

Nausea

Assessment & Management

R J Crossno, MD, CMD, FAAFP, FAAHPM

Disclosures

- Dr. Crossno discloses his employment as
 - Area Medical Director for VistaCare
- VistaCare has provided commercial support for this activity
- Palliative medicine frequently involves the use of medications for “off-label” purposes. Such use may be discussed during this presentation.

Objectives

- Discuss the prevalence of nausea in the palliative care setting, including the suffering that nausea causes
- Describe several pathophysiologic mechanisms for nausea
- Describe specific management regimens for each such mechanism

Overview

- ♦ Definitions and epidemiology
- ♦ Pathophysiology
- ♦ Pharmacology
- ♦ Case examples based on above

Definitions

- ◆ Nausea
 - Unpleasant subjective sensation perceived as a sickness in the stomach and an inclination to vomit
- ◆ Vomit
 - Regurgitation of gastric contents
 - May or may not be associated with nausea

Prevalence

- ◆ Cancer
 - More common in breast & gastric
 - More common with CTX or XRT
 - Terminal cancer: 40-70%
- ◆ Commonly occurs in other diagnoses
 - Heart Failure
 - Renal Failure
 - Liver Disease
 - AIDS

Incidence

- ◆ More frequent if
 - Female
 - Under age 65
 - Recent initiation of opioids
 - Up to 60%
 - Active infection
 - Anxiety
- ◆ Less frequent
 - Alcohol abusers (active or prior)

Suffering due to nausea

- ◆ Unlike pain, little progress in relieving nausea over the past two decades
- ◆ Poorly studied until last few years
- ◆ Cause of significant debility
 - Diminished appetite
 - Diminished fluid intake
 - Diminished functional status

Nausea assessment

Analogous to pain assessment

- Quality
- Timing
- Severity
- Triggers
- Modifying factors
- Impact on function
- Effect of treatments
- Patient perspectives

Eleven “M’s” of “Emesis”

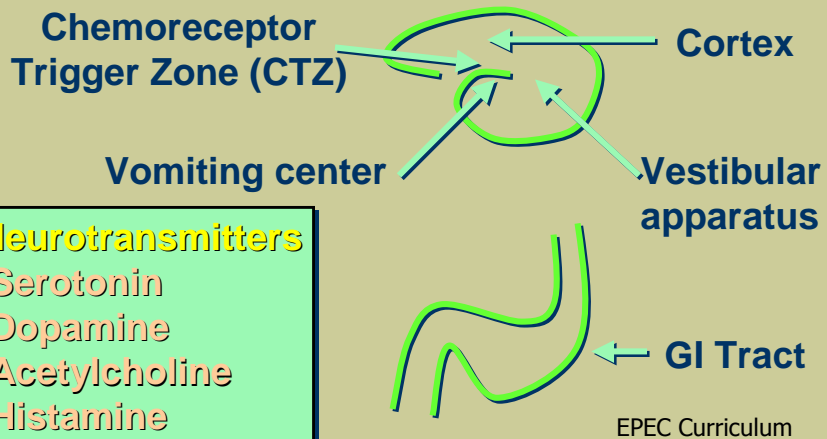
Metastases	Mechanical obstruction
Meningeal irritation	Motility
Movement	Metabolic
Mental anxiety	Microbes
Medications	Myocardial
Mucosal irritation	

EPEC Curriculum

Pathophysiology

- Think in terms of chemoreceptors
- For pain –
 - Medications block specific opioid receptors
 - Much more effective with routine dosing
- For nausea
 - Multiple mechanisms
 - But still due to neurotransmitters & receptors
 - Effective treatment often requires treating each different mechanism

Pathophysiology of nausea / vomiting



Chemoreceptor Trigger Zone (CTZ)

- ◆ A “real” place
- ◆ Area Postrema
 - Floor of the 4th ventricle
 - No effective blood-brain barrier
- ◆ Known serotonin sensitivity
 - Serotonin release with CTX/XRT
- ◆ Mechanoreceptors
 - Increase intracranial pressure
- ◆ Afferent connections to VC

CTZ (cont)

- ◆ Named because of association with chemotherapy-induced nausea by certain agents
- ◆ Related to serotonin release from dying cancer cells
- ◆ Often is delayed
- ◆ Also occurs with radiation therapy
 - Especially whole body, mediastinal & upper abdomen

Emetogenic chemotherapy agents

Severe

- ◆ Cisplatin
- ◆ Cyclophosphamide
- ◆ Cytarabine
- ◆ Dacarbazine
- ◆ Mechlorethamine
- ◆ Streptozocin

Moderate

- ◆ Carboplatin
- ◆ Carmustine
- ◆ Dactinomycin
- ◆ Daunorubicine
- ◆ Doxorubicin
- ◆ Lomostine
- ◆ Mitomycin
- ◆ Procarbazine

Medical Letter 8/4/03

Cortex

- ◆ Learned neurobehavioral responses
- ◆ Anticipatory nausea
 - Pre-CTX
- ◆ Typically not primary cause of nausea, but adjunctive modifier/modulator
- ◆ Afferent connections to VC

Vestibular Apparatus

- ◆ Motion sensors within inner ear
- ◆ Abnormal or conflicting signals
- ◆ Afferent connections to VC

GI Tract

- ◆ Mechanoreceptors
 - ◆ Poorly defined
 - ◆ Useful to evacuate if slowed motility or obstruction
- ◆ Chemoreceptors
 - ◆ Poorly defined
 - ◆ Useful to evacuate if toxic ingestion
- ◆ Afferent connections to VC
 - ◆ Vagal nerve

Vomiting Center (VC)

- ◆ Common connection from all other areas to trigger nausea &/or vomiting
- ◆ Location is not as clearly defined
 - “diffuse interconnecting neural network”
 - Nucleus of tractus solitarius
 - Reticular formation of medulla oblongata

Multiple chemoreceptors

- ◆ At least 17 identified so far
- ◆ Different receptors in different centers
- ◆ Much overlap
- ◆ Same neurotransmitters have other functions elsewhere
 - Limiting side effects of some meds
- ◆ Better picture of what is occurring

Nausea chemoreceptors

- ◆ Serotonin
 - 5HT₃ – CTZ (chemotherapy & radiation)
 - 5HT₄ – Gastrointestinal
- ◆ Dopamine
 - D₂ – CTZ & GI stasis
- ◆ Cholinergic muscarinic
 - Ach_m – Vestibular & VC
- ◆ Histamine
 - H₁ – VC
- ◆ γ -aminobutyric acid
 - GABA – Cerebral cortex

Additional nausea chemoreceptors

- ◆ Still being defined
- ◆ Neurokinase
 - NK₁ – CTZ & perhaps the neurotransmitter involved in the afferent pathways
- ◆ Opioid
- ◆ Cannabinoid

Medications

- ◆ Target the receptor
- ◆ Therefore – must:
- ◆ Identify the area involved
- ◆ Often multi-factorial
 - Mistake in switching
 - Better to “layer” meds

Serotonin (5-HT₃) antagonists

- ◆ Action
 - Blocks receptors in CTZ
- ◆ Useful for
 - Chemotherapy
 - Radiation therapy
 - Other drugs

Specific serotonin antagonists

- Dolasetron (Anzemet®)
 - 1.8mg/kg or 100mg IV once
 - 100mg po once
- Granisetron (Kytril®)
 - 10µg/kg IV once
 - 1-2mg po daily
- Ondansetron (Zofran®)
 - 4-32mg IV once
 - 8mg po q 8-12h
- Palonosetron (Aloxi®)
 - 0.25mg IV once

Serotonin antagonist bioavailability

- Think in terms of receptor blockade
 - Optimally dosed **routinely**
 - Receptor blockade $\frac{1}{2}$ -life > Serum $\frac{1}{2}$ -life
- Granisetron (Kytril®)
 - Receptor blockade $\frac{1}{2}$ -life ~ 16h
 - 80% of oral dose absorbed
 - May dose **daily** – same oral dose as IV
- Ondansetron (Zofran®)
 - Receptor blockade $\frac{1}{2}$ -life ~ 9h
 - Only 50% of oral dose absorbed
 - Must dose q 8-12h with oral:IV of 2:1

Serotonin antagonists

- Dolasetron (Anzemet®)
 - > \$70/ 100mg tablet
 - *Granisetron (Kytril®)
 - \$89/ 2mg tablet
 - *Ondansetron (Zofran®)
 - \$33/ 8mg tablet
 - Palonosetron (Aloxi®)
 - >\$300 per IV dose
- * = preferred because few drug interactions

Dopamine antagonists

- ◆ Block receptors in
 - CTZ
 - GI chemoreceptors
- ◆ Useful for
 - Chemotherapy
 - Radiation therapy
 - Other drugs
 - GI irritants

Dopamine antagonists

- Prochlorperazine (Compazine®)
 - 10-25mg po / pr q 4h prn
- Haloperidol (Haldol®)
 - 0.5mg po bid
 - Titrate up to 20mg as needed
 - Available in concentrate/injection/depo
- Most antipsychotic medications
- Metoclopramide (Reglan®)
 - Requires high doses (up to 160mg/d)

Acetylcholine antagonists (anticholinergics)

- Block anticholinergic muscarinic receptors
- Useful for
 - Vestibular
 - Adjunct in VC
- Problem!
 - Non-selective
 - Many side effects

Anticholinergic agents

- Hyoscyamine (Levsin®)
 - 0.125mg po q 4h (routine or prn)
- Atropine (Atropine ophthalmic drops)
 - 1-4 drops SL q 1-4h prn
- Scopolamine (TransDerm Scop®)
 - 1 q 72h (expensive / slow onset)
- Glycopyrrolate (Robinul®)
 - 1 – 2mg po bid – tid
 - Does not cross blood-brain barrier
 - Relatively expensive

Anticholinergic costs

- Hyoscyamine
 - 0.125mg x 60 tabs ~ \$10
- Atropine drops
 - 5ml bottle ~ \$9
- Transderm Scop®
 - Box of 4 ~ \$28
- Glycopyrrolate
 - 1mg x 90 tabs ~ \$135

