

Nausea and vomiting

— pharmacological management

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An understanding of the mechanisms of action of the drugs used to treat nausea and vomiting is important when selecting the best treatment for the patient. The drugs used vary in their efficacy depending on the cause of emesis, as described in this article



Hyoscine, available as a transdermal patch, is used to prevent motion sickness

Nausea and vomiting are complex mechanisms and the symptoms are influenced by the origin of the emetic response.

The pharmacist has a key role in providing information about the mechanism of action of antiemetic drugs, their pharmacokinetics and adverse effect profiles, in addition to monitoring antiemetic prescribing or prescribing the drugs themselves.

The pathogenesis of nausea and vomiting is complex, multifactorial and not entirely understood, as described in the first article in this special feature (p183). The development of one single treatment has not yet been possible, but the concept that the many parallel pathways involved in emesis may converge on a common output encourages the search for this target. The ultimate aim is to develop a universal or broad-spectrum antiemetic.¹ Until, and if such developments occur, the clinical cause of emesis in each patient should be considered before prescribing. This could be an important point of input for pharmacists.

The drugs currently used in the treatment of nausea and vomiting vary in their efficacy

depending on the primary cause of emesis. It is likely that a combination of anticholinergic, antihistaminergic and sedating effects contribute to the overall efficacy of an agent as an antiemetic. For the purposes of this article the drugs will be discussed based on their primary site of action.

In general, all drugs have a more pronounced effect on vomiting than on nausea. This is unfortunate because patients often report that they can cope with vomiting but the prolonged feeling of nausea is more difficult to manage. The control of nausea continues to be beyond modern medicine and to some extent is explained by our relatively poor knowledge of some of the physiological mechanisms involved.

Route of administration The route of administration of antiemetic therapy is particularly important in patients who are vomiting. Most preparations used for rescue treatment (ie, when a patient is actively vomiting) are available as intravenous or intramuscular injections. The rectal and buccal routes are also used to ensure adequate absorption of drugs administered to a vomiting patient. Scopaderm (hyoscine hydrobromide; Novartis) is the only transdermal antiemetic product licensed for use in the UK. It has a long duration of action but a delayed onset (of about four hours) so

patients should be counselled in the use of this product to ensure adequate symptom control.

Antihistamines

H₁ receptors are present in both the vestibular nucleus and the vomiting centre of the brain. The main indication of antihistamines in the treatment of emesis is in motion sickness or in post-operative emesis associated with activation of the vestibular pathways.

The antihistamines most commonly used for nausea and vomiting are promethazine and cyclizine. Others include meclizine, cinnarizine, dimenhydrinate and diphenhydramine. All have antagonist activity at the H₁ receptor and varying degrees of antimuscarinic activity, and there is some debate as to which of these activities contributes the antiemetic effect.

Drug choice Some antihistamines are markedly more sedating than others. This can be a therapeutic advantage, for example in the use of promethazine for premedication in children. Promethazine and cyclizine are commonly used in emesis associated with pregnancy (see p185). Cyclizine is used as first-line treatment for post operative nausea and vomiting (PONV) and studies have demonstrated that it is equivalent in efficacy

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Nausea and vomiting in pregnancy

The control of nausea and vomiting in pregnancy is a difficult issue. Nausea occurs in about 75 per cent of women in their first trimester of pregnancy and vomiting occurs in around 50 per cent.⁴ The difficulty in treating this is due to the fact that the first trimester of pregnancy involves major foetal development and is the period of greatest susceptibility to damage by drug administration.

Avoiding drug use where possible would be the most popular clinical decision, although a balance needs to be achieved where vomiting may be affecting the foetus. In this case first-line treatment is the use of antihistamines and second line options are prochlorperazine and metoclopramide.

First-line treatment of hyperemesis gravidarum (see p187) is metoclopramide and prochlorperazine, which can be used with no increased risk of congenital abnormalities. Pyridoxine (vitamin B6) has also been recommended for the treatment of hyperemesis gravidarum, often in combination with doxylamine. Multiple studies have shown no increased risk of congenital abnormalities with this combination, but the manufacturers of Bendectin, a combination product of pyridoxine and doxylamine, withdrew their product from the market in 1983. For persistent hyperemesis corticosteroids are recommended, in the form of intravenous hydrocortisone, followed by oral prednisolone. This regimen is not associated with an increased risk of malformations.

to both ondansetron and granisetron (5-HT₃-receptor antagonists, see p191).² Combination of cyclizine and granisetron has been shown to be superior to either drug given alone.³

Second generation antihistamines have no role in the treatment of nausea and vomiting due to their inability to penetrate the central nervous system (CNS).

