Nausea and vomiting in advanced cancer

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Nausea and vomiting are distinct symptoms, commonly occurring together but which should be assessed separately. Both are prevalent in patients with advanced cancer. Data are taken from The Cochrane Library (2010) and Ovid MEDLINE (1966–2010). Most current guidelines advocate an aetiology-based approach to the management of nausea and vomiting. Choice of anti-emetic is based on a clinical assessment of the likely pathophysiological component of the emetogenic pathway that is being triggered and selecting an anti-emetic drug that blocks the key receptors involved. Some authors propose a more empirical approach. The limited available evidence would suggest that both an empirical or aetiology-based approach may have similar overall efficacy. There are no published studies directly comparing the two. Standardized assessment and outcome tools are needed to enable well-designed studies to establish efficacy for conventional agents and also compare efficacy with the newer, more expensive ones.

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Introduction

Nausea and vomiting is common in advanced disease. The prevalence in patients with advanced cancer is up to 70% and up to 50% in non-malignant advanced disease such as heart failure, chronic obstructive pulmonary disease and renal failure.\textsuperscript{1–8} Nausea and vomiting appear to increase in prevalence as disease progresses.\textsuperscript{9}

Nausea may be defined as an unpleasant feeling of the need to vomit, often accompanied by autonomic symptoms such as pallor, cold sweat, salivation, tachycardia and diarrhoea,\textsuperscript{5,7,10} whereas vomiting is the forceful expulsion of gastric contents through the mouth through a complex reflex involving coordinated activities of the gastrointestinal tract, diaphragm and abdominal muscles.\textsuperscript{5,7,10}

Although the two symptoms are often clinically associated, they should be assessed separately.\textsuperscript{1,5} Patients may use the term ‘vomiting’ to describe a variety of problems including expectoration and regurgitation and a careful history is therefore important.
Physiology of the emetogenic pathway

The current approach to managing nausea and vomiting in advanced cancer is largely based on physiological principles, an understanding of which is therefore required to appreciate the rationale behind current recommendations.

The afferent and efferent reflexes that result in nausea and vomiting are thought to be integrated by two distinct centres at brainstem level (Fig. 1):

(i) The ‘chemoreceptor trigger zone (CTZ)’ is located in the floor of the fourth ventricle and is outside the blood–brain barrier.\textsuperscript{5,10–12} Rather than being a specific anatomical area, the CTZ is likely to exist as interconnecting neural networks penetrating into the nucleus of the tractus solitarius.\textsuperscript{12} The CTZ is stimulated by chemicals in cerebrospinal fluid and blood as well as vestibular and vagal afferents.\textsuperscript{1,5,10} It contains receptors for dopamine (D2), serotonin (5HT3), acetylcholine (ACH) and opioids (MU2).\textsuperscript{5}

(ii) The ‘vomiting centre (VC)’ is situated in the medulla oblongata and has a blood–brain barrier.\textsuperscript{5,10} The VC, again a diffuse interconnecting neural network rather than a distinct anatomical structure, receives afferent input from the CTZ; the glossopharyngeal and splanchnic nerves; cerebral cortex; thalamus; hypothalamus; and, the vagus nerve through the stimulation of stretch of mechanoreceptors and activation of 5HT3 receptors in the gastrointestinal (GI) tract.\textsuperscript{1}

Fig. 1 The emetogenic pathway.\textsuperscript{1,7,9,10,13}
The end result of the above pathways is the vomiting reflex, which results in peristalsis of the upper GI tract, relaxation of the pylorus and oesophagus and contraction of the intercostal muscles, diaphragm and abdominal wall culminating in forced expulsion of gastric contents through the mouth past a closed glottis. It is postulated that stimuli insufficient to trigger vomiting may nevertheless produce nausea through the same pathway.1

At least 17 potential neurotransmitters or receptors have been identified in the CTZ and nucleus of the tractus solitarii.8,13 Numerous receptors have been identified at the CTZ and VC and many more may exist (Fig. 1). Furthermore, there is some evidence that the efficacy of an anti-emetic drug is directly related to its binding affinity for a specific receptor.14,15

There are now five known dopamine receptors (D1–D5); historically only D2 receptors were associated with the emetogenic pathway (antagonized by drugs such as haloperidol and metoclopramide) but D3 receptors are also now felt to be involved on the basis of animal studies.12

