Palliation of nausea and vomiting

Nausea is often unrecognized or poorly managed. Understanding the central pathways involved in nausea enables clinicians to choose anti-emetics with a higher likelihood of successful symptom management.

Nausea and vomiting are separate but related symptoms that arise frequently in patients with advanced cancer and other life-limiting conditions (Dunlop, 1989; McCarthy et al, 1996; Davies and Curtis, 2000; Meuser et al, 2001). Patients rate these symptoms as highly distressing (Bliss et al, 1992). Despite advances in understanding and management of other symptoms, the palliation of nausea has improved little in the last 20 years. Good studies of anti-emetics in palliative care are lacking, partly as a result of the difficulty of investigating a single, subjective symptom (nausea) in such a complex, varied and frail population, and partly because there is an absence of a well-validated set of outcome measures for the management of nausea in this group of patients (Saxby et al, 2007).

Assessing and managing symptoms

There are guidelines for the palliation of nausea and vomiting in advanced disease (Mannix, 2004; Twycross and Wilcock, 2004) and these are based on extrapolation from animal models (Peroutka and Snyder, 1982). The models have been validated on human subjects who are either healthy (e.g. motion sickness in armed forces personnel) or who experience nausea as an isolated symptom (e.g. vestibular disease, chemotherapy-induced nausea and vomiting). These subjects with a single trigger to nausea are not identical to palliative care patients, in whom multiple triggers may co-exist.

Although clinicians often assess emesis by the frequency, volume and content of vomits, patients are usually far more distressed by nausea that may go unobserved and, therefore, untreated. Patients rate nausea as highly aversive, whereas most will accept occasional vomits (e.g. as in inoperable bowel obstruction) if nausea can be relieved.

There are many causes of nausea (*Table 1* shows some examples). The most useful palliative approach is to consider all the potential triggers of nausea and/or vomiting in a particular patient, and to seek to reverse the triggers or to block the central emetogenic pathways that mediate the symptoms. These pathways are summarized in *Figure 1*. This shows the neurotransmitter receptors present at the chemoreceptor trigger zone in the floor of the fourth ventricle, at the complex autonomic centres in the brainstem collectively referred to as the vomiting centre, and the types of stimulus that may excite each of these centres.

It is worth noting that the onset of nausea is accompanied by reduced gastric emptying; thus, the absorption of oral drugs may be reduced while a patient is

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Table 1. Common causes of nausea and/or vomiting in advanced disease, and recommended first and second line anti-emetic drugs

Cause	Examples	Symptoms	Recommended anti-emetic
Chemical triggers	Hypercalcaemia; ketoacidosis; drugs (*Figure 1*)	Unremitting nausea; nausea not relieved by vomiting	1. haloperidol 2. levomepromazine
Visceral stretch, distortion or irritation	GI obstruction; organomegaly stretching serosa; meningeal stretch; retropharyngeal tumour	Nausea, may be exacerbated by posture or movement, which may also trigger vomiting	1. cyclizine 2. levomepromazine
Upper GI tract mucosal irritation	Gastritis; post-radiotherapy mucositis; CMV infection; pharyngeal irritation by secretions or nasogastric tube	Of mucositis, plus nausea Of pharyngeal discomfort, plus nausea	1. cyclizine 2. $5HT_3$ antagonists
Delayed gastric emptying Obstruction proximal to jejunum	Drugs (*Figure 1*); pyloric inflammation or mass; raised intra-abdominal pressure (ascites; organomegaly); gut or peritoneal mass	Often little nausea except immediately before vomiting; hiccup and dyspepsia/reflux; relief of symptoms after large-volume vomit. Rapid dehydration in total high obstruction	1. metoclopramide 2. domperidone/cisapride* See text: prokinetic agents may cause colic in obstructed gut
Anxiety	Symptoms worsen when anxious; conditioned emesis with chemotherapy	Nausea, plus symptoms of anxiety Some patients are unaware of the link	Diagnosis of exclusion; management of anxiety
Chemotherapy; radiotherapy across GI tract	Radiotherapy to low thoracic or lumbar spine; palliative chemotherapy	Associated with chemotherapy or radiotherapy	Anti-emetic strategy of treatment centre; $5HT_3$ antagonists; NK_1 antagonists

$5HT_3$ = serotonin type 3 receptor; CMV = cytomegalovirus; GI = gastrointestinal; NK_1 = neurokinin type 1 receptor. *cisapride is only available on a named-patient basis

nauseated, and this may impact on management of other symptoms including pain.