Histamine (H₁) antagonists

- ◆ Blocks H₁ receptors
 - Typical antihistamines
- ◆ Useful for
 - Vestibular apparatus
 - VC

Antihistamines

- ◆ Promethazine (Phenergan®)
 - Also a weak dopamine antagonist
 - 25 – 50 mg po / pr q 4h prn
- ◆ Diphenhydramine (Benadryl®)
 - 25 – 50mg po / SC / pr q 4h prn
- ◆ Meclizine (Antivert®)
- ◆ Hydroxyzine (Vistaril®, Atarax®)
- ◆ All of these
 - Have anticholinergic properties
 - Are cheap

Histamine (H₂) antagonists

- Block H₂ receptors
 - Reduces gastric acid secretion
- H₂ receptor antagonists
 - ranitidine (Zantac®, generic)
 - cimetidine (Tagamet®, generic)
 - famotidine (Pepcid®, generic)
 - nizatidine (Axid®, generic)

GABA antagonists

- Typically effective
 - For vestibular-related nausea
 - Otherwise as an adjunct
- Benzodiazepines
 - Diazepam (drug interactions)
 - Lorazepam
 - Clonazepam
- Specific GABA antagonists (gabapentin)
 - Typically not effective for nausea

Neurokinin-1 Antagonist

- Substance P / NK-1 receptor antagonist
- Aprepitant (Emend®)
 - Only indicated for CTX-induced nausea
 - 125mg po on day 1, then 80mg po q am on days 2 & 3
 - \$300 / 3 day treatment
 - Receptor blockade $\frac{1}{2}$ -life ~ 3 days
 - Many drug interactions

Miscellaneous agents

- Other antacids
- Prokinetic agents
- Cannabinoid antagonists
- Steroids
- Miscellaneous

Antacids

- Proton pump inhibitors
 - rabeprazole (Aciphex®)
 - 20mg qd
 - esomeprazole (Nexium®)
 - 20-40mg qd
 - lansoprazole (Prevacid®)
 - 15-30mg qd
 - omeprazole (Prilosec®, generic, OTC)
 - 20-40mg qd
 - pantoprazole (Protonix®)
 - 40mg qd

Prokinetic agents

- Metoclopramide (Reglan®)
 - 5-20mg po q 6h
 - Also anti-dopaminergic at higher doses
 - Side effects in elderly
- More (supposedly) on the way

Cannabinoid receptor antagonists

- Tetrahydrocannabinol (Marinol®)
 - 5 – 20mg up to qid
 - RCT: *Worse* than placebo
 - Generally effective only in those with history of prior cannabinoid use
- Smoked marijuana
 - Anecdotally – much more effective
 - Health concerns of smoking
 - Legal concerns

Steroids

- ◆ Minimally effective alone
- ◆ Useful as adjunct
 - Additional 10-15% response rate when added to HT₃ or D₂ antagonists
- Dexamethasone
 - 4 – 16mg up to q 6h
- Prednisone
 - 20 – 100mg daily

Completely “off-label”

- Mirtazapine (Remeron®)
 - Antagonist for 5-HT₃, 5-HT₄ and H₁
 - 15mg po bid
- Olanzapine (Zyprexa®)
 - Antagonist for D₂, H₁, Ach_m, 5-HT₂
 - Limited 5-HT₃ antagonist
 - 5 – 20mg po daily
 - Considerably cheaper than alternatives
 - Up to 30% response when all others failed

CAM Therapies

- Acupressure
 - Hypothesis: activates/modulates afferent pathways
- Hypnosis
- Ginger
 - Mechanism unknown
 - ‘Ginger-Ale’
 - Meta-analysis: ginger root more effective than placebo for nausea
 - 250 – 500mg powdered ginger root qid

Example 1

- 49-yo F with metastatic breast cancer
- S/P surgery/XRT and salvage CTX
- Severe nausea with smells of food
- Wishes to avoid “mind-altering” drugs

Example 2

- 71-yo M with recurrent lymphoma
- S/P CTX
- Now with nausea on attempts to eat or with ambulation
- Insists Zofran is the only thing that works and when it fails, he insists on increasing dose rather than try “those other medicines that never work”

Example 3

- 59-yo F with end-stage heart disease
- Comorbidities: DM, Htn, GERD
- Has constant low-grade nausea and early satiety after eating
- Promethazine ineffective and causes drowsiness

Example 4

- 31-yo M with end-stage AIDS
- Recurring nausea several times a day with no clear trigger
- Promethazine is effective, but very sedating
- Insists marijuana is effective, but is now too functionally impaired to access his usual “source”

Example 5

- 40-yo F with ovarian cancer and carcinomatosis
- Has ongoing nausea, but with intermittent exacerbations, especially with certain foods or when upset
- Initially controlled with
 - Haloperidol 1mg bid
 - Metoclopramide 10mg qid
 - Kytril 2mg po daily
- Now with recurrent symptoms

Questions?

Answers?