Antihistamines have little effect on emesis resulting directly from chemotherapy. Their previous use in cancer patients may have been an attempt to address dystonic reactions caused by dopamine antagonists, or for nausea and vomiting originating in the vestibular nucleus independent of chemotherapy.

In addition to sedation, adverse effects of antihistamines include the antimuscarinic effects of dry mouth, urinary retention, dizziness and blurred vision.

— Antimuscarinics

Scopolamine (hyoscine) is the main antimuscarinic drug used in the treatment of emesis and is available as a transdermal patch. It has a non-selective, competitive antagonist action at muscarinic cholinergic receptors in the cerebral cortex and at H₁ receptors in the vestibular nucleus and vomiting centre.

Scopolamine is effective in treating emesis arising from vestibular stimulation (eg, motion sickness), and has been shown to be effective in the treatment of PONV, particularly in relation to post-surgical mobilisation or vestibular sensitivity following opioid administration.

The adverse effects are similar to those for antihistamines and include drowsiness and other antimuscarinic side effects. Scopolamine is contra-indicated in patients with narrow angle glaucoma.

— Dopamine antagonists

Dopamine antagonists comprise the benzamides, phenothiazines and butyrophenones. All have a non-selective action on dopamine receptors throughout the CNS and periphery. The chemoreceptor trigger zone (CTZ) has an abundance of dopamine receptors and the role of antagonism of these receptors in preventing emesis is relatively well documented. In addition, the fact that dopamine agonists such as apomorphine produce vomiting relatively quickly following subcutaneous injection⁴ demonstrates that dopamine receptors are involved in the pathways leading to emesis.

Current evidence, some from animal models, would seem to implicate D₂ and D₃ receptors in the CTZ.⁵ The source of the dopamine which stimulates these receptors is unclear, and emesis does not appear to be associated with high levels of circulating dopamine.

Dopamine antagonists are most effective for the treatment of emesis originating from stimulation of the CTZ such as that resulting from opioid administration.

Dopamine antagonists which penetrate the CNS have the potential to cause extrapyramidal side effects due to their non-selective action and dopamine antagonism in the basal ganglia. This unfortunate problem results in an array of unpleasant dystonic reactions, from akathisia to oculogyric crisis. This should be considered in patients with Parkinson's disease.

— Benzamides

The most common benzamides are metoclopramide and domperidone. They are effective for the treatment of moderate to severe nausea and vomiting. Both drugs antagonise dopamine D₂ receptors although

domperidone does not cross the blood-brain barrier so does not exert a central effect. This feature can be beneficial in avoiding dystonic side effects in patients with a history of such reactions or in patients with Parkinson's disease. In addition to the direct effect on the receptors of the CTZ, metoclopramide and domperidone both stimulate gastric and intestinal motility via action on peripheral dopamine receptors and, in the case of metoclopramide, a direct action on 5-HT₄ receptors. This prokinetic action is thought to contribute to the overall antiemetic effect.

Metoclopramide exhibits weak 5HT₃ antagonist effects at high doses. To some extent this explains its effectiveness in the treatment of emesis caused by highly emetogenic chemotherapy such as cisplatin. The current role of metoclopramide in the treatment of chemotherapy induced nausea and vomiting (CINV) is restricted to patients intolerant of or refractory to the 5-HT₃-receptor antagonists dexamethasone and aprepitant.⁷

The role of metoclopramide in PONV is not clear — some evidence suggests that ondansetron, granisetron and the now discontinued droperidol are more effective. The prokinetic effects of metoclopramide and the fact that it reduces bowel transit time mean that it should be avoided following bowel surgery. Metoclopramide can also cause hyperprolactinaemias due to its non-specific dopamine antagonism. Extended use may lead to galactorrhoea and menstrual disorders.

