Nausea and vomiting in advanced cancer

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A B S T R A C T

Nausea and vomiting are very common symptoms in cancer both treatment and non-treatment related. Many complications of advanced cancer such as gastroparesis, bowel and outlet obstructions, and brain tumors may have nausea and vomiting or either symptom alone. In a non-obstructed situation, nausea may be more difficult to manage and is more objectionable to patients. There is little research on management of these symptoms except the literature on chemotherapy induced nausea where guidelines exist. This article will review the etiologies of nausea and vomiting in advanced cancer and the medications which have been used to treat them. An etiology based protocol to approach the symptom is outlined.

1. Introduction

Nausea is a common complaint in advanced cancer and the effect on quality of life can be severe (Harris, 2010; Dunlop, 1989). 20–30% of people with advanced cancer suffer from nausea −70% in the last week of life (Conill et al., 1997). Studies have shown that treatment strategies can be effective but many patients continue to suffer unnecessarily (Stephenson and Davies, 2006; Davis and Hallerberg, 2010).

The National Cancer Institute defines nausea as a disorder characterized by a queasy sensation and/or the urge to vomit (National Cancer Institute, 2010). Vomiting is characterized by the reflexive act of ejecting the stomach contents through the mouth (National Cancer Institute, 2010). Retching resembles vomiting, but without stomach expulsion.

Some clinicians use a therapeutic strategy based on the likely cause and neurotransmitters involved (Bentley and Boyd, 2001; Lichter, 1993; Stephenson and Davies, 2006), while others base management on single drug trials (Bruera et al., 1996; Pereira and Bruera, 1996; Skinner and Skinner, 1999). To date, there are no trials comparing these two strategies.

Chemotherapy related nausea and vomiting is beyond the scope of this article. We will review the etiologies of nausea and vomiting in advanced cancer and suggest treatment strategies.

2. Etiology

In the etiologic approach, it is important to understand the neurotransmitters involved (Carpenter, 1990) in nausea to select the correct drug class. The chemoreceptor trigger zone (CTZ) is on the floor of the fourth ventricle. Significantly, it is outside the blood brain barrier and vulnerable to metabolic and chemical triggers. It contains various receptors: acetylcholine, dopamine, serotonin, cannabinoid and opioid (Cameron, 1990; Davis and Walsh, 2000). In contrast, the vomiting center is within the blood brain barrier and the medulla oblongata. It has acetylcholine, dopamine, gamma amino butyric acid (GABA) and serotonin receptors (Davis and Walsh, 2000). It also receives afferent neural fibers from the CTZ, the glossopharyngeal and splanchnic and vagal nerves. Within the GI tract there are dopamine receptors which affect gastric motility. There are also stretch mechanoreceptors which signal distention and organomegaly through the vagus nerve (Harris, 2010).

To improve the treatment, efforts have been made to identify etiology based guidelines (Bentley and Boyd, 2001; Glare et al., 2004; Lichter, 1993; Stephenson and Davies, 2006). The rationale is that by identifying the mechanism, treatments can be individualized. In most, a primary etiology can be identified (Bentley and Boyd, 2001). However, the multifactorial nature of nausea in advanced cancer had led others to advocate a systematic protocol to be used after reversible causes have been excluded (Gupta et al., 2013).

2.1. Medications

Of those with a reversible cause for nausea and vomiting 51% were drug related and of these 83% were due to opiates (Bentley and Boyd, 2001). This is related to multiple factors including gastroparesis, CTZ stimulation and sensitization of the labyrinth (Laugsand et al., 2011). Opioid rotation or dose reduction is effective in many to reduce symptom burden. Numerous other drugs commonly prescribed to cancer patients may cause nausea and should be stopped if possible. Drug induced nausea and vomiting is mediated through the chemoreceptor trigger zone through 5-HT_3 and dopaminergic receptors.

2.2. Central nervous system causes

2.2.1. Elevated intracranial pressure (ICP)

ICP causes nausea through mechanisms not clearly understood, but perhaps to pressure transmitted through the 4th ventricle to the vagal ganglion. Typically, in slowly progressive tumors nausea is less common; sudden occlusion of the collecting system may cause acute headache and nausea (Alomar, 2010). Both primary and metastatic lesions can elevate ICP. Tumors of the brainstem may also cause nausea from direct stimulation of the nausea and vomiting centers. Those with symptoms from leptomeningeal disease are less responsive to drug therapy and may benefit from CSF drainage.

2.2.2. Vestibular

The vestibular apparatus controls the sensation of rotation, and can trigger nausea. Tumors affecting this area can cause both nausea and vertigo (Abraham and Fowler, 2009). The vestibular system acts through cholinergic muscarinic receptors on the vomiting center provoking nausea and vomiting (Takeda et al., 1993).

