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ARTICLE

Antiemetic drugs: what to prescribe and when

SUMMARY

Nausea and vomiting are common symptoms with many possible causes, including the adverse effects of drugs. If a drug is indicated, the cause guides the choice of antiemetic drug.

The main antiemetic classes include antagonists of the serotonin, dopamine, histamine, muscarinic and neurokinin systems, corticosteroids and benzodiazepines. Some antiemetics appear more effective for specific indications.

Serotonin and neurokinin antagonists, such as ondansetron and aprepitant, are highly effective in treating chemotherapy-induced nausea and vomiting. Metoclopramide and antihistamines are first-line options for nausea and vomiting in pregnancy.

Serotonin antagonists and some dopamine antagonists, such as metoclopramide, can prolong the QT interval on the ECG. Dopamine antagonists can cause extrapyramidal adverse effects, particularly in children.

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Introduction

Nausea and vomiting are commonly encountered symptoms with multiple causes. These include infections, cancer, pregnancy and the adverse effects of many drugs.

Physiology

Multiple neurohumoural pathways can induce nausea and vomiting. Key foci include the chemoreceptor trigger zone in the floor of the fourth ventricle and the vomiting centre in the medulla with inputs from the nucleus tractus solitarius and vagus nerve.[1] The emetic response is mediated through multiple neurotransmitters including histamine, dopamine, serotonin, acetylcholine and neurokinin.[2] With the exception of neurokinin, cannabinoids modulate the activity of these neurotransmitters to influence the emetic response.[3]

Classes of antiemetics

The various classes of antiemetics target different pro-emetic pathways to alleviate nausea and vomiting. Some target more than one pathway (Table 1).[1,4-14] The classes of antiemetics include antagonists of dopamine, serotonin, neurokinin, histamine and acetylcholine. The cannabinoid agonists,[3] corticosteroids and benzodiazepines also have antiemetic actions.

Treatment of specific causes of nausea and vomiting

Although a number of antiemetics are suitable for the treatment of nausea and vomiting from a range of conditions (Table 2), there are certain circumstances when one drug may be preferred over another.

Gastroenteritis

Acute gastroenteritis is caused by viral, bacterial or protozoal infections. Therapeutic options available for adults with vomiting secondary to gastroenteritis include dopamine antagonists such as metoclopramide or prochlorperazine and serotonin antagonists such as ondansetron.[15]

Nausea and vomiting resulting from acute gastroenteritis is particularly challenging in children. Until the early 2000s, antiemetics including promethazine, metoclopramide and prochlorperazine were widely used in children, however their use is now controversial due to reports of adverse events including sedation and extrapyramidal reactions.[16]

When an antiemetic drug is indicated, serotonin antagonists such as ondansetron are now recommended in guidelines, such as those published by the Royal Children's Hospital Melbourne.[17] These guidelines recommend a single weight-based dose of oral ondansetron. Children weighing 8–15 kg should receive 2 mg, children weighing 15–30 kg should receive 4 mg and children weighing more than 30 kg should receive 8 mg. Ondansetron is not recommended in children under six months of age or less than 8 kg in weight.[17]

A systematic review reported that oral ondansetron reduced vomiting, hospitalisation and the need for intravenous rehydration in children with acute gastroenteritis.[18] Intravenous ondansetron or metoclopramide also reduced vomiting and hospitalisation. A single study in the review reported that rectal dimenhydrinate was effective at reducing vomiting.[18]

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Table 1 **Antiemetics available in Australia**