— Phenothiazines

Prochlorperazine and perphenazine are the most common phenothiazides, although drugs such as chlorpromazine, trifluoperazine and levomepromazine also exhibit antiemetic activity. Phenothiazides block dopamine D₂ and 5HT receptors in the CTZ as well as having weak antimuscarinic and histamine-blocking activity.

The phenothiazines are moderately effective in emesis resulting from vestibular stimulation, agents which directly stimulate the CTZ (opioids and chemotherapeutic agents) and gastrointestinal stimulation. In CINV phenothiazines are now mostly used for the management of breakthrough emesis.

Phenothiazines are also used for the treatment of PONV, and there is evidence that prochlorperazine is superior to ondansetron in the management of nausea after total knee replacement surgery. Some phenothiazines which are particularly sedating, such as levomepromazine, are useful in palliative care to reduce restlessness and emesis.

The side effects of phenothiazines are similar to those caused by metoclopramide and are mainly extrapyramidal effects, including tardive dyskinesia. All have the potential to induce hypotension, particularly when used in combination with other drugs such as opioids or anaesthetics.

— Butyrophenones

Haloperidol is the main butyrophenone and is chiefly used in palliative care for emesis induced by opioids. It acts by blockade of D₂ receptors in the CTZ, and has a similar effect and adverse event profile as the phenothiazines.

Olanzapine, an atypical neuroleptic, is showing promise in the treatment of CINV in patients receiving moderately and highly emetogenic chemotherapy. Trials using olanzapine in combination with dexamethasone and 5-HT₃-receptor antagonists have demonstrated the effectiveness of this combination in controlling both acute and delayed emesis.

Olanzapine has a mixed activity at dopamine, histamine and 5HT receptors. The exact influence of this activity on acute and delayed CINV supports the concept that emesis is a result of activation of multiple receptor sites.

— 5-HT₃-receptor antagonists

5-HT₃-receptor antagonists (5HT₃-RAs) effectively block 5-HT₃ receptors in the gut, the CTZ and in the nucleus tractus solitarius. The mechanism of emesis involving 5-HT involves local free radical formation caused by cytotoxic agents or other potentially toxic substances. These free radicals cause release of large amounts of 5-HT from gastric enterochromaffin cells. This released 5-HT then stimulates 5-HT₃ receptors on the adjacent vagal afferent neurones resulting in a profound emetic response. Furthermore, stimulation of the 5-HT₃ receptors seems to sensitise the vagus nerve to other excitatory substances.

5-HT₃-RAs are the cornerstone of the control of nausea and vomiting in chemotherapy patients. The introduction of 5HT₃-RAs and other drugs over the past 25 years has meant that vomiting can now be prevented in 70-80 per cent of patients on chemotherapy.⁸ Before this, postponement or refusal of treatment because of acute emesis was common.

Licensed 5HT₃-RAs include ondansetron, granisetron, palonosetron and tropisetron. To date most trials in this area have failed to demonstrate any significant differences in efficacy between the members of this group and it is generally accepted that the drugs are equivalent in efficacy and adverse effect profile.⁹

Delayed CINV The effectiveness of the 5HT₃-RAs in the control of delayed CINV is less well established although they are still used for this purpose. Metoclopramide combined with a corticosteroid has shown similar efficacy to 5HT₃-RAs plus a corticosteroid in the treatment of delayed CINV. The relative lack of efficacy of 5HT₃-RAs in delayed CINV compared with acute CINV

can be explained by considering that delayed nausea and vomiting may not be associated with release of 5HT in the same way that acute emesis is. This theory is supported by studies investigating serotonin metabolism which suggest that the peak release of serotonin occurs about six hours after administration of a dose of cisplatin-based chemotherapy with no further peaks after this time.¹⁰

Palonosetron has demonstrated some efficacy in delayed CINV and has been shown to be superior as a single agent to both ondansetron and dolasetron. This may be due to differences in the pharmacokinetic profile of palonosetron and needs to be investigated further before conclusions can be made. Current guidelines suggest that 5HT₃-RAs should not be used for delayed phase nausea and vomiting caused by highly emetogenic chemotherapy but that they are an option in that caused by moderately emetogenic chemotherapy.