Effective management of nausea and vomiting requires comprehensive assessment, reversal of any reversible causes, and treatment with an appropriate anti-emetic by a non-oral route. This includes a detailed history of nausea and its duration, exacerbating and relieving factors and any relationship to changes in drugs; a similarly detailed history of any vomiting; a clinical examination; review of the patient's drug history; and screening for infection and metabolic disturbance.

Selecting an anti-emetic regimen

Anti-emetics appear to work at different points in the emesis pathway – selection of an appropriate regimen therefore requires diagnosis of the most likely cause(s) of nausea and/or vomiting, in order to select an anti-emetic that is active in the appropriate area. Attention to hydration, oral comfort and hygiene, and avoidance of strong odours (including food preparation) are all important considerations. *Table 2* list anti-emetics according to their places in the pathway.

Anti-emetic drug efficacy is predicable from the drug's binding affinity for its receptor in the brain. *Table 2* indicates drug binding: note that some drugs bind other receptors and these account for side effects like hypotension (α-adrenergic receptors) or dry mouth and drowsiness (muscarinic cholinergic receptors).

From *Table 2* it is apparent that the most effective anti-emetic at the chemoreceptor trigger zone is haloperidol; a dose of 1.5 mg daily is sufficient in most adults by oral or subcutaneous routes. It has a long half-life, making once daily administration possible. Side effects include dystonic effects which are more likely if other antidopaminergic or anticholinergic drugs are co-prescribed.

At the vomiting centre, the most effective H_1 antagonist is cyclizine, which is a relatively non-sedating antihistamine. The usual adult dose is 50 mg 8-hourly by mouth or subcutaneous injection. Redness at injection sites is a problem in 10% of adults. Hyoscine hydrobromide is an effective anti-emetic because it crosses the blood–brain barrier to block CNS muscarinic receptors, but its CNS anticholinergic effects also include dry mouth, drowsiness and urinary retention in some patients.

Figure 1. Pathways and neurotransmitters involved in nausea and vomiting. $5HT_{2,3}$ = serotonin type 2,3; Ach_m = muscarinic cholinergic; D_2 = dopamine type 2; H_1 = histamine type 1; NK_1 = neurokinin type 1.