Class	Mechanisms of action	Pharmaceutical Benefits Scheme restrictions
Dopamine antagonists Benzamides – metoclopramide Benzimidazoles – domperidone Phenothiazines – prochlorperazine,* chlorpromazine* Butyrophenones – droperidol,* haloperidol* Atypical antipsychotics – olanzapine*	Block dopamine type 2 (D2) receptors centrally in the chemoreceptor trigger zone and peripherally in the gastrointestinal tract. Domperidone blocks peripheral D2 receptors only. At higher doses, effects on other receptors are seen. These include blockade of serotonin, histamine, adrenergic and muscarinic receptors.	Metoclopramide (parenteral) – palliative care medicine Metoclopramide and paracetamol combinations – available as non-prescription medicines
Serotonin antagonists Ondansetron Granisetron Palonosetron Tropisetron	Block 5-HT_3 receptors in the chemoreceptor trigger zone and gastrointestinal tract.	Ondansetron – chemotherapy or radiation-induced nausea and vomiting Granisetron – chemotherapy or radiation-induced nausea and vomiting Palonosetron – chemotherapy-induced nausea and vomiting Tropisetron – chemotherapy-induced nausea and vomiting
Neurokinin antagonists Aprepitant Fosaprepitant Netupitant Netupitant/palonosetron fixed-dose combination	Block neurokinin type 1 receptors in the central and peripheral nervous system.	Chemotherapy-induced nausea and vomiting
Antihistamines Doxylamine Cyclizine Pheniramine Promethazine	Block H_1 receptors Cyclizine, doxylamine, promethazine and pheniramine all block muscarinic receptors. Promethazine also blocks dopamine D2 receptors.	Available as non-prescription medicines
Anticholinergics Hyoscine	Block muscarinic receptors in vestibular nuclei, vomiting centre and higher brain centres.	Hyoscine (parenteral) – palliative care medicine. Hyoscine (oral) – available as non-prescription medicine.
Corticosteroids Dexamethasone	Central inhibition of prostaglandin synthesis and encephalin release. When combined with 5-HT_3 antagonists there are reduced serotonin concentrations in the gut and increased sensitivity of 5-HT_3 receptors to antiemetics.	Nil
Benzodiazepines Lorazepam	Agonist action at the $GABA_A$ receptor provides anxiolysis. Action at the chemoreceptor trigger zone to suppress the activity of dopamine.	Nil
Cannabinoids † Tetrahydrocannabinol Nabilone Dronabinol Nabiximols	Activate cannabinoid CB1 (inhibitory) receptors in the central nervous system and peripheral nervous system to modulate release of neurotransmitters.	Not applicable

* Also block serotonin, histamine, adrenergic and muscarinic receptors
† Not currently registered as antiemetics in Australia
Source: references 1, 4-14

Opioid-induced

The role of antiemetics to manage opioid-induced nausea and vomiting is poorly defined. Evidence is lacking and confounded by studies focused on postoperative nausea and vomiting (where patients were given opioids and anaesthetic drugs). As a result, the choice of antiemetic for opioid-induced nausea and vomiting will depend on factors such as medical comorbidities, the adverse effects of the drug, its cost and the clinician's familiarity with it.

A systematic review reported that low-dose droperidol (less than 4 mg per day) was effective at reducing opioid-induced nausea and vomiting.[19] Ondansetron at doses of 8 mg or 16 mg per day was effective,[20] but metoclopramide is not superior to placebo.[21] The role of serotonin antagonists may be limited because opioid-induced nausea and vomiting is not an indication which is currently subsidised by the Pharmaceutical Benefits Scheme (PBS).

Migraine-related

Migraines are commonly associated with nausea, vomiting and reduced gastrointestinal motility.[1] Due to this impaired motility and delayed drug absorption, parenteral routes of antiemetic administration may be required.[1]

Metoclopramide, a prokinetic antiemetic, reduces the absorption lag time of oral aspirin and non-steroidal anti-inflammatory drugs in patients with migraine.[22,23] In one study it reduced the time for aspirin to reach a maximum plasma concentration, from 24.6 to 18 minutes[22] and reduced the time for tolfenamic acid (not available in Australia) from 2 hours 51 minutes to 2 hours 19 minutes.[23] Additionally in healthy volunteers, administration of metoclopramide with paracetamol resulted in both a higher peak plasma concentration of paracetamol and a shorter time to peak plasma concentration.[24] The average time taken to reach the peak plasma concentration of paracetamol was reduced from 120 minutes to 48 minutes.[24] Consequently, metoclopramide has been incorporated into numerous guidelines as it may be beneficial in reducing nausea while enhancing the efficacy of concurrent analgesics.[1,25]

Dopamine antagonists such as prochlorperazine or chlorpromazine are effective in controlling nausea and vomiting.[26] Data are lacking on the efficacy of serotonin antagonists in migraine.