2.2.3. Emotional

Patients can experience anticipatory nausea prior to events like chemotherapy (Roscoe et al., 2011) or procedures due to anxiety. Anxiety itself can cause nausea as can depression or pain (American Gastroenterological Association, 2001). These cortical functions cause nausea through GABA receptors.

2.3. Gastrointestinal causes

2.3.1. Motility

Impaired gastric motility can be caused by medications (including opiates, acid suppressing medications and tricyclic antidepressants) and autonomic dysfunction. Peristalsis may also be impaired by direct tumor invasion of the bowel wall. Organomegaly can cause nausea through stretched visceral capsules like hepatomegaly which causes vagal stimulation and in turn delayed gastric emptying (Abraham and Fowler, 2009).

2.3.2. Constipation

Constipation can lead to a sense of fullness and perhaps nausea (Larkin et al., 2008). As it is generally easily reversible it should be ruled out in all cases.

2.3.3. Obstruction

Malignant bowel obstruction occurs in 3–15% of cancer patients (Tuca et al., 2012). It is more common in ovarian (20–50%) and

colon cancer (10–29%). Obstruction can be functional or mechanical from direct tumor effects from peritoneal metastases or adhesions. Bowel obstruction can be complete or partial. Gastric outlet obstruction causes early, occasionally projectile vomiting after eating; on exam you may find a succession splash. Partial bowel obstruction may present with a colicky abdominal pain and continued bowel movements whereas in complete bowel obstruction most do not have bowel movements (Dolan, 2011; Tuca et al. 2012).

2.4. Metabolic causes

In advanced cancer, multiple organ systems may fail leading to metabolic causes of nausea. Uremia can cause persistent nausea and anorexia (Friend and Cummins, 1954). Hypercalcemia typically causes nausea and constipation as presenting symptoms. These are mediated through the CTZ. Other metabolic causes of nausea include hyponatremia, hyperthyroidism, acidosis and adrenal disorders (Abraham and Fowler, 2009).

3. Treatment

3.1. Non pharmacological methods

Limited data suggests a role for alternative medicines for symptomatic relief. Ginger root (Lee and Oh, 2013) and peppermint oil (Tayarani-Najaran et al., 2013) may be effective for some. Acupuncture was effective in several studies (Garcia and McQuade, 2013).

3.2. Procedures

When obstructions cannot be released, or where the obstruction is functional, decompression using a nasogastric tube or preferably a venting percutaneous endoscopic gastrostomy tube (PEG) can be performed. These were found to be effective in managing vomiting in up to 84% of patients with malignant bowel obstruction from ovarian cancer (Campagnutta et al., 1996). Stents have been used to resolve obstructions of the gastric outlet or lower bowel (Çaglar and Dobrucali, 2013; Jung et al., 2010). In selected patients surgical resection of the obstructing lesion or diverting ostomies may be effective in resolving the symptoms.

3.3. Medications

3.3.1. Serotonin antagonists

The 5-HT_3 receptor is a subtype of serotonin receptor in the vagus nerve, brain and gut enterochromaffin cells. Serotonin is produced in the small bowel in response to chemotherapy so these medications are highly effective in this setting (Schwartzberg et al., 2011). They are also indicated in radiation induced nausea (Urba, 2007). There is no evidence they help as single agents in opioid induced nausea or motion sickness (Hardy et al., 2002a, 2002b). Available agents include dolasetron, granisetron, ondansetron, palonosetron and tropisetron (not available in the United States). A randomized trial of tropisetron, metoclopromide and chlorpromazine in various combinations in advanced cancer found improved control with tropisetron (Mystakidou et al., 1998). While generally well tolerated they can cause constipation which could then lead to nausea.

3.3.2. Dopamine antagonists

Phenothiazines like chlorpromazine, prochlorperazine (Homberger and Smithy 1957a, 1957b) and levomepromazine (Skinner and Skinner, 1999) are effective antiemetics in many non-cancer settings but have also been used in malignancy. They work on dopamine receptors in the CTZ and the periphery. Use may be limited by side effects – particularly anticholinergic effects of chlorpromazine and extra pyramidal actions of prochlorperazine.