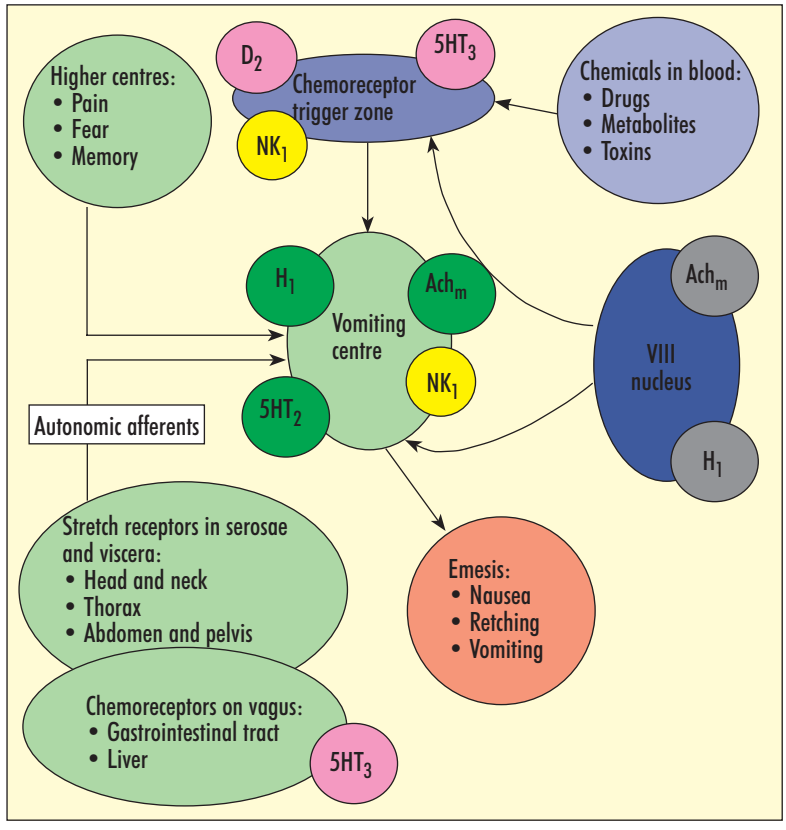

Table 2. Receptor binding affinities of commonly-used receptor-specific anti-emetic drugs

Receptor binding		D_2 (CTZ)	$5HT_2$ (VC)	Ach_m (VC and VIII nucleus)	H_1 (VC and VIII nucleus)	$5HT_3$ (vagal afferent endings)	NK_1 (? CTZ and VC)	αAd (antagonists cause hypotension)
Drug	Haloperidol	+++	–	–	–	–		–
	Metoclopramide	++	–	–	–	(+)		–
	Cyclizine	–	–	(+)	+++	–		–
	Levomepromazine	+	+++	+	–	–		+
	Domperidone (does not cross blood–brain barrier)	+	–	–	–	–		–
	Prochlorperazine	+	–	+	+	–		+
	Hyoscine hydrobromide	–	–	+++	–	–		–
	Granisetron, ondansetron	–	–	–	–	+++		–
	Aprepitant						+++	

CTZ = chemoreceptor trigger zone; VC = vomiting centre. Key to receptors: $5HT_{2,3}$ = serotonin receptor types 2 and 3; αAd = α-adrenergic; Ach_m = muscarinic acetylcholine receptors; D_2 = dopamine type 2; H_1 = histamine type 1; NK_1 = neurokinin type 1 (substance P). Binding affinity: +++ = very strong; + = weak; – = no binding

Levomepromazine is a $5HT_2$ antagonist with strong binding at the vomiting centre. Because it also binds weakly to D_2 receptors in the chemoreceptor trigger zone, it is sometimes referred to as a 'broad spectrum' anti-emetic (Twycross et al, 1997). However, dose escalation is limited by hypotension and drowsiness, and it is best considered a useful vomiting centre anti-emetic at very low doses (6 mg daily by mouth or subcutaneous injection). Side effects are unusual at this dose. At higher doses, its combined anti-D_2 and anti-Ach_m effects make it a useful second-line anti-emetic for both chemoreceptor trigger zone and vomiting centre triggers to nausea, if drowsiness is an acceptable side effect.

Management of nausea and vomiting requires attention to detail and consideration of the co-morbidities of the patient; a drug suitable for palliation of nausea caused by chemotherapy may not be effective for nausea from a different cause. In particular, the $5HT_3$ antagonists are widely over-prescribed. These drugs are highly effective when emesis is caused by local release of serotonin in the gut in response to emetogenic chemotherapy or to radiotherapy that crosses the gut, e.g. spinal radiotherapy or irradiation of a retroperitoneal mass. The locally-released serotonin acts on $5HT_3$ receptors on terminals of the vagus in the gut wall and liver, which respond to stimulate the vomiting centre (*Figure 1*). In conditions that cause gut inflammation, local serotonin release may have a role in causing nausea. However, most causes of nausea and vomiting in palliative care are not associated with serotonin release, making these drugs inappropriate (*Tables 1* and *2*).

Clinical applications

Nausea is a symptom, not a diagnosis, but often needs to be identified and assertively managed in parallel with treatment of the underlying cause. Nausea as a symptom of biochemical disturbance (e.g. ketoacidosis, uraemia, hypercalcaemia) can persist for hours to days after correction of the biochemistry: this is a clinical illustration of the importance of treating the patient and not the blood test results.

Case Study

A 45-year-old woman with carcinoma of the cervix presented with nausea, vomiting and colicky abdominal pain. She was found to have bowel obstruction at multiple levels as a result of peritoneal disease and was deemed inoperable.

