Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol

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Nausea and vomiting are common and distressing symptoms in advanced cancer. Both are multifactorial and cause significant morbidity, nutritional failure, and reduced quality of life. Assessment includes a detailed history, physical examination and investigations for reversible causes. Assessment and management will be influenced by performance status, prognosis, and goals of care. Several drug classes are effective with some having the added benefit of multiple routes of administration. It is our institution's practice to recommend metoclopramide as the first drug with haloperidol as an alternative antiemetic. Dexamethasone should be used for patients with central nervous system metastases or bowel obstruction. If your patient is near death, empiric metoclopramide, haloperidol or chlorpromazine is used without further investigation. For patients with a better prognosis, we exclude reversible causes and use the same first-line antiemetics, metoclopramide and haloperidol. For those who do not respond to first-line single antiemetics, olanzapine is second line and ondansetron is third. Rarely do we use combination therapy or cannabinoids. Olanzapine as a single agent has a distinct advantage over antiemetic combinations. It improves compliance, reduces drug interactions and has several routes of administration. Antiemetics, anticholinergics, octreotide and dexamethasone are used in combination to treat bowel obstruction. In opiod-naïve patients, we prefer haloperidol, glycopyrrolate and an opioid as the first-line treatment and add or substitute octreotide and dexamethasone in those who do not respond. Non-pharmacologic interventions (mechanical stents and percutaneous endoscopic gastrostomy tubes) are used when nausea is refractory to medical management or for home-going management to relieve symptoms, reduce drug costs and rehospitalization.

Nausea and vomiting are common in advanced cancer and frequently unrelated to chemotherapy or radiation therapy. About 60% of cancer patients experience nausea and 30% vomiting.[1–3] Both are distressing, cause significant morbidity, and reduce quality of life. Nausea and vomiting contribute significantly to nutritional deterioration and increased pain intensity. Patients dread nausea more than pain while physicians focus more on emesis than nausea.

Pathophysiology/etiology

There are multiple causes of nausea and vomiting including gastrointestinal (GI), central nervous system, metabolic, medication, and psychiatric etiologies (Table 1). In a subset of patients, the cause remains unknown despite laboratory and radiologic investigations.[2]

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History

An important part of assessing nausea and vomiting is a detailed history (Table 2). The history provides clues as to causes which will direct drug management.

Nausea, an uncomfortable feeling of the need to vomit, is associated with autonomic symptoms (pallor, cold sweats, tachycardia, and diarrhea). Vomiting, forceful expulsion of gastric contents results from relaxation of the stomach, esophageal sphincter and pylorus with simultaneous contraction of the abdominal muscles, and retroperistalsis from the small bowel. Vomiting is a brainstem response, whereas nausea is a cerebral sensation. Vomiting pathways are well characterized (through animal studies) whereas little is known about the neuroanatomy of nausea. Retching, a rhythmic spasmodic movement of the diaphragm and abdominal muscles without gastric content expulsion, is frequently classified as vomit.[1]

TABLE 1 Pathophysiology of nausea and vomiting

Etiology	Causes
Gastrointestinal	Bowel Obstruction
	Gastroparesis
	Ulceration
	Constipation
	Peritoneal Carcinomatosis
	Typhlitis etc
Central Nervous System	Increased Intracranial Pressure
	Tumors
	Hydrocephalus
	Hemorrhage
	Vestibular
Metabolic	Hypercalcemia etc
Medication	
Psychiatric	Anxiety
	Depression etc

TABLE 2 Characteristics of nausea/vomiting

Characteristic	
Quality	Nausea, vomiting, retching, regurgitation
Duration	Over months or acutely
Character	Persistent or intermittent
Intensity	Low grade, able to eat or precludes eating
Nature of vomitus number of episodes	Large volume, fecal like
Associated symptoms	Pain, altered bowel habit, headache, colic
Aggravating factors	Sight/smell of food, worse after eating, moving
Relieving factors	Medications, over-the-counter remedies, alternative non-pharmacologic measures
Temporal factors	Relation of vomiting to nausea
Drug history	Opioid, nonsteroidal anti-inflammatory drugs
Recent anticancer treatment	Within the week, during radiation