Pregnancy

Nausea and vomiting are common during the first trimester of pregnancy, affecting up to 90% of women.[27] If drug treatment is needed, antihistamines

Table 2 **Indications and scheduling for antiemetic drugs**

Indication	Therapeutic options (Scheduling)
Gastroenteritis	Dopamine antagonists (S4)
	Serotonin antagonists (S4)
Opioid-induced nausea and vomiting	Serotonin antagonists (S4)
	Dopamine antagonists (S4) • droperidol
Migraine-related nausea and vomiting	Dopamine antagonists (S4) • metoclopramide with paracetamol (S3) • metoclopramide (S4) • prochlorperazine (S3 or S4)
Vestibular causes of nausea and vomiting	Antihistamines (S3)
	Anticholinergics (S3)
	Dopamine antagonists (S4)
Chemotherapy-induced nausea and vomiting	Serotonin antagonists (S4)
	Neurokinin-1 antagonists (S4)
	Corticosteroids (S4) • dexamethasone
	Dopamine antagonists (S4) • olanzapine, haloperidol
	Benzodiazepines (S4) • lorazepam
Radiation-induced nausea and vomiting	Serotonin antagonists (S4)
	Corticosteroids (S4) • dexamethasone
	Dopamine antagonists (S4)
Postoperative nausea and vomiting	Dopamine antagonists (S4)
	Serotonin antagonists (S4)
	Antihistamines (S3)
	Corticosteroids (S4) • dexamethasone
	Neurokinin-1 antagonists (S4)
	Benzodiazepines (S4) • lorazepam

S3 pharmacist-only medicine
S4 prescription-only medicine

including doxylamine and diphenhydramine are efficacious, without an increased risk of congenital malformations.[27] Metoclopramide is also effective with no increased risk of congenital malformation, spontaneous abortion or reduced birthweight.[28] Other dopamine antagonists are not recommended due to conflicting evidence of safety during pregnancy.

The use of serotonin antagonists, such as ondansetron, in pregnancy has been increasing. However, ondansetron has limited safety data. A 2018 study reported no increased risk of cardiac malformation, but a slightly increased risk of oral clefts.[29] Ondansetron is therefore not recommended as a first-line treatment.

Vestibular disorders including motion sickness

Nausea and vomiting from conditions such as benign paroxysmal positional vertigo and motion sickness are due to stimulation of the vomiting centre via the vestibular nuclei. The primary neurotransmitters involved in this pathway are histamine receptors and acetylcholine muscarinic receptors.[1] The main treatments are therefore antihistamines such as promethazine, anticholinergics such as hyoscine, and dopamine antagonists such as prochlorperazine.[1,30]

Palliative care

The causes of nausea and vomiting in palliative care can broadly be divided into:

- disease state-related (e.g. cancer burden, ileus, uraemia in kidney disease or gastrointestinal oedema in heart failure)
- treatment-related (e.g. chemotherapy-induced or opioid-induced)
- biochemical (e.g. hypercalcaemia)
- toxin-mediated (secondary to anorexia-cachexia syndrome).[13]

Evidence to guide the choice of antiemetics in palliative care is lacking. Metoclopramide 10 mg three times daily is effective in up to 40% of cases.[13] Haloperidol 1.5–5 mg daily is effective in up to 47% of cases,[31] while chlorpromazine 25 mg four times daily is effective in up to 70% of cases.[32] Olanzapine 2.5–7.5 mg daily is also considered effective, but the precise response rate is unknown.[33] Adverse reactions such as sedation and anticholinergic effects, particularly with olanzapine and chlorpromazine, may limit the usefulness of dopamine antagonists.[13]

There are conflicting data on the use of serotonin antagonists in refractory nausea and vomiting in palliative care. In a single randomised trial, tropisetron was more effective than metoclopramide or chlorpromazine, even when they were combined with dexamethasone. The combination of tropisetron, dexamethasone and chlorpromazine was most effective.[34] However, another trial examining opioid-induced nausea and vomiting in palliative care reported that ondansetron was not more effective than metoclopramide or placebo.[35] There are no randomised trials examining the efficacy of antihistamines, however an uncontrolled study based on patient reports suggested cyclizine had efficacy.[13,36]

Anticholinergics such as hyoscine are used in palliative care, but not primarily for nausea. They are often prescribed for excessive gastric secretions and in terminal bowel obstruction.[13]

Corticosteroids such as dexamethasone (4–8 mg daily) are effective at managing chemotherapy-induced nausea and vomiting, bowel obstruction and raised intracranial pressure.[13] Dexamethasone, at doses as low as 2 mg daily, enhances the control of nausea and vomiting when added to combination treatment with tropisetron and either metoclopramide or chlorpromazine.[34]

Chemotherapy-induced

The emetogenic potential of chemotherapy drugs varies. For example, nausea and vomiting resulting from low emetogenic chemotherapy, such as paclitaxel, can be treated with a serotonin antagonist, while highly emetogenic chemotherapy, such as cisplatin, will require a combination of a serotonin antagonist, neurokinin antagonist and dexamethasone.[12]

