Update in
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Antiemetic drugs: pharmacology and an overview of their clinical use

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Summary
This article describes the pharmacology underlying our commonly used antiemetics. The physiology of nausea and vomiting is outlined with practical advice on use of antiemetic drugs to prevent and treat postoperative nausea and vomiting.

INTRODUCTION

Nausea and vomiting are feared and frequently very distressing symptoms that have multiple triggers including drugs, motion, pregnancy, fear, vestibular disease, migraine and gastrointestinal pathology. Postoperative nausea and vomiting (PONV) is one of the most common causes of patient dissatisfaction after anaesthesia. Untreated, PONV occurs in approximately 30% of the general surgical population and up to 70–80% of high-risk surgical patients. The adverse effects of PONV include distress, increased pain, wound dehiscence and bleeding, as well as risk of aspiration of gastric contents. If protracted, PONV may lead to electrolyte imbalance and dehydration. Such adverse consequences prolong recovery and have the potential to delay discharge from hospital, leading to increased health care costs.

PHYSIOLOGY OF THE VOMITING CENTRE

The vomiting centre coordinates vomiting and is composed of a collection of effector neurones in the medulla. This collection projects to the vagus and phrenic nerves and also to the spinal motor neurones supplying the abdominal muscles, which together bring about the vomiting reflex.

The vomiting centre receives afferent impulses from the chemoreceptor trigger zone (CTZ), vestibular apparatus, cardiovascular and abdominal afferents (via the vagus nerve), peripheral pain pathways and the limbic cortex (Figure 1). The CTZ is situated in the area postrema, on the lateral walls of the fourth ventricle, outside the blood–brain barrier (BBB). It is rich in dopamine (D_2) and serotonin (5-hydroxytryptamine, 5-HT_3) receptors. Drugs (e.g. opioids) and neurotransmitters (e.g. dopamine, noradrenaline, acetylcholine, 5-HT) can stimulate the CTZ. Motion sickness is primarily a central nervous system response mediated by the vestibular apparatus. Acetylcholine and histamine receptors are found in the vestibular centre. Acetylcholine is important in neural transmission from the vestibular apparatus. The limbic system is associated with expression of mood, emotions and feelings, as well as memory recall. Anxiety, fear and other emotions may play a role at this site in the perception of nausea and vomiting.

ANTIEMETIC AGENTS

The treatment of nausea and vomiting aims to antagonise the afferent supply to the vomiting centre. Antiemetic drugs can be classified according to the receptor at which they act:

- dopamine antagonists
- anticholinergics
- antihistamines
- serotonin antagonists
- miscellaneous.

DOPAMINE ANTAGONISTS

The CTZ is rich in dopamine receptors; hence most drugs that antagonise D_2 receptors have antiemetic properties. The dopamine antagonists used clinically as antiemetics can be divided into three groups: phenothiazines, butyrophenones and benzamides.

Phenothiazines

Phenothiazines are most commonly used as antipsychotic drugs and have a limited role in the treatment of PONV.

Chlorpromazine

Chlorpromazine is available as a tablet, syrup or straw-coloured solution for injection. It is used to prevent and treat nausea and vomiting in palliative care patients in whom other agents have been unsuccessful. It is also used in schizophrenia for its sedative properties and for the treatment of intractable hiccough. Chlorpromazine antagonises D_2, muscarinic, noradrenergic (α_1 and α_2), histaminergic (H_1) and 5-HT_3 receptors. Blockade of D_2 receptors results in an increased threshold for vomiting at the CTZ. Central nervous system effects include sedation, extrapyramidal effects and, rarely, neuroleptic malignant syndrome. Cardiovascular effects include negative