Patterns of nausea and vomiting provide clues.[2] Nausea relieved by vomiting is likely to be generated by gastrointestinal pathology. Nausea and vomiting from bowel obstruction, gastric outlet obstruction or stasis is commonly accompanied by abdominal pain, bloating, colic, change in bowel habit, early satiety and/or stool consistency.[4] Radiation to the abdomen, which also occurs when one radiates the thoracic or lumbosacral spine, is emetogenic.[5] In advanced cancer, autonomic failure is common and may result in gastroparesis, nausea, vomiting and constipation.[6] Pseudo-obstruction occurs from paraneoplastic dysfunction of gastrointestinal smooth muscle or enteric neurons.[7] Toxic megacolon and typhlitis may also resemble a bowel obstruction.[8–9] It is important to recognize these last 2 disorders since management is distinctly different; and both disorders are associated with catastrophic complications.

Movement-related nausea is often associated with vestibular dysfunction, but also occurs with mesenteric traction from peritoneal metastases.[10] Early morning occipital headaches and/or recent onset of neurologic deficits, focal neurologic signs and altered cognition on physical examination suggests elevated intracranial pressure from a posterior fossa tumor or central nervous system metastases.[11–13] Brain imaging is indicated if one is suspicious of brain metastases, leptomeningeal carcinomatosis, strokes, subdural hematoma or intracerebral bleed. Persistent nausea unrelieved by vomiting occurs more often from drug or metabolic causes.[14] Patients with nausea and altered sensorium should also be suspected of having a metabolic abnormality such as hypercalcemia, hyponatremia, or uremia. Polyuria and polydipsia are common with diabetes insipidus, hypercalcemia or hyperglycemia.[3]

Adrenal insufficiency occurs when the metastases destroys both adrenal glands or from inadvertent discontinuation of corticosteroids or high-dose progesterone. Primary adrenal insufficiency presents with hyperkalemia, hyponatremia and hypotension. Nausea, occasional vomiting, abdominal pain or diarrhea that alternates with constipation, are common and correlate with severity of primary adrenal insufficiency. Vomiting and abdominal pain often herald adrenal crisis, and loss of fluid due to vomiting or diarrhea may precipitate the crisis.

Medications are reviewed with the initial history and should include over-the-counter medications. Complementary therapies, including herbs and vitamins, may or may not be volunteered and are commonly used in our population. Removing the offending drugs will avoid antiemetics and drug-drug interactions.[3] Patients should be screened for depression and anxiety as causes of psychogenic nausea.

Physical examination

The physical examination is commonly unremarkable; however, certain findings are helpful in uncovering the

underlying cause.[3] Candidiasis, mucosal ulceration, vesicular oral herpetic lesions are clues to treatable gastrointestinal causes of nausea and dysphagia. Pertinent abdominal findings are hepatomegaly, splenomegaly, and ascites. A succussion splash suggests impaired gastric emptying or gastric outlet obstruction.[15,16] The sign will be lost if the patient has recently vomited. A "Sister Mary Joseph" node, a palpable periumbilical node, may be found with advanced intra-abdominal carcinoma.[17] A rectal examination is important to assess for sphincter tone, fecal impaction and possible pelvic malignancy. A "Blumer's shelf", a rim of tumor felt during the rectal examination, is found with advanced abdominal or non-abdominal cancers with "drop" metastases or in pelvic cancers with local infiltration.[18] Bowel sounds may be helpful if they are hyperactive, high pitched or if borborygmi is heard suggesting small bowel or colonic obstruction.[18] Most upper abdominal obstructions produce greater symptoms than lower abdominal obstructions which, in our experience, seem to produce more signs than symptoms. Papilledema though rare, occurs with increased intracranial pressure.[3,19] Fever and confusion of rapid onset are signs of sepsis and metabolic abnormalities (liver failure, renal failure, and hypercalcemia).

Investigations

After a detailed history and physical examination, further investigations will depend on the goals of care, the patient's condition, and prognosis.

Laboratory. A metabolic panel which includes sodium, potassium, calcium, blood urea nitrogen, creatinine, and albumin screens for most metabolic abnormalities and is also helpful for assessing complications related to nausea and vomiting. Persistent vomiting will produce azotemia which is largely prerenal, and often associated with hyponatremia. Hyponatremia will need to be differentiated from the syndrome of inappropriate antidiuretic hormone (SIADH). Elevated blood urea nitrogen, hyperuricemia and low urinary sodium content is frequently observed.[20–22] SIADH is a diagnosis of exclusion but must fulfill the 5 diagnostic criteria: (1) hyponatremia with hypotonicity of plasma; (2) high urine osmolality relative to plasma osmolality; (3) increased renal sodium excretion; (4) absence of edema or evidence of volume depletion; and (5) normal renal and adrenal function. Measuring arginine vasopressin (AVP) levels is not particularly helpful in diagnosing SIADH.

