0	Cardiac arrhythmias	Few trials demonstrate efficacy compared with placebo

IM, intramuscular; IV, intravenous.

Table 2

Comparisons between intravenous ondansetron and other anti-emetics

Comparator (IV)	Surgery	Result
Metoclopramide	Laparoscopic cholecystectomy	Ondansetron superior to metoclopramide in females (males showed little PONV)
Dimenhydrinate	Adenotonsillectomy	Ondansetron superior (42% of children given it vomited compared with 79% of those given dimenhydrinate)
Droperidol	Laparoscopy	Both drugs equally effective in preventing nausea; ondansetron slightly superior in preventing vomiting
Droperidol Metoclopramide	Strabismus surgery	Ondansetron and droperidol equally effective and better than metoclopramide in decreasing pre-discharge vomiting, but none is effective in decreasing vomiting after patients are discharged

IV, intravenous; PONV, postoperative nausea and vomiting.

Table 3

significantly better than placebo. Tropisetron metabolism involves the cytochrome P-450IID6 enzyme system, which may be absent in a minority of patients, resulting in poor metabolism of the drug in those individuals.

Comparative studies between individual 5-HT_3 antagonists in PONV have not been carried out, but there are some reports of comparisons with other anti-emetics. Some examples involving intravenous ondansetron are summarized in Table 3. Most clinical trials involving ondansetron used single doses and the equivalence of the dose of comparator (i.e. the standard drug with which ondansetron is compared) may be questioned. In general, the 5-HT_3 antagonists appear to be more effective and to exhibit fewer adverse effects than alternative anti-emetics used for PONV. However, the cost of treating all patients at risk of PONV with these relatively new agents must be considered.

Other anti-emetics

Although the glucocorticosteroids and the cannabinoid nabilone have been used as anti-emetics for cancer chemotherapy, they have not been used extensively in anaesthesia. The intravenous anaesthetic propofol has also been used to treat PONV, although sedation could be a problem if the dose was too high. Moderate doses were effective and, when compared with placebo, shortened the stay in the post-anaesthetic care unit.

Experimental studies have suggested the NK_1-receptor antagonists might have a wider anti-emetic spectrum of activity than 5-HT_3 antagonists, and there have been reports of trials of these compounds such as aprepitant in PONV. Aprepitant was as effective as ondansetron up to 24 hours after surgery and more effective 24–48 hours after surgery.[4] Others such as casopitant have completed some phase III trials but FDA (Food and Drug Administration) approval has been delayed.

Other uses of anti-emetic drugs

Travel sickness: the histamine H_1-receptor antagonists and the muscarinic antagonists for acetylcholine are most commonly used for travel sickness. Dopamine antagonists are not useful for motion sickness unless they have coincident muscarinic cholinoceptor antagonist properties.

Nausea and vomiting in early pregnancy: nausea affects about 75% of women and 50% experience vomiting. Since these symptoms occur in early pregnancy when the developing foetus is at its most vulnerable to teratogenic drugs, a careful balance must be made between the risk to the mother and baby of constant vomiting and the risk from the drugs. According to a Cochrane review, the drugs most commonly used to treat nausea are antihistamines, the combination drug *Debendox* (despite the fact that it has been withdrawn for the last 20 years), vitamin B_6 (pyridoxine) and P6 acupressure. Pyridoxine is more effective than other newer drugs in reducing the severity of nausea, and the effects of acupressure are equivocal. There is no evidence that any treatment is effective in hyperemesis gravidarum (excessive nausea during pregnancy). Although fetal outcome was not routinely followed up in the trials, there was no evidence of teratogenicity, despite that fact that *Debendox* had been withdrawn because of threatened litigation with respect to this side effect.

Cytotoxic drug-induced emesis: neither muscarinic antagonist nor antihistaminic drugs are useful in treating emesis caused by chemotherapy. The 5-HT_3 antagonists were originally developed to treat this type of nausea and vomiting and it was an additional bonus that they were also useful in PONV. Dexamethasone, either alone or in combination, is useful for chemotherapy-induced nausea and vomiting. Oral aprepitant, in combination with other anti-emetics, is indicated for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. A water-soluble aprepitant pro-drug, fosaprepitant, is undergoing trials for patients who cannot tolerate an oral preparation.[5] ◆

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