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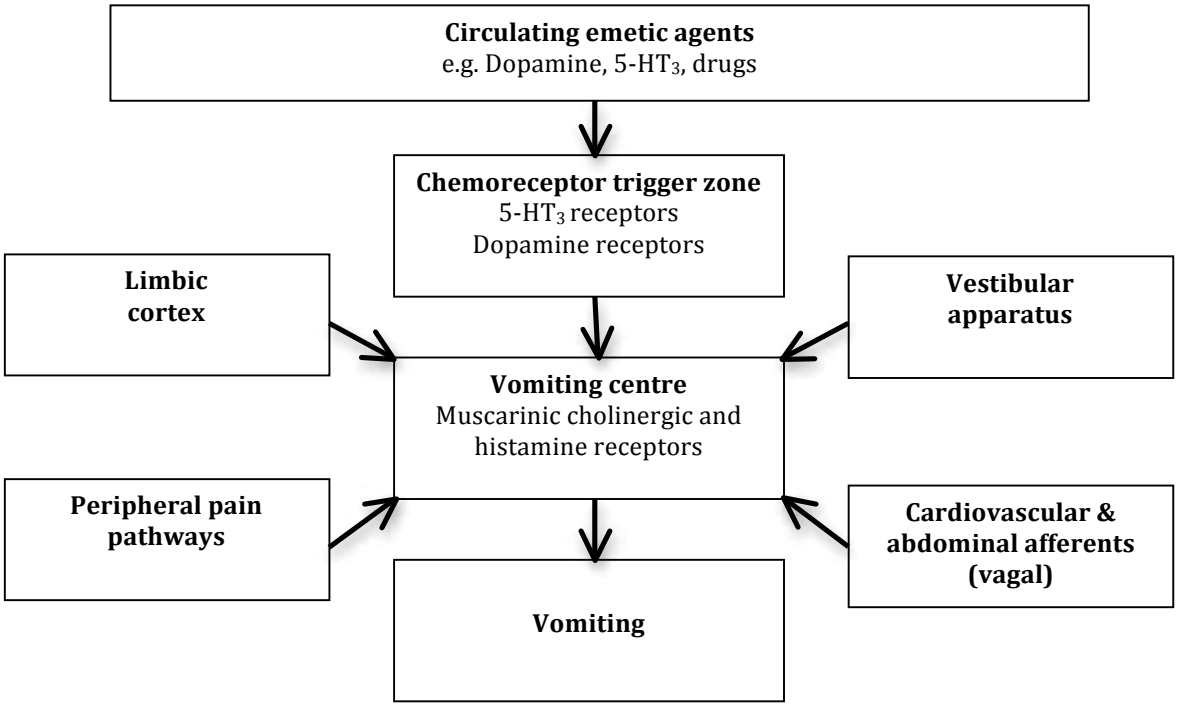

Figure 1. *Pathways involved in the vomiting reflex*

inotropy, peripheral vasodilatation, hypotension and increased heat loss. Gastrointestinal effects include increased appetite, decreased salivation and gastric secretions. Other recognised side-effects are anticholinergic effects, cholestatic jaundice, agranulocytosis and haemolytic anaemia. Chlorpromazine is usually given parenterally to avoid extensive first-pass metabolism; it is excreted in the urine and bile.

Prochlorperazine

Prochlorperazine is available as tablets, syrup, suppositories and a clear, colourless solution for injection. It is mainly used as an antipsychotic and for the treatment of PONV and vertigo. It antagonises central D_2 receptors; high doses have an inhibitory effect at the vomiting centre. It has a similar side-effect profile to chlorpromazine; however, extrapyramidal reactions are more commonly seen, especially in children. In contrast to chlorpromazine, it has milder sedative and anticholinergic effects. Oral bioavailability is low due to extensive first-pass metabolism. It is active within 10–20 minutes of intramuscular (IM) administration and its effects last 3–4 hours.

Butyrophenones

Droperidol

Droperidol is available as tablets, syrup and as a clear solution for injection. It is the only butyrophenone used in anaesthesia; however, its use has declined because it has been associated with cases of QT interval prolongation. It was previously commonly used in the prevention and treatment of PONV, for neuroleptanaesthesia and in the control of mania. Droperidol antagonises central dopamine receptors at the CTZ and its side-effect profile is similar to that of the phenothiazines. Sedation is more pronounced and the incidence of extrapyramidal effects increases at higher doses. It can cause a distressing 'locked-in syndrome'. Cardiovascular effects include hypotension resulting from peripheral α-adrenergic blockade. It has good absorption following IM administration and is 90% protein bound in the plasma. Droperidol is metabolised by the liver and excreted in the urine.

Domperidone

Domperidone is available as tablets, suspension and suppositories. The intravenous (IV) preparation was withdrawn following association with serious arrhythmias. It antagonises peripheral dopaminergic receptors, resulting in increased gastrointestinal motility and tone. It is used for the symptomatic treatment of nausea and vomiting, particularly following chemo- and radiotherapy. It does not cross the BBB; thus, it is less likely to cause sedation and extrapyramidal effects. It can increase prolactin levels and may cause galactorrhoea and gynaecomastia.