There are several groups of serotonin receptors of which 5HT3 has had the most interest since metoclopramide was found to be a weak 5HT3 receptor antagonist. Selective 5HT3 receptor antagonists were subsequently developed with ondansetron being one of the first drugs in this category.8,12

Other important receptors involved in the emetogenic pathway include histamine, ACH, endorphins, gamma-aminobutyric acid and cannabinoids.12 In contrast to other anti-emetics, cannabinoids appear to exert their effect by agonism at the cannabinoid (CB1) receptor.12

The above pathophysiological process forms the basis of most current guidelines: choice of anti-emetic is based on a clinical assessment of which component of the emetogenic pathway is being triggered, which receptors are involved and selecting an anti-emetic drug which therefore blocks those specific receptors (Table 1 and Fig. 1).1,4

Clinical application

On the above basis, current recommendations advocate a structured approach to choosing an anti-emetic in clinical practice.1,3,4,7–11,13

(i) Clinical assessment to ascertain the most likely cause of the symptoms (history, examination and appropriate investigations).

(ii) Identify the pathway by which each cause triggers the emetogenic pathway and vomiting reflex.

(iii) Treat any reversible cause, e.g. hypercalcaemia.
(iv) Identify the likely neurotransmitter receptor(s) involved in each pathway.

(v) Choose an anti-emetic that antagonizes the receptor(s) identified.

(vi) Give each anti-emetic by a route that ensures absorption (therefore unlikely to be oral in the frequently vomiting patient).

(vii) Give regularly, titrate the dose and reassess the patients symptoms.

(viii) Use non-pharmacological measures in combination with the selected pharmacological agents.

Common mechanisms in advanced cancer are delayed gastric emptying (prevalence of 35–44% in case series\(^3,16\)), chemical (prevalence of 30–33% in case series\(^3,16\)) and gastrointestinal causes such as bowel obstruction and constipation (prevalence of 31–32% in case series\(^3,16\)).

Clearly the effectiveness of aetiology-based guidelines depends on the ability to identify the underlying cause of the nausea/vomiting. It is suggested that this can be done clinically in 90% of cases.\(^4,16,17\) This figure can obviously only be an estimate as there is no gold standard diagnostic test for nausea–vomiting aetiology against which it can be tested. Furthermore, many patients (up to 25% in some studies) may have multiple causes.\(^3,16,18\)
Specific anti-emetics

Metoclopramide
Metoclopramide is a pro-kinetic anti-emetic (through agonism of 5HT4 receptors, antagonism of peripheral D2 receptors and possible antagonism of 5HT3 receptors) and therefore useful in nausea and vomiting related to gastric stasis. There are a few small placebo-controlled trials to support its efficacy. Pro-kinetic agents which act through 5HT4 receptors require ACH as a mediator at the myenteric plexus and so are, in theory, antagonized by anticholingeric medication (cyclizine may potentially therefore antagonize the pro-kinetic effect of metoclopramide). Domperidone is an alternative pro-kinetic to metoclopramide: it does not cross the blood-brain barrier and extrapyramidal side effects are therefore less likely.

Haloperidol
Haloperidol is an anti-emetic principally acting in the area postrema. It is a very potent D2 antagonist. It is widely used in palliative care, usually in the context of chemical causes of nausea and vomiting. A systematic review of its efficacy in the management of nausea and vomiting found that evidence of use is limited to case reports and case series with no controlled studies. Consensus-based recommendations advocate use in chemical or metabolic causes of nausea and vomiting.

Cyclizine
Cyclizine is classified as an H1-antihistaminic anticholinergic anti-emetic and principally acts by decreasing excitability of the inner ear labyrinth and blocking conduction in the vestibular–cerebellar pathways as well as acting directly at the vomiting centre in the brainstem. It is particularly advocated for nausea and vomiting where the underlying aetiology is felt to be increased intracranial pressure, motion sickness, pharyngeal stimulation or mechanical bowel obstruction. Current recommendations for use are largely based on ‘consensus’ (based on clinical experience). As mentioned above, pro-kinetic agents such as metoclopramide are potentially antagonized by anticholinergic medication such as cyclizine and should not in theory be used together.

Levomepromazine
Levomepromazine is a phenothiazine which antagonizes 5HT2, histamine, alpha-adrenergic receptors, D2 and muscarinic cholinergic
receptors. It is a broad-spectrum anti-emetic often used where first-line options have failed, particularly for nausea and vomiting of multiple or indeterminate cause. There are no randomized controlled trials to support its use in this context but there is some evidence from open label studies. Typical starting doses are 6.25 mg once daily. Drowsiness can be the main dose limiting side effect.

**Steroids**

Steroids are used as a prophylactic anti-emetic for chemotherapy and may have a wider adjuvant role in the management of nausea and vomiting. In the context of chemotherapy, studies have demonstrated that dexamethasone improves the effect of other anti-emetics (metoclopramide and more recently 5HT3 and NK1 receptor antagonists) in preventing chemotherapy-induced nausea and vomiting. It has also been shown to have a beneficial effect over placebo when used alone in this context. Dexamethasone (and possibly other corticosteroids) possibly act by reducing the permeability of the area postrema (where the chemoreceptor trigger zone is located) and the blood–brain barrier to emetogenic substances. Alternatively, its action may also relate to depleting the inhibitory amine gamma-aminobutyric acid. In symptomatic bowel obstruction there is some evidence that corticosteroids (e.g. 6–16 mg daily) may help resolve the obstruction with a number needed to treat of six (but confidence interval 3 to infinity). There is some anecdotal evidence of benefit in nausea due to other causes in terminal cancer (e.g. liver metastases). Dexamethasone has a half-life of up to 36 h which allows once-daily dosing.

**Benzodiazepines**

Anticipatory nausea and vomiting can be a learned response, e.g. following previous chemotherapy, but can also occur without prior specific experiences depending on patient emotional distress and expectations of the patient. Benzodiazepines have been documented to help in adult patients in combination with psychological techniques.

**5HT3 receptor antagonists**

5HT3 receptor antagonists, e.g. ondansetron, granisetron, tropisetron, dolasetron and palonosetron. 5HT3 receptors are implicated in the emetogenic pathway in relation to massive release of 5HT from enterochromaffin cells in the bowel wall, immediately following...
chemotherapy for example (and block the amplifying effect of 5HT on
the vagal nerve). Serotonin antagonists appear to exert their
anti-emetic effect via 5HT3 receptors both peripherally (enterochro-
maffin cells of the enteric nervous system) and centrally (nucleus
tractus solitaries and CTZ). There is good evidence of efficacy in redu-
cing acute vomiting in patients receiving chemotherapy compared with
metoclopramide-based regimes (particularly cisplatin-based chemother-
apy). Previously there has been limited use in palliative care practice
outside the context of chemotherapy-related nausea and vomiting and
concern about side effects, particularly constipation. There is some
argument, and a small amount of evidence, that these agents may be at
least as effective, or possibly even more effective, than anti-emetics tra-
titionally used. Current consensus guidelines advocates use for
chemical causes of nausea and vomiting refractory to haloperidol and
levomepromazine or when clinically it is felt that the cause of the
symptoms may relate to massive release of 5HT/serotonin from enterochro-
maffin cells, e.g. bowel obstruction and renal failure, as well as the
more recognized indications related to chemotherapy and
radiotherapy.

Olanzapine

Olanzapine is an atypical antipsychotic agent which blocks multiple
receptors including dopaminergic (D1–D4), serotonergic (5HT2,
5HT3), histaminic (H1) and muscarinic. This mode of action at
multiple receptors has therefore led to its experimental use as a second-
line anti-emetic in patients with refractory nausea. Small uncon-
trolled studies have shown efficacy in this context.