Radiology. To screen for ileus, constipation or bowel obstruction, we recommend a plain x-ray of the abdomen (also called kidneys ureter and bladder x-ray [KUB]).[23] The abdominal plain x-ray is helpful in managing patients with constipation and nausea and vomiting. A computed tomography (CT) scan of the abdomen and pelvis provides additional diagnostic information (eg, the presence of peritoneal carcinomatosis, site or sites of obstruction, extent of intra-abdominal cancer, location of bowel obstruction, and whether or not palliative surgical intervention is an option). Magnetic resonance imaging (MRI) of the abdomen and ultrasounds are rarely done but could substitute for CT scans in those who cannot take oral contrast.[24] Gastrografin enemas are used to look for colonic obstruction and may also relieve intractable constipation.[25] We order an MRI of the brain in those whose history and physical examination suggests a central neurologic etiology (eg, intractable nausea, vomiting, and/or new neurological deficits). When a patient is terminally ill or imminently dying, decisions to intervene are complicated and need to be based on patient/family goals of care and the risks and benefits of the intervention.

Interventions

We routinely use single agents in a sequential fashion based upon response; and, on occasion, we use drug combinations for refractory nausea. Several drug classes are effective as antiemetics and offer some versatility, such as multiple routes of administration.[26]

Management

Any identifiable, reversible cause is treated first. All medications are reviewed and non-essential medications (digoxin, statins, iron, etc) are discontinued. Patients may also receive standard antiemetics such as metoclopramide or haloperidol to treat nausea and vomiting. Opioids are rotated if one appears to be the offending agent despite standard antiemetics. Suppositories, enemas and/or manual disimpaction are required in patients with fecal impaction. Bisacodyl suppositories have a dual action of mechanical and chemical colonic stimulation. Enemas are only used as rescue measures. Cotton seed enemas soften a hard stool and help relieve a hard impaction. Docusate and magnesia hydroxide is used in the initial management of constipation.[27] For individuals who failed to respond to standard laxatives, cotton seed oil enemas and methylnaltrexone is used. We infrequently use senna since it causes significant cramps. Hypercalcemia, common in multiple myeloma, squamous cancers and breast cancers is treated with hydration, bisphosphonates, and salmon calcitonin for the first 48 to 72 hours. Salmon calcitonin is used for individuals who are experiencing complications related to hypercalcemia including azotemia, confusion or sedation. If refractory, gallium nitrate has been used. Monthly bisphosphonates are ordered to prevent recur-

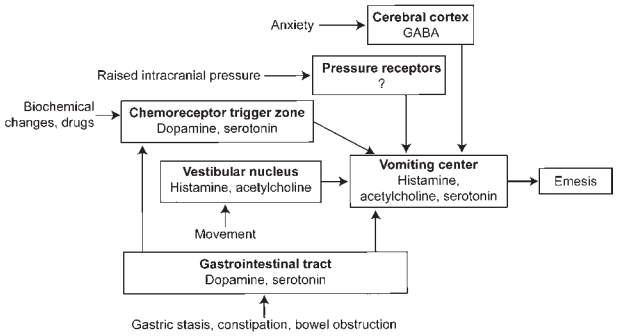

FIGURE 1 Causes and proposed mechanisms of nausea and vomiting.

rent hypercalcemia in those who have months to survive; but they are discontinued when a patient enters hospice, has rapidly advancing disease, is imminently dying, or whose goals are care and comfort.