Benzamides

Metoclopramide

Metoclopramide is available as tablets, slow-release capsules, syrup and a clear, colourless solution for injection. It acts primarily by antagonising dopamine receptors at the CTZ, but is also a weak antagonist at 5-HT_3 receptors. It also acts a prokinetic, increasing gastric emptying and oesophageal sphincter tone. In addition, metoclopromide also has an antagonistic action on serotonin receptors and this may contribute to some of its antiemetic properties. It is used for the symptomatic treatment of nausea and vomiting, digestive disorders, migraine and postoperative gastric hypotonia. It appears to be most effective for PONV if 20 mg is given at the end of anaesthesia

rather than at induction. Metoclopramide crosses the BBB and can precipitate extrapyramidal effects up to 72 hours after administration. Such effects are more common in young females. Sedation is noted more often with long-term administration. Cardiovascular effects include hypotension, tachycardia and bradycardia following rapid IV administration. Metoclopramide is rapidly absorbed orally, is conjugated in the liver and excreted in the urine.

ANTICHOLINERGICS

Anticholinergics are effective antagonists at the muscarinic receptors; they have minimal activity at the nicotinic acetylcholine (Ach) receptors, found in autonomic ganglia and the neuromuscular junction. Naturally occurring tertiary amines such as atropine and hyoscine are able to cross the BBB; their central effects include sedation, amnesia, antiemesis and the central anticholinergic syndrome. Atropine is not used to treat PONV because of its cardiovascular effects. Glycopyrrolate is a synthetic quaternary amine that is unable to cross the BBB and therefore has no centrally mediated effects.

Hyoscine

Hyoscine is an ester of tropic acid and scopine. It is a racemic mixture in which only L-hyoscine is active. Hyoscine butylbromide is presented as a clear solution for IV, IM and subcutaneous (SC) injection. It can also be administered orally and via transdermal patch. It competitively antagonises ACh at muscarinic receptors. It is used in the prophylaxis of motion sickness and, when administered together with an IM opioid, has been shown to reduce PONV. In addition, hyoscine decreases muscle tone (anti-spasmodic) and gut secretions, which may contribute to its antiemetic effect. Other effects include sedation, initial tachycardia followed by bradycardia, decreased bronchial secretions, mild bronchodilatation and respiratory stimulation. At toxic levels it can cause central anticholinergic syndrome, characterised by excitement, ataxia, hallucinations and behavioural abnormalities. It can precipitate porphyria in susceptible patients. Absorption of hyoscine following oral administration is poor; it is absorbed well following SC and IM administration and is most effective in reducing PONV by such routes. It undergoes extensive metabolism by liver esterases and 2% is excreted unchanged in the urine and 5% in the bile.

ANTIHISTAMINES

Cyclizine

Cyclizine is a piperazine derivative, and is available as tablets or as a clear, colourless solution for IV or IM injection. It is used as to treat motion sickness, radiotherapy-induced emesis, PONV and opioid-induced emesis and for symptom control in Ménière's disease. It is a histamine (H_1) antagonist but also has anticholinergic properties that contribute to its antiemetic properties. Side effects include tachycardia, drowsiness, blurred vision and pain on injection.

SEROTONIN (5-HT_3) ANTAGONISTS

Ondansetron

Ondansetron is a synthetic carbazole, and is availabe as tablets, a suppository or a clear solution for slow IV injection. It is widely used in the management of nausea and vomiting induced by chemo- or radiotherapy as well as in the perioperative period. It is ineffective for vomiting induced by motion sickness or dopamine agonists. The activation of 5-HT_3 peripherally and centrally appears to induce vomiting. Chemo- and radiotherapy may cause the release of 5-HT from enterochromaffin cells. Peripheral 5-HT_3 receptors in the gut are then activated and stimulate vagal afferent neurones that connect to the vomiting centre via 5-HT_3 receptors. Ondansetron is a highly selective antagonist at 5-HT_3 receptors both centrally and peripherally. Side-effects include headache, constipation, flushing and bradycardia and in higher doses it may cause QT interval prolongation. It undergoes significant hepatic metabolism and the dose should be reduced in patients with hepatic impairment.

Granisetron

Granisetron is available in tablet form and as a solution for slow IV injection. Granisetron is a serotonin antagonist that is similar to ondansetron and is licensed for use in PONV.

MISCELLANEOUS

Dexamethasone

Dexamethasone has been shown to be useful in the treatment of PONV and for nausea and vomiting related to chemotherapy. Its mode of action is unclear but may be due to a reduction in the release of arachidonic acid, reduced turnover of 5-HT or decreased permeability of the BBB. Caution should be exercised in diabetic patients owing to its negative effects on glycaemic control.

Acupuncture

A Cochrane review has shown acupuncture to be effective in the prevention of PONV.[1] The acupuncture site is Pericardium 6: 4 cm proximal to the distal wrist skin crease, between the flexor carpi radialis and palmaris longus tendons. Acupuncture should be performed on awake patients and is free from side-effects.