Nausea was attributed to vomiting centre stimulation by autonomic afferents from her distended segments of bowel; cyclizine 50 mg subcutaneously 8-hourly controlled her nausea within hours. Her colic was controlled using intermittent hyoscine butylbromide 20 mg subcutaneously.

She returned home with a small infusion device delivering subcutaneous cyclizine 150 mg over 24 hours and hyoscine butylbromide 80 mg over 24 hours. She was able to eat and drink at will; she vomited once or twice daily but was not troubled by nausea. She was able to care for her family and to go on holiday.

Three months later, while continuing to take regular cyclizine, she again complained of nausea and increased vomiting. Her other medications were unchanged. Investigations revealed hypercalcaemia, and a test dose of haloperidol 1.5 mg subcutaneously relieved her nausea completely. Her hypercalcaemia was treated with intravenous bisphosphonates, and haloperidol 1.5 mg daily was used to manage her nausea until she had been normocalcaemic for 3 days.

Gastric stasis

In some circumstances, use of centrally acting anti-emetics is less appropriate than use of prokinetic agents. Reduction in rate of gastric emptying by raised intra-abdominal pressure (ascites, hepatomegaly) or reduced peristalsis (anticholinergic drugs, autonomic dysfunction) results in a recognizable syndrome of early satiety, epigastric fullness, belching, heartburn and hiccups; a short period of premonitory nausea precedes large volume vomiting (often containing undigested food) and this emptying of the upper gut relieves the other symptoms.

Palliation of this 'gastric stasis syndrome' consists of prokinetic agents (metoclopromide, domperidone) which increase gastric and upper small intestinal peristalsis, relax the pylorus and increase lower oesophageal tone (thus reducing reflux while promoting gastric emptying), and reduction of volume of gastric contents by reducing gastric secretion (protein pump inhibitors or H_2 antagonists). Advice to eat and drink 'little and often' is helpful. Antacids help to reduce oesophageal discomfort caused by reflux through a distended oesophago-gastric junction. In gastric stasis, any drugs with anticholinergic effects should be avoided if possible: these drugs will slow gastric emptying and upper gastrointestinal tract transit and, in theory, could block the action of prokinetic drugs. It is possible that higher doses of prokinetic drugs may still be effective in the presence of anticholinergic drugs.

Use of prokinetic agents will result in colic if there is complete obstruction of the small intestine (see below).

Gastrointestinal obstruction

If the gastrointestinal tract becomes blocked, e.g. by an obstructing malignant mass or adhesions, then restoring patency of the gut is the best palliation. However, in advanced disease such as abdominal and pelvic malignancies with peritoneal involvement, or extensive adhesions related to longstanding inflammatory bowel disease or peritoneal disease, surgery may not be possible. Similarly, surgery may not be desirable for a patient close to death or with multiple co-morbidities. It is possible to manage the symptoms of gastrointestinal tract obstruction (nausea, vomiting, colic) and enable a patient to remain at home if preferred (*Case study*).

In gastrointestinal tract obstruction, the triggers to nausea and vomiting may include:

- Gut distension proximal to the obstruction: the obstructed segment then dilates, triggering autonomic afferent stimulation of the vomiting centre (*Figure 1*)

- Pain: distension in the obstructed segment increases muscle tension and causes colic. Pain is both uncomfortable and frightening, and further increases stimulation of the vomiting centre (*Figure 1*)
- Toxins: gut stasis can allow bacterial toxins and fermentation products to be absorbed into the blood. This then triggers nausea via the chemoreceptor trigger zone (*Figure 1*).

Nausea triggered via the vomiting centre will respond to cyclizine 50 mg 8-hourly or 150 mg/24 hours by subcutaneous injection. If nausea persists, consider the possibility of an additional trigger via the chemoreceptor trigger zone, and add haloperidol 1.5–3 mg daily.

