PALLIATIVE PEARLS
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Nausea and Vomiting, Sources and Palliative Management
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PATIENT CASE

AN is a 67-year-old male admitted to hospice 2 weeks ago. He has a primary diagnosis of prostate cancer with probable bone metastases, no other medical conditions and no drug allergies. He lives at home with his wife.

Current medications include:

- MS Contin® 60 mg by mouth every 12 hours
- Morphine 20 mg/ml oral concentrate, 0.75 ml (15 mg) by mouth every 3 hours as needed
- Dexamethasone (Decadron®) 6 mg, 1 tablet by mouth at breakfast and lunch
- Senna; 2 tablets by mouth at bedtime
- Tamsulosin (Flomax®) 0.4 mg, 1 capsule by mouth daily
- Finasteride (Proscar®) 5 mg, 1 tablet by mouth daily

AN is experiencing new onset nausea and abdominal discomfort. The nausea is persistent, and his wife tells you he has vomited a few times. He has tried ginger ale and a bland diet; neither have been effective. Nausea is not associated with any smells, tastes, events or time of day. AN reports "regular" bowel movements every other day, reporting that he feels content and not full after eating. He is currently able to tolerate taking medications orally despite the nausea and vomiting.

AN does not appear dehydrated and drinks about 4 large glasses of water every day. During his assessment, AN states that he also has been unable to pass urine for the past day. The only recent change in medications were increases in his long-acting and short-acting morphine regimens 1 week ago. MS Contin was increased to "60mg every 12 hours" from "30 mg every 12 hours" and morphine breakthrough dose increased to 15 mg from 5 mg per dose with the same frequency, as needed. AN has a tolerable level of pain and averaging 1-2 breakthrough doses per day since the morphine regimens changed – this is an improvement in pain management.

NAUSEA AND VOMITING AT END OF LIFE

Nausea and vomiting (N/V) are common symptoms near the end of life, often occurring as a symptom cluster, that can significantly impact quality of life. Nausea is "the sensation of needing to vomit, of feeling 'queasy' or 'sick to your stomach'." Vomiting is "a protective reflex, which leads to the expulsion of gastric contents through the mouth" while retching differs and is described as "the strong, involuntary effort to vomit without expulsion of gastric contents, also called 'dry heaves'."[1]

There are numerous potential causes of nausea and vomiting in palliative care, often multifactorial in

nature, particularly in patients with cancer. They occur simultaneously or sequentially in any individual patient.[2] Left unmanaged, nausea and/or vomiting leads to complications such as dehydration, electrolyte disturbances, anorexia, weight loss, and emotional distress.[1]

MECHANISMS OF NAUSEA AND VOMITING – THE FOUR EMETIC PATHWAYS[1]

The area of the brainstem that processes signals from the four emetic pathways is called the **vomiting center**. Causes of nausea and vomiting (N/V) transmit signals to the vomiting center via one or more of the following pathways:

1. **Chemoreceptor Trigger Zone (CTZ)**
    - Stimulated by the following to cause N/V: Biochemical abnormalities (hypercalcemia, hyponatremia, hepatic failure, renal failure, uremia), sepsis, medications
    - Mediated by: Dopamine and serotonin

2. **Gastrointestinal Tract**
    - Stimulated by the following to cause N/V: Anything that irritates, obstructs, or slows down the gastrointestinal tract
    - Mediated by: Dopamine and serotonin

3. **Vestibular Tract**
    - Stimulated by the following to cause N/V: Motion sickness, vestibular tumor, inflammation (e.g. vestibular neuritis)
    - Mediated by: Histamine and acetylcholine

4. **Cerebral Cortex**
    - Stimulated by the following to cause N/V: Anxiety, unpleasant sights, smells, and tastes, elevated intracranial pressure, meningeal irritation, psychiatric disorders
    - Mediated by: Gamma-aminobutyric acid (GABA) and histamine

A helpful acronym that aids in recalling the multiple mechanisms of nausea and vomiting is **V.O.M.I.T.:**[2]

- **V**estibular
- **O**bstruction of bowel
- **M**otility - Drug dys**M**otility of the upper gut (delayed gastric emptying)
- **I**nfection, **I**nflammation, **I**rritation
- **T**oxins stimulating the chemoreceptor trigger zone (CTZ)

NONPHARMACOLOGIC MANAGEMENT[3]

- Dietary measures, where feasible
    - Avoid offending foods or odors
    - Eat bland foods
    - East small frequent meals, with low-fat, non-gas-forming foods

  - Experiment with sour foods: Lemons, pickles, hard sour candy, lemon sherbet
  - Eat cold food or those served at room temperature
  - Drink clear liquids and carbonated beverages
  - Avoid eating and drinking 1-2 hours after vomiting
- Ginger: Capsules, tablets, candy, tea
- Identify and reverse the underlying cause (e.g., discontinue medications)

PHARMACOLOGIC SELECTION BASED ON INDICATION & SUSPECTED MECHANISM[1]

Determine and block the relevant emetic pathway neurotransmitter(s) by use of one or more of the following:

Dopamine Receptor Antagonists

- **Drugs**: Prochlorperazine (Compazine®), promethazine (Phenergan®), haloperidol (Haldol®), chlorpromazine (Thorazine®), metoclopramide (Reglan®)
- **Indications**: Chemotherapy and toxin (CTZ, GI tract) associated nausea and vomiting
- **Mechanism**: Block emetic pathways originating from the GI tract and CTZ, antidopaminergic, direct prokinetic effect (metoclopramide)
- **Side effects**: Extrapyramidal side effects (EPS), sedation, hypotension
- **Cautions**: Avoid use of metoclopramide in complete bowel obstruction

Serotonin Receptor (5-HT_3) Antagonists

- **Drugs:** Ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®), palonosetron (Aloxi®)
- **Indications:** Chemotherapy and toxin (CTZ, GI tract) associated nausea and vomiting
- **Mechanism:** Block emetic pathways occurring through vagal stimulation, 5-HT_3 receptors in the GI tract and/or CTZ
- **Side effects:** Constipation, headache

Antihistamines/Anticholinergic/Antimuscarinic

- **Drugs:** Antihistamines – Diphenhydramine (Benadryl®), hydroxyzine (Atarax®), meclizine, doxepin
- **Indications:** Vestibular (motion), inner ear pathology, **adjuvant to other agents**
- **Mechanism:** Uncertain action at the vomiting center
- **Side effects:** Sedation, constipation, confusion, orthostatic hypotension, dry mouth

Anxiolytics/Benzodiazepines

- **Drugs:** Lorazepam (Ativan®), oxazepam (Serax®), diazepam (Valium®)
- **Indications:** Anxiety, PTSD post chemotherapy, **useful as an adjuvant**
- **Mechanism:** Works via the cerebral cortex pathway
- **Side effects:** Sedation, confusion, falls and fractures

Corticosteroids

- **Drugs:** Dexamethasone (Decadron®), methylprednisolone (Medrol®), prednisone
- **Indications:** Bone pain, appetite stimulation
- **Mechanism:** May relieve cancer-associated nausea through effects on reducing inflammatory mediators, tumor edema, pressure on GI tract, and reducing intracranial pressure from tumor mass. The exact mechanism in nausea and vomiting is unknown. **Often used as an adjuvant to other agents.**
- **Side effects:** Fluid retention, increased blood pressure, mood swings, weight gain, increased risk of infections, thinning bones (osteoporosis) and fractures

Cannabinoids

- **Drug:** Dronabinol (Marinol®)
- **Indications:** Nausea unresponsive to conventional treatment; may be used in combination with other antiemetic therapies
- **Mechanism:** Cannabinoid receptors are widespread in the central nervous system and the mechanism of action is unknown
- **Side effects:** Tachycardia, low blood pressure, blood shot eyes, muscle relaxation, slowed digestion, dizziness, depression, hallucinations, paranoia

TRANSDERMAL PLURONIC LECITHIN ORGANOGEL (PLO) GELS

PLO is a type of topical dosing form to provide a means of administering medications once the oral, rectal or parenteral routes can no longer be utilized or are no longer appropriate.[4,5]

Topical compounds in PLO are composed of the active drug(s) suspended in a vehicle consisting of water and two plant derivatives, pluronic acid and lecithin. In theory, these components work together to temporarily disorganize the outer most layer of the skin to enhance the absorption of the drug, but without causing skin damage.[6]

Topical compounds in PLO differ from other types of topical creams, gels or ointments in that they *generally* work systemically rather than locally. This means that when applied, medications incorporated in the gel should penetrate the skin, where they can be carried away by the bloodstream. However, there is evidence that many medications in PLO gel are not absorbed systemically and should be considered as last line therapy. In contrast, PLO gels for <u>local effect</u> work best when applied directly to the affected area (e.g., ketoprofen PLO, ketamine PLO) and are supported in the literature.[7-11]

Bottom line, the evidence base for systemic PLO's is quite weak and, in some instances, conflicting:

- Historically used based on anecdotal benefit
- Studies show no transdermal absorption
- No clinical benefits shown in studies evaluating symptoms or vomiting episodes vs. placebo
- Evidence doesn't support its use
- Alternative routes should be used

ASSESSMENT

Since AN's nausea is (1) new onset and (2) seems to coincide with the start of the opioids, (3) is generalized and not linked to any time or activity, (4) is not associated with constipation, anxiety, and fullness after eating, opioid-induced nausea and vomiting seems like the most probable cause in AN. Tolerance to opioid-induced nausea and vomiting occurs quickly in many patients.[3] When persistent however, medications are often needed to provide relief. When we suspect toxins, like opioids, are stimulating the CTZ, dopamine receptor antagonists, like prochlorperazine and haloperidol, and serotonin receptor antagonists, like ondansetron, should be considered.

Prochlorperazine is available in oral tablet and rectal suppository form and haloperidol in oral tablet and concentrated liquid, rectal suppository and injectable formulations. While appropriate for this situation, the comparative high cost of ondansetron products would not make it a second line agent unless cost is not a factor for the patient.

Opioid-induced urinary retention results in inhibition of the voiding reflex.[12] It is a common side effect though no preventative strategies have been established.[3] AN has acute urinary retention attributed to morphine and exacerbated by an increase in morphine dose.

RECOMMENDATIONS

- Prochlorperazine and haloperidol are drugs of choice and may be administered orally
- Ondansetron would also be effective but may be cost-prohibitive in comparison
- Attempt to decrease dose of scheduled morphine and titrate up on dexamethasone to create an opioid-sparing effect and relieve urinary retention[3]
- Straight urethral catherization is indicated if reduced morphine dose does not relieve urinary retention[3]

For additional information on this topic, please review these references:

Enclara Pharmacia's On Demand Educational Webinars, "Management of Opioid-induced Adverse Drug Events in Palliative Care" and "Gastrointestinal Complications in Hospice". Click here to log in.

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