3.3.3. Haloperidol

Haloperidol is a butyrophenone neuroleptic discovered while trying to improve pethidine. It acts at D_2 receptors in the CTZ and has been used in various settings with responses (Hardy et al., 2010). Concerns about pro-arrhythmic effects have limited intravenous use although this may be less relevant in advanced disease. There are no randomized studies of haloperidol in nausea and vomiting (Perkins and Dorman, 2009). A recent study of nausea unrelated to chemotherapy in 42 cancer patients treated with oral or subcutaneous haloperidol showed an overall response rate of 74% in those available for analysis at day 5 (Hardy et al., 2010). Typical starting doses for nausea are 0.5 mg every 4–6 h IV or subcutaneously; it may also be given as a continuous infusion of 5–20 mg over 24 (Prommer, 2012). In addition to QTc prolongation, extrapyramidal effects are seen particularly at higher doses.

3.3.4. Metoclopramide

Metoclopramide is a competitive antagonist at dopaminergic (D_2) receptors and a weak competitive antagonist at 5-HT_3 receptors. It also increases gastric motility through acetylcholine mediator; promotility effects may be counteracted by anticholinergic medications (Davis and Walsh, 2000). It can be given orally (PO) (10 mg before meals and before bed), intravenous (IV) (10 mg q4–6 h as needed) or as a continuous infusion of 40–120 mg/24 h (Gupta et al., 2013). Extrapyramidal side effects (particularly tardive dyskinesia) increase with dose and duration of treatment. Studies have been inconsistent with one randomized trial showing no benefit (Hardy et al., 2002a, 2002b) compared to placebo and one showing benefit (Bruera et al., 2000).

3.3.5. Corticosteroids

Steroids are the drug of choice in nausea associated with raised intracranial pressure. The central antiemetogenic mechanism is unclear. Steroids are increasingly used combined with other antiemetics. Studies in chemotherapy induced nausea show the combination with 5-HT_3 agents to be more effective than 5-HT_3 agents alone (Gralla et al., 1999). They may be dosed at 8 am and noon to avoid sleep interference. Steroids may also be effective in malignant bowel obstruction in combination with metoclopromide (Laval et al., 2000; Mercadante et al., 2004).

3.3.6. Antihistamines

H1 receptors are in the vomiting center of the medulla, the vestibular nucleus and the CTZ and these agents may be effective in chemical and vestibular causes of nausea (Davis and Walsh, 2000). Available agents include cyclizine, diphenhydramine, hydroxyzine, meclizine, and promethazine. Cyclizine is not available in the United States. Side effects include drowsiness, urinary retention and confusion. Recently, concerns emerged about cyclizine as a drug of abuse due to a "high" with IV use (Bailey and Davies, 2008).

3.3.7. Antihcholinergics

Anti-cholinergics such as scopolamine can help vestibular sources of nausea and vomiting. In a recent case series of three advanced cancer patients nausea and vomiting related to motion were effectively treated with scopolamine (LeGrand and Walsh, 2010). It has also been found effective in the multi-drug management of bowel obstruction (Davis and Hallerberg, 2010).

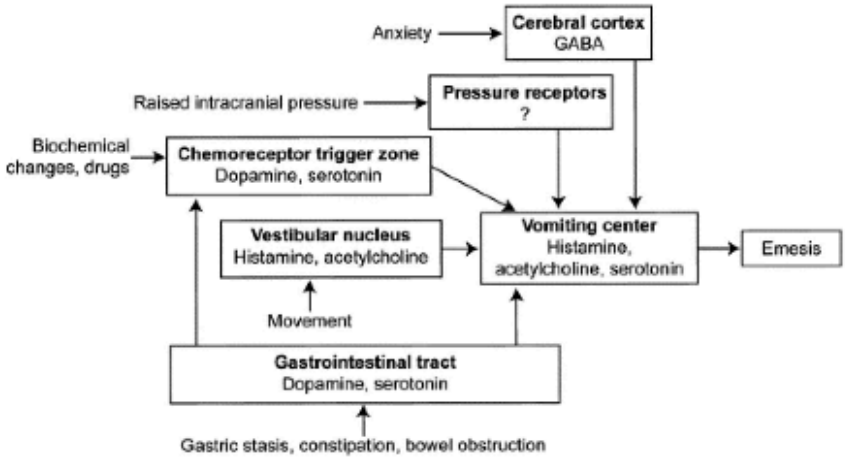

Fig. 1. Causes and proposed mechanisms of nausea and vomiting.

