Nausea and Vomiting in Palliative Care: Antipsychotics as Antiemetics

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Advanced Practice Selective in Palliative Care

Wednesday, October 9, 2013
Objectives

- **Overview of Nausea and Vomiting in Palliative Care**
  - Definitions
  - Epidemiology
  - Etiology

- **Overview of Management**
  - General strategy
  - Neurotransmitters and the Emesis Pathway
  - Receptor profiles of common antiemetics

- **Antipsychotics as antiemetics**
  - Evidence for Haloperidol as an antiemetic
  - Haloperidol as antiemetic in Palliative Care
Nausea and Vomiting in Palliative Care

• **Nausea**
  » Unpleasant sensation (or sensations) immediately preceding vomiting
  » Can occur alone or can accompany vomiting
  » Entirely subjective experience

• **Vomiting**
  » Rapid, forceful evacuation of gastric contents in retrograde fashion
  » Usually preceded by nausea (but not always)
  » Highly specific physical event

**SOURCES:**
Nausea and Vomiting in Palliative Care

• Epidemiology
  » Generally considered a common symptom in palliative care population
    • 62% of terminally ill cancer patients¹
    • 71% of patients admitted to palliative care unit reported nausea during last week of life²

  » Study by Solano, et al suggests nausea and vomiting is less common than pain, breathlessness, fatigue³

Sources:
Nausea and Vomiting in Palliative Care

- **Common Causes**
  - Toxic/metabolic disturbances
    - Drugs
    - Organ failure
    - Metabolic
  - Disorders of viscera
    - Obstruction
    - Gastroparesis
    - Inflammation / irritation
  - CNS Causes
    - Increased intracranial pressure
    - Vestibular dysfunction
    - Anxiety

**SOURCES:**
Management Approach

• **Three basic steps**
  » Clarify what patient is experiencing and identify etiology

  » Identify and correct consequences of nausea and vomiting
    • Fluid depletion
    • Electrolyte imbalances (hypokalemia)
    • Metabolic alkalosis

  » Treat nausea and vomiting
    • Correct underlying cause (if possible)
    • Symptom management
      » Non-pharmacologic methods
      » antiemetics
Neurotransmitters and the Emetic Pathway

Major Neurotransmitters and Receptors:
- Acetylcholine (muscarinic)- M₁
- Dopamine - D₂
- Histamine - H₁
- Serotonin - 5HT₂-₄

SOURCES:
# Receptor Profiles of Common Antiemetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>D2</th>
<th>H1</th>
<th>M1</th>
<th>5HT</th>
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<tr>
<td><strong>Anti-cholinergic:</strong></td>
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<td>Hyoscine (Scopolamine)</td>
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<td><strong>Antihistamine:</strong></td>
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<td>Promethazine (Phenergan)</td>
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<td><strong>Selective 5HT antagonists:</strong></td>
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<td>Ondansetron (Zofran)</td>
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<tr>
<td><strong>Dopamine Receptor Antagonists:</strong></td>
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<td>Prochlorperazine (Compazine)</td>
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<td>Chlorpromazine (Thorazine)</td>
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<td>Metoclopramide (Reglan)</td>
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<td>Haloperidol (Haldol)</td>
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<tr>
<td>Olanzapine (Zyprexa)</td>
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**SOURCES:**
Haloperidol

- **Butyrophenone derivative**
  - Discovered in 1958
  - FDA approved in 1967 as antipsychotic
- **Dopamine (D2) receptor antagonist**\(^1,2\)
  - Chemoreceptor trigger zone (CTZ)
- **Adverse effects**\(^1\)
  - Extrapyramidal side effects
  - QT Interval Prolongation
  - Seizures
  - Neuroleptic Malignant Syndrome

SOURCES:
Haloperidol as an Antiemetic

- Widely used as antiemetic despite limited data

- 2004 Meta-analysis by Büttner, et. al evaluated data in three general areas
  - Chemotherapy and Radiotherapy
  - Nausea and Vomiting related to Gastrointestinal diseases
  - Postoperative Nausea and Vomiting

Source:
Haloperidol as an Antiemetic

**Chemotherapy and Radiation Therapy**

» No conclusions drawn from meta-analysis\(^1\)
  
  • Neidhart et. al. (1981) comparing Haloperidol vs. Benzquinamide\(^2\)
    
    » Patients preferred haloperidol for control of emesis induced by cis-platinum (78 vs. 22%) and nitrogen mustard (67 vs. 16%)
    
    • Cole et. al (1974) Radiation therapy trial comparing Haloperidol to placebo\(^3\)
      
      » 96% of patients taking haloperidol reported reduced vomiting compared to 20% of placebo

**Gastrointestinal Diseases**

» Meta-analysis demonstrated efficacy for both 1mg and 2 mg doses at controlling nausea and vomiting\(^1\)

  • 12 hrs post haloperidol therapy:
    
    » 1 mg IM haloperidol vs. placebo RB 2.59 (CI 95% 1.74-3.91) NNT 2.5 (CI 95% 1.9 – 3.8)
    
    » 2 mg IM haloperidol vs. placebo RB 3.84 (CI 95% 1.93 – 7.65) NNT 2.1 (CI 95% 1.5-3.5)

Source:
Haloperidol as an Antiemetic

- Prevention of postoperative Nausea and Vomiting (PONV)
  - Meta-analysis revealed efficacy for prevention of PONV at doses between 0.5 – 4 mg haloperidol (but not for 0.25 mg) \(^1\) - no evidence of dose responsiveness

- Two more recent RCTs comparing haloperidol to ondansetron in PONV
  - Lee et. al. 2 mg haloperidol vs. 4 mg ondansetron demonstrated low incidence of PONV (<30% incidence, no significant difference; expected incidence of 60%) \(^2\)
  - Rosow et. al. 1 mg haloperidol vs. 4 mg ondansetron demonstrated complete resolution of PONV (78.2% vs. 76.8% respectively, no significant difference) \(^3\)

Source:
Haloperidol in Palliative Care

• Haloperidol considered one of the 20 essential drugs in palliative care

• Evidence for haloperidol as antiemetic in palliative care patients?
  » No RCTs studying haloperidol in palliative care patients
  » 2010 Cochrane Review: “There is not enough evidence to be able to recommend haloperidol for the treatment of nausea and vomiting in adult patients suffering from incurable progressive medical conditions”
  » Observational study on efficacy of haloperidol in management of nausea and vomiting in palliative care cancer patients
    • 61% patients reported response (complete or partial) (CI 95% 44-77%) after treatment with haloperidol
    • 24% of patients reported complete response (CI 95% 10-39%) after treatment with haloperidol
  » Consensus, based largely on case series, that haloperidol is an effective antiemetic for chemical and metabolic causes of nausea and vomiting

Source:
Conclusions

• Nausea and vomiting are common symptoms encountered in palliative care patient population

• Treatment is often complex and requires thoughtful evaluation of the patient’s symptoms

• Evidence behind use of haloperidol as antiemetic in palliative care patients is limited
  » Recommended dose: 0.5 mg IV q4-6 hours

Source: