Module: Nausea and Vomiting

Learning Objectives

Attitudes

- Reflect on past good and bad experiences managing nausea and vomiting
- Nausea is a common symptom reported by patients at the end of life. Nausea has a significant negative impact on quality of life

Knowledge

- Understand the role of the chemoreceptor trigger zone (CTZ)and the vomiting center in the mediation of nausea and vomiting.
- Describe three anatomic sites that send afferent input to the medullary vomiting center.
- Know at least two causes of nausea and vomiting from each of the following categories: gastrointestinal, central nervous system(CNS), drugs, metabolic, and psychological.
- Identify at least one drug, and understand its mechanism of action and relative cost from each of the following classes: a) dopamine antagonist, b)serotonin antagonist, c)glucocorticoid, d)benzodiazepine, e)cannabinoid, f)antihistamine, g)neurokinin-1 antagonist
- Understand the role of behavioral treatments for nausea.

Skills

- Demonstrate communication skills necessary to take a thorough history from a patient with nausea
- Construct a differential diagnosis for at least three patients with nausea
- Develop an initial treatment plan for at least three patients with nausea
- Demonstrate skill at treating nausea that is refractory to an initial treatment approach.
- Understand resources for managing nausea refractory to standard pharmacologic management
- Prescribe antiemetics in a cost-effective manner.

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Overview:

Nausea and vomiting are caused by the stimulation of one of the 4 pathways as outlined in the diagram below [Figure 1]. Each of these has a final common pathway that affects the vomiting center in the brainstem, with resultant nausea and vomiting. The chemoreceptor trigger zone is functionally outside the blood brain barrier and is exposed to toxins in the bloodstream and CSF that can trigger vomiting. The cerebral cortex contributes to nausea by the direct input from the 5 senses, as well as by anxiety, meningeal irritation, and increased intracranial pressure. The cortex supplies many afferents to the vomiting center. Peripheral pathways are triggered by mechanoreceptors and chemoreceptors in the GI tract, serosa, and viscera and are transmitted via the vagus and splanchnic nerves, sympathetic ganglia, and glossopharyngeal nerves. The vestibular system impacts the vomiting center via the vestibulocochlear nerve, with nausea being triggered by motion. (1,2)
Knowledge and familiarity with these pathways and the receptors that mediate these signals allow a receptor- or mechanism-based approach to the treatment of nausea. Common causes of nausea in the surgical patient include opioids, chemotherapy, malignant bowel obstruction, and the impaired GI motility associated with advanced cancer. These will be discussed individually, with reference to the mechanisms, receptors involved and usual medications for treatment.

Although the mainstay of treatment of nausea is medication-based, the nonpharmacological treatment of nausea can be quite helpful. Avoiding strong smells or other triggers, eating small, frequent meals, and limiting oral intake when symptoms are intense are helpful. Relaxation techniques have also been shown to be beneficial. Acupuncture and acupressure, in particular P6 stimulation (just above the wrist) have been helpful in the chemotherapy and postoperative setting. (3,4)

Opioid-induced nausea and vomiting is seen in up to 40% of patients with advanced cancer. The mechanism can be exacerbated by constipation, stimulation of the CTZ, gastroparesis, and sensitization of the labyrinth. The CTZ effects are mediated by central dopamine-2 (D2) receptors. Gastroparesis is mediated by peripheral D2 receptors. If possible, a dose reduction or rotation of opioid can often alleviate nausea while not compromising analgesia. Beginning treatment with antiemetics that target the D-2 receptor, such as haloperidol, droperidol and metoclopramide, is a reasonable approach in many patients.