PONV 5HT₃-RAs are also effective in the treatment of PONV with studies suggesting superiority to other routinely used drugs. The high cost of these drugs if used first-line in all patients undergoing surgery must be considered, and a more suitable strategy may be to reserve its use for patients at higher risk of PONV.

The 5HT₃-RAs have a particularly good adverse effect profile, limited to mild headache, diarrhoea, asthenia, constipation and dizziness. Changes in electrocardiograms have been noted but without serious or clinically relevant cardiovascular complications.⁹

— NK1 receptor antagonists

Substance P is a potent tachykinin which acts at the neurokinin-1 (NK1) receptor. NK1 receptors are distributed in large numbers in the gastrointestinal tract, the CTZ and the nucleus tractus solitarius.¹¹ 5-HT is released acutely from enterochromaffin cells and probably exerts an excitatory effect on the afferent vagus as well as having central actions in the transmission of the vomiting reflex. The development of drugs which can

act as NK1 antagonists, both peripherally and centrally, has resulted in clinical evidence demonstrating extensive effects on vomiting and, to a lesser extent, nausea, associated with chemotherapy, motion, direct CTZ stimulation (apomorphine) and alcohol.

Studies demonstrating the efficacy of NK1 antagonists in PONV have been encouraging and, when compared to ondansetron, have resulted in statistically significant reductions in PONV.⁹ These studies are relatively small and the place of NK1 antagonists in PONV requires further clinical investigation. Aprepitant is the only drug from this class currently licensed in the UK.

Aprepitant Aprepitant is used to prevent acute and delayed nausea in patients receiving highly emetogenic chemotherapy (eg cisplatin). Its use in patients receiving moderately emetogenic chemotherapy is accepted but further clinical investigation is under way to clarify its efficacy.

Aprepitant is used in combination in the treatment of both acute and delayed CINV resulting from moderately and highly emetogenic chemotherapy. Various treatment regimens involving the use of a 5-HT₃-RA and a corticosteroid have been shown to be clinically effective.^{8,13} Aprepitant is not currently licensed for use in PONV.

Adverse effects with aprepitant appear to be fairly minor, including headache, abdominal pain, dizziness and hiccups. No increase in adverse effects has been noted in clinical trials of aprepitant when added to a regimen of dexamethasone and ondansetron compared with a combination of ondansetron and dexamethasone alone.⁷ Aprepitant has effects on cytochrome P450 enzymes, particularly CYP3A4 and CYP2C9, so may interact with drugs which act as substrates for these isoenzymes. In particular, the dose of dexamethasone, a CYP3A4 substrate, should be reduced by 50 per cent when co-administered with aprepitant.

— Corticosteroids

Dexamethasone is an effective drug for the treatment of CINV and PONV. It is currently used in combination therapy with a

Combination therapy

The use of drugs in combination for the treatment of nausea and vomiting is logical providing that drugs which act at different receptor sites are combined. This is of benefit in the treatment of acute and delayed CINV where various drugs are combined depending on the chemotherapy regimen. The combination of dexamethasone with a 5-HT₃ receptor antagonist or metoclopramide and aprepitant appears to be effective in the control of emesis associated with chemotherapy.

The use of combination therapy in PONV has been shown to be effective, particularly in procedures where PONV carries significant surgical morbidity, eg, wound dehiscence or in the case of faciomaxillary surgery where patients may have had their jaws wired. In these cases patients should be assessed for their risk of developing PONV and combination therapy should be used accordingly.

5-HT₃-RA and aprepitant but has demonstrable efficacy as monotherapy in both CINV and PONV, equivalent to that of ondansetron.

The antiemetic mechanism of action of corticosteroids is not clear. It has been suggested that their anti-inflammatory action, facilitated by their well-documented effects on eicosanoid metabolism, plays some part. This is supported by the fact that corticosteroids appear to be ineffective in the treatment of vomiting induced by apomorphine and ipecacuanha (ie, vomiting with a rapid onset which is unlikely to have an inflammatory component).¹ In addition, there is some evidence that corticosteroids have an effect on 5HT release or on the subsequent activation of 5-HT₃ receptors in the gastrointestinal tract.