Cannabinoids

Nabilone is a synthetic cannabinoid with antiemetic properties. Its acts on the CB_1 and CB_2 cannabinoid receptors and is used to treat chemotherapy-induced nausea and vomiting. Side-effects include drowsiness, dizziness, dry mouth, psychotic reactions, hypotension and tachycardia.

Propofol

Total IV anaesthesia using a propofol infusion avoids exposure to volatile anaesthetic agents and dramatically reduces the incidence of PONV. Propofol appears to exhibit inherent antiemetic activity and

when administered in subhypnotic doses to postoperative patients and patients undergoing chemotherapy it results in a significant reduction in nausea and vomiting. The mechanism for this effect has not been fully elucidated.

CLINICAL MANAGEMENT OF PONV

Risk factors for PONV

Administering antiemetic drugs to all patients regardless of risk would expose many patients to unwanted side effects and is not a cost effective strategy. To reduce the incidence of PONV, prophylactic antiemetic regimens should be tailored to groups of patients where risk factors are present (Table 1).

Data from large studies investigating risk factors for PONV have been used to create risk scores that attempt to predict the likelihood of a patient developing PONV. The most commonly used is the Apfel simplified score (Table 2).[2]

Efficacy

When comparing different antiemetics and the evidence for and against their use, it is helpful to determine the number needed to treat (NNT), or the number of patients who must be exposed to a particular intervention in order for one patient to benefit over receiving placebo or no treatment (Table 3). Studies have shown that high-risk patients are best managed with a combination of agents rather than just agent in isolation.

Table 1. *Risk factors for postoperative nausea and vomiting*

	Odds ratio	Effects
Patient factors		
Female gender	3	
Non-smoker	2	
History of motion sickness or PONV	2	
Young age		Increased incidence in younger patients
Anaesthetic factors		
Intra- and postoperative opioid use		Dose dependent. Delays gastric emptying, causes bowel distension and triggers vomiting reflex
Volatile anaesthetics	2	Dose dependent
Nitrous oxide	1.4	Small increase in risk although not proven in children
Prolonged anaesthesia		Prolonged exposure to emetogenic stimuli
Surgical factors		
Gynaecological surgery		Less reliable data on impact of type of surgery on PONV risk
ENT surgery		
Squint surgery		
Thyroid surgery		
Laparoscopic procedures		
Severe pain		

Table 2. *Apfel simplified score*

Risk factor	Female gender
	Non-smoker
	Prior history of PONV or motion sickness
	Postoperative opioid use
Incidence based on number of risk factors	0 – 10%
	1 – 21%
	2 – 39%
	3 – 61%
	4 – 78%

Table 3. *Number needed to treat for common prophylactic antiemetics*

Antiemetic agent	NNT for prevention of PONV (0–24 hours)
Droperidol	5
Metoclopramide	
10 mg	30
25 mg	16
50 mg	1
Ondansetron	6–7
Dexamethasone	4
Propofol (total IV anaesthesia)	5

Figures taken from Gan and Diemunsch et al.[3] See paper for full references

Clinical strategies

The use of antiemetic drugs for prophylaxis should be guided first by the presence of risk factors and second by consideration of potential morbidity arising from PONV.

The presence of two or more of the risk factors described above correlates with a high risk of PONV, and this group of patients are likely to benefit from prophylactic use of antiemetic drugs. The physical implications of retching and vomiting may result in additional morbidity following procedures on the upper gastrointestinal tract such as hiatus hernia repair, and for this population prophylaxis continuing into the early postoperative period is advised.

The choice of which antiemetic agents to administer depends largely on the potential side-effects, drug availability and personal preference. Low-risk patients usually do not require prophylactic antiemetics and should be prescribed rescue therapy if necessary. High-risk patients will benefit from a multimodal approach combining avoidance of any modifiable risk factors (including consideration of total IV anaesthesia strategy) as well as combination antiemetic drug therapy.

First-line agents typically include dexamethasone and ondansetron ,which can be given together intraoperatively with additional antiemetics prescribed 'as required' for the postoperative period.

SUMMARY

The complex physiology of vomiting means that there are multiple pathways that can be targeted when attempting to prevent and treat PONV. The choice of antiemetic drug should be tailored to the individual patient's needs and an awareness of the pharmacological actions when choosing an antiemetic is essential to improve effectiveness and reduce undesirable side-effects.

Use of a risk scoring system allows for quantification of the risk of PONV, and many advocate prophylactic antiemetic use when there are two or more risk factors present. Administering prophylactic antiemetics to low-risk patients is of questionable value because the NNT approaches the number needed to harm (NNH) in many cases. Rescue strategies for those with established nausea and vomiting should include the use of an antiemetic from a different class to those already administered.

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