Treatment of nausea and vomiting at the Cleveland Clinic, Harry R Horvitz Center for Palliative Medicine inpatient unit consists of metoclopramide or haloperidol as first-line treatment, olanzapine or chlorpromazine as second-line treatment, and ondansetron as third-line therapy. Little is known about pathways that generate nausea which tends to respond less well to antiemetics. Some approach the management of nausea and vomiting based upon "emetogenic receptor pathways" to select agents.[14,28] We have not used these empiric-based guidelines, but have chosen to use sequential single-agent therapy. There is little evidence that an antiemetic choice based upon emetogenic receptor pathways is any better than empiric single-agent therapy (Figure 1).[26]

Metoclopramide and haloperidol are antiemetics of choice as first-line agents (Figure 2). Metoclopramide has the greatest evidence for efficacy in advanced cancer.[26] Both dexamethasone and 5HT3 receptor antagonists (ie, ondansetron) are recommended for vomiting from abdominal and chest radiation. Abdominal paracentesis relieves nausea associated with ascites. Dexamethasone for cerebral edema is our treatment of choice for intracranial tumors. Promethazine, owing to its anticholinergic and antihistaminic action is helpful for vertigo and is occasionally used though scopolamine is our preferred choice.[29] Radiation therapy can palliate cranial metastasis and leptomeningeal cancer. Antiseizure medications such as gabapentin and carbamazepine may reduce nausea and vomiting from a variety of causes, including leptomeningeal disease with gabapentin being the preferred agent due to fewer drug interactions.[29–34] We have had only anecdotal experience with leptomeningeal metastases.

Bowel obstruction

Malignant bowel obstruction requires a highly individualized approach, tailored to the particular medical situation, prognosis, and goals of care.[35] Each symptom present may require a different approach and drug class.[35] As an example, metoclopramide has been effective in partial small bowel obstruction and ileus but may worsen nausea, vomiting, and the pain of a complete mechanical obstruction. Worsening colic and nausea and vomiting on metoclopramide may be an indication of an evolving complete bowel obstruction. Partial bowel obstruction and ileus may respond to parenteral metoclopramide. Many malignant obstructions are partial. Opioids relieve the continuous abdominal pain from peritoneal implants and retroperitoneal invasion but can aggravate colic by stimulating circular smooth muscles, increasing segmental contractions.[36] Opioid-sparing adjuvant drugs (ie, ketorolac or corticosteroids) may improve colic, lessen continuous pain, and prevent a partial obstruction from becoming complete.[37] Nausea and vomiting from bowel obstruction frequently requires both antisecretory and anticholinergic drugs (octreotide and glycopyrrolate) which reduce GI secretions and distention as well as colic.[38–39] In addition, a low-residue diet often called a gastrointestinal soft diet should be used to prevent a complete bowel obstruction.[40] The combination of an anticholinergic plus octreotide reduces nausea and vomiting in those individuals who failed to respond to either agent alone.[41] Glycopyrrolate, morphine, octreotide and haloperidol are compatible in a solution and can be combined.[39] These agents can be administered intravenously (IV) or subcutaneously (SC), and hydration if needed can be given IV or by hypodermoclysis. Octreotide is well tolerated, reduces the need for a nasogastric tube insertion without resulting in severe xerostomia (unlike anticholinergics). Some patients prefer octreotide rather than an anticholinergic.[42] However, the high cost of octreotide limits its use in American hospices due to the Medicare capitation system of reimbursement; therefore, we use octreotide as a second-tier drug. Octreotide doses are 100 to 200 μg every 8 hours.[10] Total daily doses as high as 900 μg/day are reported.[42]

A partial small-bowel obstruction or ileus may respond to metoclopramide. Metoclopramide has a short half life. Doses are 10 mg before meals and at bedtime. We also give this parenterally either IV or SC starting with doses of 40–60 mg daily and titrating to 120 mg per day. Patients who have not responded to 120 mg per day are switched to haloperidol, chlorpromazine or olanzapine. Initial haloperidol doses are 1 mg twice a day and as needed every 4 hours by mouth. For those who require parenteral haloperidol, 5 mg is given IV or SC over 24