Gut distension may be reduced by treatment with octreotide or anticholinergic agents to reduce pancreatic and other exocrine secretion along the gut (Ripamonti et al, 2000). Reducing the large volumes of fluid secreted by the pancreas also reduces the tendency for patients to become dehydrated, so that oral rehydration remains possible provided obstruction is lower than the jejunum.

Vomiting may continue, and it is important that patients appreciate that this mechanical process is a result of bowel blockage. Patients may eat and drink what they wish for comfort and pleasure, but should expect intermittent vomiting.

If obstruction is higher than the jejunum, then large-volume vomiting and rapid dehydration can be a problem. Palliative approaches may include parenteral fluid replacement (subcutaneous is least intrusive and is possible in a variety of settings including at home) and possibly a regularly-evacuated tube to the stomach to prevent or reduce vomiting. Patients find nasogastric tubes uncomfortable; pharyngeal irritation causes both pain and nausea. Many patients prefer to vomit rather than tolerate a tube. A venting percutaneous gastrostomy may be easy for an experienced operator to insert (Holm and Baron, 2007); sometimes a jejunal extension can be inserted over a guide wire to allow enteral hydration and drug administration beyond the obstruction (Watson et al, 1997). A short hospital visit may thus reduce some very unpleasant symptoms and enable even very frail patients to enjoy a better quality of life.

The development of gastrointestinal stents has also improved palliation of single-level gut obstruction. The advice of a palliative care team and an experienced gastroenterology physician or surgeon may greatly improve a patient's quality of life.

A proportion of patients with intestinal obstruction caused by a tumour will have some reduction in mass size, and therefore reduction of symptoms, from high doses of corticosteroids, e.g. dexamethasone 16–20 mg daily. Steroids also have intrinsic anti-emetic action, although the mechanism is not understood.

Recent developments

The importance of substance P as a neurotransmitter in the CNS has been long-recognized, and the action of substance P at particular subset of receptors (neurokinin type 1 receptors, NK_1) has been investigated. NK_1 receptors are involved both in mediation of nausea (Dando and Perry, 2004) and modulation of mood (Gobbi and Blier, 2005). This overlap of functions may partly explain the profound distress experienced by nauseated people. NK_1 antagonists have antidepressant activity, and are also anti-emetic.

An NK_1 antagonist anti-emetic, aprepitant, is now commercially available for chemotherapy-induced emesis. It acts to markedly reduce late-onset emesis, but has no effect in the first few hours following chemotherapy, when $5HT_3$ antagonists are most effective (Hesketh et al, 2003). This sequential activation of neurotransmitter receptors is further evidence that the best palliation of nausea and vomiting is reached by understanding and applying knowledge of the receptors activated by different triggers to nausea and vomiting.

Complementary approaches

Acupuncture is a recognized treatment for nausea; studies show that needles or electro-stimulation of the P6 acupuncture point (found over the palmar crease in front of the wrist) is effective in reducing nausea. Intriguingly, this effect is not produced if the acupuncture takes place under general anaesthetic (Vickers, 1996).

Psychological approaches including hypnotherapy, deep relaxation and cognitive behaviour therapy have been shown to be useful in reducing nausea and vomiting in patients receiving chemotherapy and radiotherapy (Burish and Tope, 1992; Morrey and Greer, 2002; Richardson et al, 2007); there are no specific studies in palliative care patients.

Conclusions

Nausea and vomiting should be evaluated separately, and a treatment plan should be devised according to the most likely cause of the symptoms. Anti-emetics should be used to control symptoms while the underlying cause is treated. Where reversal of the underlying cause is not possible, nausea can be palliated for long periods using appropriate anti-emetics given by the appropriate route.

KEY POINTS

- Nausea is invisible, but is rated as far more distressing than vomiting by most patients. Always enquire about nausea specifically.
- Until nausea is controlled, use of a non-oral route for anti-emetics is recommended.
- A patient may have more than one cause of nausea; it may be necessary to prescribe more than one anti-emetic drug to palliate the symptom.
- $5HT_3$ antagonists are rarely indicated outside chemotherapy-induced nausea and vomiting.
- Reversible causes of nausea and vomiting should always be excluded; appropriate anti-emetic prescribing and reversal of an underlying cause can proceed together.

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