Haloperidol and olanzapine are effective for chemotherapy-induced nausea and vomiting.[37] Olanzapine is now recommended as part of first-line management of highly emetogenic chemotherapy.[9,38]

Antihistamines, metoclopramide and prochlorperazine are less effective in chemotherapy-induced nausea and vomiting. Benzodiazepines such as lorazepam may be used as adjunctive therapy. They function to reduce anxiety and anticipatory nausea and vomiting.[39] There is a lack of data regarding the use of anticholinergics.[4]

While not registered in Australia, cannabinoid products have been tried for chemotherapy-induced nausea and vomiting. A systematic review concluded that cannabinoids were superior to placebo but not prochlorperazine. The data were inadequate to determine efficacy compared to metoclopramide, domperidone or chlorpromazine.[40] Cannabinoids have not been compared to newer antiemetics such as serotonin or neurokinin antagonists. They may have a role for patients with chemotherapy-induced nausea and vomiting that fails to respond to first-line treatment.[40] However, cannabinoids are only available through the Special Access Scheme.

Radiation-induced

The severity of radiation-induced nausea and vomiting depends on the irradiated body area. For example, total body irradiation has a high risk of nausea and vomiting and requires combination treatment with a serotonin antagonist and dexamethasone. Radiation to the head and neck has a lower risk and can be managed with a serotonin antagonist alone.[41]

Serotonin antagonists are more effective than dopamine antagonists alone or in combination with dexamethasone. Adding dexamethasone to a serotonin antagonist further reduces radiation-induced nausea and vomiting.[42]

Postoperative

A systematic review found that serotonin antagonists (ondansetron, granisetron and tropisetron), dexamethasone, droperidol and cyclizine were all more effective than placebo for the treatment of postoperative nausea and vomiting.[19] Depending on the clinical situation, certain antiemetics may need to be avoided. For example, given the constipating effect of serotonin antagonists, they should either be avoided or used with caution in patients at high risk of intestinal obstruction, as they may worsen or mask a progressive ileus.

Metoclopramide, at the standard 10 mg dose, is less effective than serotonin antagonists[43] and no more effective than placebo.[44] Although doses of metoclopramide greater than 25 mg may be more effective,[45] the increased risk of adverse events such as dystonia limit its use.

A recent study demonstrated that benzodiazepines such as lorazepam may be beneficial at reducing postoperative nausea and vomiting. Compared with placebo, 1 mg of orally administered lorazepam 60 minutes before general anaesthesia significantly reduced both postoperative nausea and vomiting and the requirement for antiemetic treatment during the postoperative period.[46]

Studies have also demonstrated that neurokinin antagonists such as aprepitant are effective at reducing postoperative nausea and vomiting.[47] However, they are not currently PBS subsidised for this indication.

Adverse effects

The mechanisms of action of antiemetics, such as antagonising neurotransmitters, contribute to some of their adverse effects.

QT prolongation

The risk of prolonging the QT interval on the ECG is important to consider when prescribing antiemetic drugs. While the effect may not be significant in isolation, the risk of dysrhythmia increases with other risk factors affecting the QT interval, such as drugs, hypokalaemia and hypocalcaemia.

Serotonin antagonists cause a reversible dose-dependent prolongation of the QT interval.[4] While this is a class effect, the risk varies among drugs. Both ondansetron and granisetron prolong the QT interval when administered intravenously at doses over 8 mg and 10 micrograms/kg respectively. However, there have been no reports of QT prolongation following oral administration.[48,49] Palonosetron and tropisetron are not associated with QT prolongation.[4,50]

A systematic review in children did not report any major adverse events with the use of serotonin antagonists such as ondansetron.[18] However, it is important to note that there have been multiple cases of cardiac arrhythmia or death in children associated with repeated administration of parenteral ondansetron.[51]

Dopamine antagonists cause QT prolongation and the US Food and Drug Administration (FDA) has issued 'black box' warnings for droperidol and haloperidol. However, the Australian DORM[52] and DORM-2[53] studies did not report an increased rate of QT prolongation with parenteral droperidol 10 mg compared to midazolam. Additional evidence suggests that higher doses of droperidol, up to 20–30 mg, are not always associated with QT prolongation.[54] Furthermore, as the dose needed to achieve an antiemetic effect is less than 4 mg/day,[55,56] the risk is insignificant. Haloperidol prolongs the QT interval at cumulative intravenous doses as low as 2 mg,[57] but the usual antiemetic dose is 1 mg.[4]