Chemotherapy-induced nausea and vomiting arises from several mechanisms. Chemotherapy causes direct stimulation of the CTZ via the 5-HT-3 and neurokinin1 receptors. Damage to the GI mucosa by chemotherapy causes the release of neurotransmitters, including 5HT-3, which is transmitted via vagal and splanchnic nerves to stimulate both the CTZ and the VC. 5-HT-3 antagonist Ondansetron and the atypical antipsychotic Olanzapine, which is a weak inhibitor of all the nausea receptors, are often effective. Neurohormonal changes related to chemotherapy infusion alter arginine vasopressin and prostaglandin levels. Anxiety can trigger symptoms of nausea via central pathways, and explains the phenomenon of anticipatory nausea. This entity is usually well treated by anxiolytics such as the benzodiazepine lorazepam. (1,5)

The nausea associated with ***malignant bowel obstruction*** is a result of the stimulation of peripheral pathways by bowel wall distension, and the colicky pain associated with the accumulation of food and fluid proximal to the obstruction. The CTZ can also be triggered by inflammatory mediators and bacterial toxins. The operative and interventional management of malignant bowel obstruction is discussed elsewhere. Nasogastric decompression can help attenuate symptoms. The basics of management begin with treating the associated pain with analgesics. Utilizing antisecretory agents, such as hyoscyamine or octreotide can

decrease secretions, resulting in less distension and less peristalsis, with attendant decrease in pain. Using the receptor-based pharmacologic approach, Haloperidol, the most potent D-2 antagonist, is the mainstay of treatment. H1 blockade is efficacious for both the peripheral pathways as well as the vomiting center. Corticosteroids are utilized for their effect on tumor-associated inflammation. If antiemetic and antisecretory treatment are insufficient in controlling the nausea and emesis, venting gastrostomy can be considered. (6,7)

The impaired GI tract motility associated with advanced cancer, in particular gastroparesis and constipation, can result in autonomic dysfunction. Symptoms cer are triggered by activation of peripheral pathways due to stretch of the gut wall related to this decrease in motility. The etiology of the autonomic failure includes malnutrition and cachexia, chemotherapeutic and other drugs, radiation therapy, paraneoplastic syndromes, nerve invasion by tumor, and comorbid diseases such as diabetes mellitus. (1,2)

When traditional receptor-based antiemetic treatment is not helpful, other, centrally acting agents may be of benefit. Olanzapine, an atypical antipsychotic has weak affinity for the D-2, H-1, ACh, and serotonin receptors, and can have tremendous effect. Cannabinoids have been shown to improve symptoms in cancer patients, but have the side effects of hallucinations and confusion, among others. (1,8)

Key Points: Review

Vomiting Center: control center in medulla for coordinating the efferent output of vomiting motor sequence (vomiting reflex).

Sources of afferent input to the vomiting center:

- Chemoreceptor trigger zone (CTZ): entry point for emetogenic blood or cerebrospinal fluid-borne substances; located in the area postrema outside the blood brain barrier (morphine, hypercalcemia, uremia)
- Cerebral cortex: Limbic system (anxiety, anticipatory nausea)
- Visceral afferent: vagal stimulation, pharynx, GI tract (mechanoreceptors, chemoreceptors, responding to inflammation)
- Midbrain ICP receptors: increased ICP
- Vestibular system: neurotoxins, morphine, infections, tumor

Differential Diagnosis:

- Gastrointestinal: Mechanical obstruction, (constipation, intrinsic/extrinsic obstruction), dysmotility, (gastric and bowel stasis), squashed stomach syndrome (compression of stomach, usually by an enlarged liver), inflammation (GI infection, gastroesophageal reflux disease, gastritis, abdominal carcinomatosis, acute effect of abdominal radiation or chemotherapy.

- CNS: Elevated ICP, posterior fossa tumors/bleeding, infection, neoplastic meningitis

- Drugs: Opioids, chemotherapy, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, antibiotics, iron

- Metabolic: Hypercalcemia, liver failure, renal failure

- Psychological: anxiety, pain, conditioned response (anticipatory nausea/vomiting)

  i. Nausea via stimulation of CTZ

  ii. Nausea via gastric/gut slowing

  iii. Nausea via stimulation of vestibular system

  iv. Nausea via stimulation of gut chemoreceptors and vagal afferents

TREATMENT:

- Nondrug Therapy:

  i. Behavioral treatments: relaxation, guided imagery, distraction, music

  ii. Nasogastric drainage: indicated mainly for acute management of gastric stasis/obstruction or bowel obstruction refractory to conservative management

  iii. Percutaneous gastrostomy: Indicated for long-term decompression for gastric stasis/obstruction or bowel obstruction refractory to conservative management.