Dexamethasone has proven effectiveness when administered with a 5-HT₃-RA in the treatment of acute CINV resulting from low, moderate and highly emetogenic chemotherapy and in the treatment of delayed CINV resulting from moderate and highly emetogenic chemotherapy. Evidence supports the superiority of dexamethasone over 5-HT₃-RAs, metoclopramide and neuroleptics in the treatment of delayed CINV from both cisplatin and non-cisplatin based therapy.

The adverse effect profile of corticosteroids is considered to be acceptable and includes insomnia, indigestion, headache, agitation, increased appetite and weight gain. These last two effects may have some therapeutic benefit in cancer patients who have lost their appetite or who are losing weight at an uncontrollable rate.

— Benzodiazepines

The benzodiazepines lorazepam and midazolam can be particularly useful when used as adjunct treatment in certain circumstances. Lorazepam is often added to antiemetic regi-

mens for its antianxiety effects, minimising anticipatory nausea and vomiting in chemotherapy patients. However, it does not demonstrate sufficient antiemetic activity to be used as monotherapy. Midazolam is used in refractory PONV and CINV and is added to optimum therapy to improve the management of agitated patients.

— Cannabinoids

Nabilone is the only synthetic derivative of tetrahydrocannabinol licensed in the UK. It has demonstrable benefit in the treatment of emesis and is licensed for use in CINV. The use of nabilone in PONV is less common and its efficacy has not been well investigated. Currently, nabilone is used for CINV when hospital patients are refractory to conventional treatments. The mechanism of action is thought to be action at the cannabinoid CB₁ receptor, modulation of 5HT₃ receptor activity in the CNS and substance P release from the spinal cord and potentially from other sites in the body.⁷

Nabilone has been found to be equivalent or slightly superior in efficacy to drugs such as metoclopramide, the phenothiazines and haloperidol. However, its use is limited by adverse effects such as dizziness, dysphoria and hallucinations. Nabilone can also cause euphoria and sedation which, in a similar way to the benzodiazepines, can be therapeutically advantageous.

— References

1. Sanger GJ, Andrews PLR. Treatment of nausea and vomiting: Gaps in our knowledge. *Autonomic Neuroscience: Basic and Clinical* 2006;129:3–16.
2. Grimsehl K, Whiteside JB, Mackenzie N. Comparison of cyclizine and ondansetron for the prevention of postoperative nausea and vomiting in laparoscopic day-case gynaecological surgery. *Anaesthesia* 2002;57(1):61–5.
3. Johns RA, Hanousek J, Montgomery JE. A

comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. *Anaesthesia*. 2006;61(11):1053–57.

4. Pleuvry BJ. Physiology and pharmacology of nausea and vomiting. *Anaesthesia and Intensive Care Medicine* 2006;7(12):473–77.
5. Mitchelson F. Pharmacological agents affecting emesis — a review (part 1). *Drugs* 1992;43:295–315.
6. Darmani NA, Zhao W, Ahmad B. The role of D₂ and D₃ dopamine receptors in the mediation of emesis in *cryptotis parva*. *Journal of Neural Transmission* 1999;106:1045–61.
7. Jordan K, Schmolll HJ, Aapro MS. Comparative activity of antiemetic drugs. *Critical Reviews in Oncology/Haematology* 2007;61:162–75.
8. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin — the Aprepitant Protocol 052 Study Group. *Journal of Clinical Oncology* 2003;21:4112–19.
9. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-HT₃ receptor antagonists. *Annals of Pharmacotherapy* 2003;37:1276–86.
10. Wilder-Smith OH, Borgeat A, Chappuis P, Fathi M, Forni M. Urinary serotonin metabolite excretion during cisplatin chemotherapy. *Cancer* 1993;72:2239–41.
11. Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. *Drugs* 2000;60:533–46.
12. Gesztesi Z, Scuderi PE, White PF, Wright W, Wender RH, D'Angelo R, Black LS, Dalby PL, Maclean D. Substance P (neurokinin-1) antagonist prevents postoperative vomiting after abdominal hysterectomy procedures. *Anesthesiology* 2000;93(4):931–37.
13. Warr DG, Hesketh PJ, Gralla RJ. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *Journal of Clinical Oncology* 2005;23:28–2830.