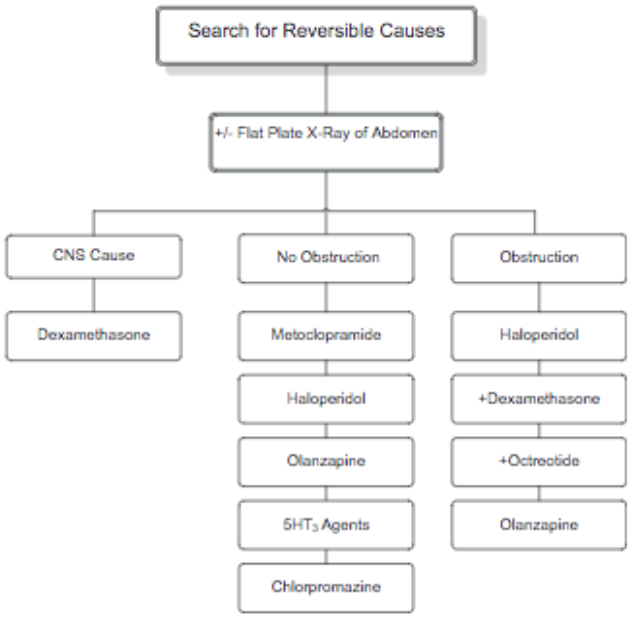

Fig. 2. The Cleveland Clinic Horvitz Center approach to managing nausea and vomiting in a palliative inpatient unit.

3.3.8. Atypical antipsychotics

Olanzapine is a thiobenzodiazepine, an atypical antipsychotic used in schizophrenia and mania. It has effects at multiple transmitters including 5-HT3, dopamine, histamine and catecholamines. Olanzapine is effective in chemotherapy induced nausea (Navari et al., 2004, 2012) and may be an effective anti-emetic in other causes (Dorman and Jefferson, 2006; Licup and Baumrucker, 2010; N Passik et al., 2002). Side effects include dry mouth, diabetes mellitus and dizziness. It may offer additional effects in palliative settings like increased appetite and weight gain (Navari and Brenner, 2008). Typical doses are 5–10 mg/day by mouth. Daily 5–10 mg has been used in chemotherapy induced delayed nausea and vomiting. It is available as an oral dissolving tablet helpful in those unable to swallow or given medications via PEG tube. There is an intramuscular form although a recent study has shown it may be safe to be given subcutaneously (Elsayem et al., 2010).

3.3.9. Octreotide

Octreotide is a somatostatin analog which reduces gastric secretions through inhibition of vasoactive intestinal polypeptide activity. It may have a role in nausea in bowel obstruction (Mercadante et al., 2000).

3.3.10. Cannabinoids

Although the cannabis plant contains multiple compounds, dronabinol and nabilone have been synthetically produced and shown to have antiemetic properties. A study of nabilone in 112 cancer patients (Maida et al., 2008) showed that patients treated with nabilone in combination with other agents had significantly lower Edmonton Symptom Assessment Scores (ESAS) scores for nausea. Both agents have been approved for chemotherapy induced nausea unresponsive to conventional antiemetics (Todaro, 2012) but their role in non-chemotherapy induced nausea is less well established.

4. Therapeutic protocol

An assessment of etiology-based guidelines for nausea and vomiting in advanced cancer (Stephenson and Davies, 2006) showed that at the end of one week of 32 patients assessed only 12 had residual nausea and of these 9 described it as slight (4). Another study (Bentley and Boyd, 2001) showed treatment on the clinical presentation can provide nausea relief (28 of 34) patients and vomiting relief (26 of 31) cases. An additional study (Lichter, 1993) looked at 100 episodes of nausea and vomiting treated by the proposed mechanism which provided relief in 93% (13). These studies show that nausea can be effectively controlled if the cause can be identified (Fig. 1).

A Horvitz Center protocol (Gupta et al., 2013) uses an etiologically based strategy for non-chemotherapy related nausea and vomiting in cancer. This first step is to find and resolve any reversible causes such as metabolic derangements or medications. If none is found and sypmtoms are suggestive then a flat plate of the abdomen is done to evaluate for obstruction or constipation. If constipation is present, it should be appropriately treated. If the patient has intracranial lesions then corticosteroids are the first line medication. Metoclopramide is used as a first line agent for other causes of nausea. It is used in combination with dexamethasone for partial bowel obstructions. If complete obstruction is found, haloperidol is used for nausea to avoid increasing colic symptoms from prokinetic activity. If there is no obstruction, a step wise approach from metoclopramide to haloperidol to

olanzapine is used. If these agents are ineffective chlorpromazine may be used but has a less favorable side effect profile. 5-HT_3 agents are rarely used (Fig. 2).

5. Conclusions

The management of nausea and vomiting in cancer is a complex challenge. The ability to give clear guidelines is limited by the lack of good quality studies in this population. More aggressive treatments with combinations of medications may be needed but there are not guidelines for combination use. We recommend a neurotransmitter receptor based approach, selecting the medication most likely to block the offending pathway.

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