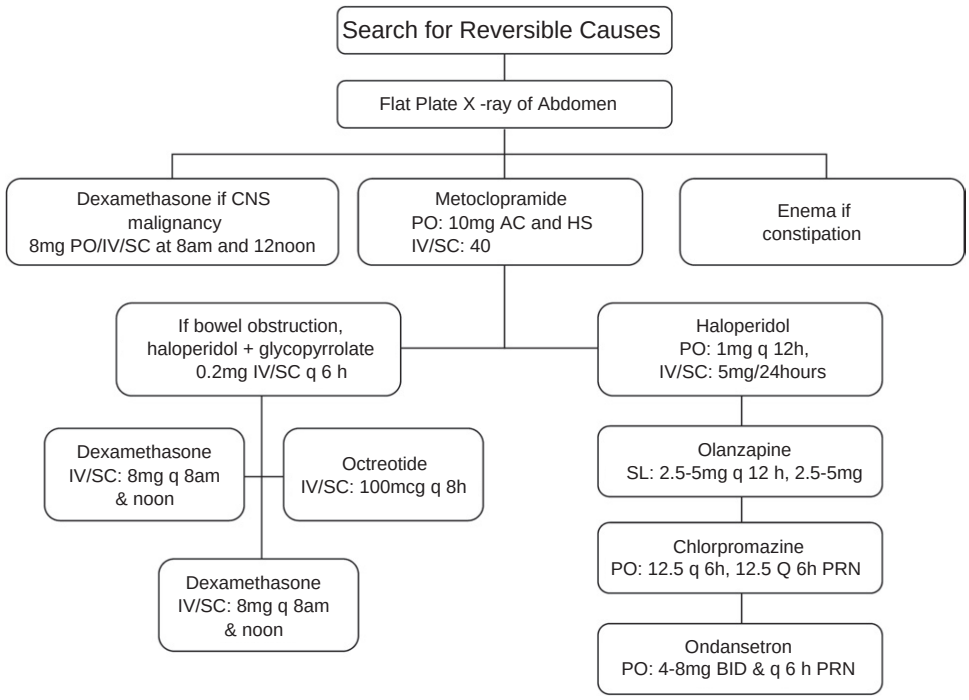

FIGURE 2 The cleveland clinic approach to managing nausea and vomiting in a palliative inpatient unit.

hours with a rescue dose of 1 mg every 4 hours as needed. There is a concern for the "black box" warning about prolonged repolarization (prolonged QTc interval) with haloperidol. We have not routinely obtained electrocardiograms since most of our patients are terminally ill with few options. Chlorpromazine doses are 12.5 mg IV every 4 hours as needed and titrated to response which can be as high as 100 mg every 4 hours. Sedation can be an issue with chlorpromazine. Olanzapine doses are 5 mg as a dissolvable disc at night and every 6 hours as needed. Twice-daily doses as high as 10 mg have been used in chemotherapy-related nausea and vomiting. Olanzapine has been reported to be well absorbed SC; hence, this is the route that we prefer for those who are unable to take it by mouth.[43] Ondansetron is a third-line agent. Dosing for ondansetron is 4 to 8 mg oral twice a day and 4 mg every 6 hours as needed. Dexamethasone 8 mg oral/IV/SC at 8 am and noon is our standard dosing schedule. We rarely use a cannabinoid.[44]

Nonpharmacologic intervention

In our experience, when a patient's nausea and vomiting persists despite standard antiemetics, the patient should be evaluated for CNS metastases, achalasia from tumor infiltration in the lower esophageal sphincter, gastritis, linitis plastica, gastric ulcer or strictures. These causes for nausea and vomiting may respond to a botulin toxin injection, dilatation, a proton pump inhibitor, or stenting.[45] For patients with poor performance status, progressive disease, peritoneal carcinomatosis, life expectancy of days to weeks, or multiple levels of obstruction, a venting percutaneous endoscopic gastrostomy (PEG) tube is considered if maximum medical therapy is ineffective or if the patient is going home with hospice. Symptoms of malignant gastrointestinal obstruction that improve with a nasogastric tube predicts the benefits of a "venting" PEG tube. PEG tube drainage reduces drug costs and potential readmissions which is important in hospice.

Conclusion

Patterns of nausea and vomiting are helpful. Based on our experience, empiric single-drug therapy is as effective as antiemetic choices based on mechanism. Metoclopramide has the greatest evidence for benefit and hence is our first-line treatment in those who have not been on metoclopramide before. Haloperidol is also used particularly in the face of a complete bowel obstruction. Second-line agents used by our institution are the atypical antipsychotic, olanzapine, phenothiazine, or chlorpromazine. Antiemetic rotation, titration, antiemetic combinations with complementary receptor activities have low levels of evidence in managing refractory nausea. Nonpharmacologic approaches should be used depending on the clinical circumstance and patient prognosis.

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