  iv. Fluid restriction: Patients with GI obstruction may benefit from restriction of oral fluids and/or discontinuing IV fluids to decrease GI fluid output and vagal stimulation

DRUG THERAPY:

- Certain disorders respond best to a drug from a specific class due to its mechanism of action:

  i. Movement-related nausea: Antihistamine

  ii. Anxiety/anticipatory nausea: Benzodiazepine

  iii. Tumor-related elevated ICP: Glucocorticoid

  iv. Gastric stasis: metoclopramide (indirectly causes acetylcholine release, which stimulates motility. This action is antagonized by drugs with anticholinergic properties such as promethazine or chlorpromazine

  v. Stimulation of CTZ (drugs, uremia): Dopamine or serotonin antagonist

  vi. Constipation: Laxative

Nausea.Model.pdf

Figure 1: Nausea Receptor Pathways and Treatment Options

Module: Nausea and Vomiting

Pre/Post Test

Questions

1. List three anatomic sites that send afferent input to the medullary vomiting center.

2. List four gastrointestinal causes of nausea.

3. List the most appropriate class of antiemetic drugs to use in the following conditions oral intake
   a. elevated intracranial pressure
   b. gastric stasis
   c. hypercalcemia
   d. middle ear infection

4. List one drug that can be used as a continuous infusion for refractory nausea.

Answers

1. Frontal cortex, CTZ, vagus nerve
2. Gastritis, bowel obstruction, ulcer, gastric stasis
3. a) steroid, b) promotility agent, c) dopamine antagonist, d) antihistamine
4. Metoclopramide or chlorpromazine

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Module: Nausea and Vomiting

Objectives

1. Review the assessment of nausea and vomiting
2. Develop a differential diagnosis for nausea and vomiting
3. Develop a patient management plan for nausea and vomiting

Teaching Points

1. Workup for suspected recurrent cancer must not supersede management of the patient's chief complaint/symptom management

2. The complaint of "nausea" may represent one of many different sensations, symptoms, or syndromes, including GI reflux, anorexia, labyrinthine dysfunction, regurgitation, bowel obstruction, medication effects, anxiety, etc. The assessment provided in the case is inadequate to determine exactly what the patient means by "nausea." Only through a more detailed assessment can a differential diagnosis be established.

3. The patient has constant nausea. If it is thought to be of gastrointestinal cause, around-the-clock antiemetics, at least for 24 hours, may be more appropriate than PRN orders. There should be better assessment and documentation of response after a PRN antiemetic is given to know if the prescribed medication is effective.

4. Prochlorperazine (Compazine) is a reasonable starting drug for nausea in a case in which a dopamine antagonist may be helpful (see diagram) or for nausea of unclear etiology. When this drug is not successful, reassessment is needed, and targeted drug therapy should be used whenever possible. Gastric compression and the associated dysmotility (squashed stomach syndrome due to an enlarged liver) is a possible cause. Early satiety with eating would be a strong hint in favor of dysmotility. Metoclopramide, a prokinetic, could be considered as an alternative drug in this case.

Case 1

Mrs. L is admitted to your service late one evening because of 4 days of nausea and poor po intake. She has a history of AJCC stage IIIA colon cancer at initial staging with no known interval metastases. Her physical examination is significant for mild pallor, dehydration, and a hard, enlarged, nodular liver. Plain

abdominal radiographs show a nonspecific bowel gas pattern and an enlarged liver. Surgical evaluation in the Emergency Department before admission ruled out an acute surgical abdomen.

You think that Mrs. L has metastatic colon cancer. IV fluids were begun, and computed tomography of the chest, abdomen and pelvis ordered. On rounds the next morning, Mrs.L says that she is still nauseated and that this feeling is constant. Admission orders include the following: prochlorperazine (Compazine), 10 mg po q 6 hrs PRN for nausea. Review of the nursing notes and MAR show that only one dose of prochlorperazine was given shortly after admission 12 hours ago and that there has been no recorded vomiting.

Questions

1. Describe a differential diagnosis for nausea in this patient.
2. Is this an appropriate initial treatment plan? If not, describe the changes that you would make.
3. If the nausea fails to respond to prochlorperazine, what would you do next?