Substance P antagonists (NK1 receptor antagonists)

Substance P is a neuropeptide found in the gut and central nervous
system and may induce nausea by binding the specific neuroreceptor
neurokinin1 (NK1). Several NK1 receptor antagonists have been
developed in the context of chemotherapy-induced nausea and
vomiting and post-operative nausea and vomiting. Aprepitant
does not appear to be superior to ondansetron or granisetron in the
context of chemotherapy-induced vomiting (and to a lesser extent
nausea) but may increase their efficacy when used together with
dexamethasone.
Cannabinoids

Initially reports of a lower incidence of chemotherapy-induced nausea and vomiting amongst marijuana smokers led to exploration of cannabinoids in the treatment of nausea and vomiting. A brainstem cannabinoid receptor has now been identified but as some of the anti-emetic effects of synthetic cannabinoids are reversed by naloxone part of their action may be at the opioid mu receptor. A systematic review found that the cannabinoids oral nabilone, oral dronabinol and intramuscular levonantradol were more effective in reducing nausea and vomiting in patients receiving chemotherapy than prochlorperazine, metoclopramide, chlorpromazine, haloperidol, domperidone and alizapride. They were however also associated with significant greater side effects such as sedation, euphoria, dizziness, depression, hallucinations and paranoia and a significantly higher patient withdrawal rate from studies because of adverse effects. As yet cannabinoids are not widely used in this context in clinical practice, particularly as they often appear to be associated with a high burden of side effects.

Non-pharmacological strategies

Non-pharmacological strategies are very important in the overall management of the patient. Examples include avoiding food with strong tastes and smells; small but frequent meals; control of malodour from wounds or ulcers, behavioural approaches (e.g. distraction, relaxation) and acupuncture/acupressure. There are positive Cochrane reviews for acupuncture in the prevention of post-operative nausea and vomiting and chemotherapy-induced nausea.

Evidence base

A previous systematic review of the efficacy of anti-emetics in advanced cancer found 21 appropriate published studies, which included two systematic reviews, seven randomized controlled trials and 12 uncontrolled studies. A more recent systematic review of nausea and vomiting in people with cancer and other chronic diseases found nine studies that met the inclusion criteria. Difficulties encountered in the quality of these studies included small sample sizes; high attrition rates; difficulty controlling for confounding variables (patients with ‘advanced cancer’ are a very heterogeneous population); and, differing outcome measures. These problems in methodology are common in studies in palliative care.
Evidence for individual anti-emetics is weak or non-existent. However, little or no evidence does not mean they are ineffective: ‘absence of evidence is not evidence of absence’. There are some small placebo-controlled trials for some anti-emetics such as metoclopramide. A systematic review of the efficacy of haloperidol was unable to find enough studies of sufficient quality to draw any specific conclusions but it is advocated by consensus-based guidelines. There is however a greater evidence base for treatment-related causes of nausea and vomiting (radiotherapy and chemotherapy). The latter seems to be an area that has attracted more interest from the pharmaceutical industry and hence drug development (such as the 5HT3 antagonists).

Whilst the above aetiology-based approach to treating nausea and vomiting is widely endorsed in palliative care guidelines it should be noted that there is limited evidence to support the recommendations (through a paucity of evidence rather than negative studies). In practice it may sometimes be difficult to clinically ascertain the specific emetogenic pathway and therefore receptors involved.

The few studies and retrospective audits that have been conducted have shown generally favourable outcomes through use of the above approach with improvement in nausea in 56–82% of patients and vomiting in 84–93%. These studies have largely been uncontrolled, and the few randomized controlled studies that have been performed have shown lower response rates. Of note, similar response rates have been found when an ‘empirical’ drug selection method has been used. There has been no direct comparison between the two approaches.

Conclusion

The aetiological-based approach to choice of anti-emetic is a useful overall framework and remains the recommended practice in most current guidelines. As with many areas of palliative care, the lack of evidence for current practice is due to an absence of evidence rather than evidence of absence (i.e. lack of robust clinical studies rather than a collection of negative ones).

However, considering the multifactorial nature of nausea and vomiting in many patients with advanced cancer; the multidimensional aspects to nausea and vomiting (with anxiety and other psychological factors playing an important role); and, the fact that many anti-emetic drugs are known to affect multiple receptors, it is important to think outside a mono-mechanistic treatment approach when facing a patient with nausea and vomiting.
Future research in this area should include randomized controlled trials of the empirical versus aetiology-based approaches, as well as direct comparisons of the newer anti-emetic agents with those historically used in a wider context than trials of chemotherapy-induced emesis alone. On-going basic science research to enhance our understanding of the neurophysiology of the emetogenic pathway is also fundamental to identify new potential mechanisms of anti-emetic drug action.

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