Other dopamine antagonists including metoclopramide, chlorpromazine and prochlorperazine are associated with QT prolongation,[4] but the minimum dose that causes ECG changes is unknown. Domperidone causes QT prolongation, but a recent randomised controlled trial in healthy volunteers found no effect on QT interval for doses as high as 80 mg per day.[58] However, remaining within the recommended dose and exercising additional caution is required in the older patient who may be at increased risk of adverse events compared with a healthy volunteer. Olanzapine has no effect on the QT interval at therapeutic doses.[59]

Extrapyramidal symptoms

There is a range of possible extrapyramidal effects including dystonia, akathisia and parkinsonism,[60] and the risk is greater with rapid intravenous administration. They are mediated through blockade of dopamine receptors in the substantia nigra and striatum.[61] The incidence of extrapyramidal symptoms in patients treated with metoclopramide is 4–25%, while the incidence with prochlorperazine is

25–67%[62] increasing with higher doses. These highly variable rates reflect a wide range of antiemetic doses, varying routes of administration and different rates of administration, such as a bolus injection versus intravenous infusion. There is an increased risk of tardive dyskinesia in patients treated with metoclopramide for more than 12 weeks.[4]

The FDA issued warnings about droperidol and haloperidol because of the risk of extrapyramidal symptoms. An incidence of 1–4% is reported after acute administration of droperidol, but this was not reported in the DORM-2 study.[53] Haloperidol has a higher incidence of extrapyramidal symptoms, even at doses under 4 mg.[63] Olanzapine, at doses of 5–20 mg, has also been associated with extrapyramidal symptoms.[63]

In case reports, serotonin antagonists including ondansetron have been associated with extrapyramidal symptoms. These occurred with repetitive intravenous doses of ondansetron totalling 7.5–37.5 mg daily.[64] While it has been suggested that intravenous doses as low as 4 mg may be sufficient to precipitate extrapyramidal symptoms,[64] the association is inconsistent.

Due to the risk of extrapyramidal symptoms, particularly with dopamine antagonists at higher doses, caution is required in the older patient, particularly those with Parkinson's disease. An option for these patients is domperidone, a peripherally acting dopamine antagonist that does not cross the blood–brain barrier.[1] Dopamine antagonists should be avoided in children due to the high incidence of extrapyramidal symptoms, particularly dystonic reactions.

Sedation

Dopamine antagonists are commonly associated with sedation. While in certain circumstances sedation may be a desired effect, it can limit the usefulness of these drugs as antiemetics. In psychosis, droperidol is more sedating than both olanzapine and haloperidol, however the doses are higher than those required for antiemetic use.[65] At doses of 0.25–1.25 mg, droperidol caused sedation in up to 17% of cases.[66] Low-dose olanzapine (2.5–7.5 mg) is associated with sedation in 20% of cases, while haloperidol is reported to cause sedation in up to 21% of cases at doses of 1–5 mg daily.[67]

Chlorpromazine, prochloperazine and metoclopramide are associated with sedation, but the precise rate is uncertain. Antihistamines such as doxylamine, cyclizine or promethazine are also associated with sedation. Promethazine is more sedating than either metoclopramide or prochloperazine.[68-70]

Serotonin antagonists are typically thought to be non-sedating, however a randomised trial reported that ondansetron may be as sedating as metoclopramide, but less than promethazine.[69] Benzodiazepines and cannabinoids cause significant sedation which may limit their use as antiemetics.[40]

Anticholinergic effects

Many antiemetic drugs have anticholinergic adverse effects including confusion, delirium, hallucinations, visual disturbance, urinary retention, constipation and tachycardia. In older patients, anticholinergic adverse effects are associated with an increased risk of developing cognitive impairment, falls and all-cause mortality.[71] Dopamine antagonists,[72] antihistamines[4] and hyoscine are known to have anticholinergic effects. Dopamine antagonists such as chlorpromazine and olanzapine, and antihistamines such as doxylamine and promethazine are likely to pose the greatest risk.

Constipation

Constipation is a well-described adverse reaction to serotonin antagonists such as ondansetron and anticholinergic drugs such as hyoscine.[4] Dopamine antagonists such as metoclopramide and domperidone are prokinetic so may be a better choice for patients with constipation.

Conclusion

While numerous antiemetics are available and broadly useful, the choice of a particular drug in an individual patient can vary depending on numerous considerations. These include the age of the patient, the indication for treatment, pregnancy, medical comorbidities and the risk of adverse effects. ≺

Conflict of interest: none declared

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