Donepezil-Related Intractable Hiccups

Therapeutic Case Report
Ian R. McGrane, Pharm.D., BCPS
Shodair Children’s Hospital, Helena, MT
imcgrane@shodair.org

Learning Objectives
- Describe medications believed to contribute to hiccups causation
- Explain theoretical effects of neurotransmitter modulation in regards to hiccups causation

Hiccups
- Persistent
- Intractable

### Hiccup Reflex Arc

- **Higher Centers**
  - Respiratory Center
  - Medullary Reticular Formation
  - Phrenic Nerve Nuclei
- **Higher Centers**
  - Hypothalamus
- **Cervical Spinal Cord**
  - Hiccup Center C3-C5
- **Vagus Nerve**
- **Thoracic Spinal Cord**
- **Sympathetic Chain**
- **Respiratory Center**
- **Phrenic Nerve**
- **Diaphragm**
- **Phrenic Nerve**
- **Glottis Closure**

### Patient Case

- 76-year-old gentleman
- **PMH:**
  - Alzheimer’s dx, GERD, COPD, osteoporosis, normocytic anemia, BPH, insomnia, peripheral edema, RLS, hypothyroidism, hx alcohol and marijuana use
- Initiated donepezil in 2011

### Drugs Prior to Initial Hospitalization

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose and Frequency</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25 mg once nightly</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Baclofen</td>
<td>5 mg every 8 hours PRN</td>
<td>Hiccup</td>
</tr>
<tr>
<td>Dissected thyroid</td>
<td>1 grain every morning</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Donepezil IR</td>
<td>15 mg once nightly</td>
<td>Alzheimer’s dx</td>
</tr>
<tr>
<td>Fluticasone nasal</td>
<td>50 mcg once daily</td>
<td>Congestion</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 mg once daily PRN</td>
<td>Edema</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg twice daily</td>
<td>GERD</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>1 mg once nightly</td>
<td>RLS</td>
</tr>
</tbody>
</table>
Acute Care Admission #1 (Oct 2013)

• Problems:
  – Urosepsis
  – Atrial fibrillation
  – Hiccups

• Discharged after 8 days
  – Outpatient
    • Jan 2014: D/C haloperidol, start memantine XR
    • Feb 2014: start metoclopramide 10 mg PRN

Acute Care Admission #2 (March 2014)

• Problems:
  – Acute renal failure
  – Hiccups
  – Aspiration pneumonia (?)

• Computed Tomography

• Laboratory

Acute Care Admission #2 (March 2014)

[Diagram showing medication changes over days]
**Acute Care Admission #3 (April 2014)**

Hiccups and Medications

**Therapeutic MOAs**
- Dopamine antagonism
- DAergic
- GABAergic
- 5-HT1a agonism
- Corticosteroid
- Anticholinergic
- Ca++/Na+ channel blockade

**Causative MOAs**
- Dopamine partial agonism
- DAergic
- GABA agonism
- 5-HT1a agonism
- Corticosteroid
- Cholinergic

Pharmacotherapy 1996;16(6):986-995
Ann Pharmacother 2013;47:897-903
J Neuropsychiatry Clin Neurosci 2006;18(4)551-2
Pharmacotherapy 2014;34(1):e4-e8
J Pharm Pract 2014; 27(6)587-590
Mov Disord 2007;22:1667–8

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**Donepezil**

**Absorption:** oral F 100%

**Distribution:** 12 L/kg; linear kinetics

**Metabolism:** CYP2D6, CYP3A4, glucuronidation

**Excretion:** Urine (active compound and 4 metabolites)

- **Formulations**
  - IR: peak concentration 3-4h; t1/2 80h
  - SR: peak concentration 7-9h

Donepezil [package insert] Philadelphia, PA; 2009
Br J Clin Pharmacol 1998;46(sup):1-12
Clin Ther 2010;32:1234-51
Neurotransmitter Model

Naranjo ADR Probability Scale

1. Are there previous conclusive reports on this reaction? + 0
2. Did the ADR occur after the suspected drug was administered? + 2
3. Did ADR improve when drug discontinued or antagonist administered? + 1
4. Did the ADR reappear when the drug was readministered? + 2
5. Are there alternative causes that could have caused the reaction? - 1
6. Did the reaction reappear when a placebo was given? + 0
7. Was the drug detected in the blood in toxic concentrations? + 0
8. Was reaction more severe when dose increased or less severe when dose decreased? + 1
9. Did patient have similar reaction to the same/similar drugs previously? + 1
10. Was ADR confirmed by objective evidence? + 0


Total Score = 6

Conclusions

- Medical and medication causes
- Naranjo scale probability
- Speculative mechanism
Audience Assessment
Which of the following medications has been most implicated to contribute to hiccups causation?

a) Omeprazole  
b) Baclofen  
c) Gabapentin  
d) Aripiprazole

Audience Assessment
Modulation of which neurotransmitter system(s) has best support for hiccups causation?

a) ACh, DA and GABA modulation  
b) Adrenoceptor modulation  
c) Dopaminergic agonism  
d) Dopaminergic antagonism

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Internal Medicine  
Providence St. Joseph Medical Center, Polson, MT
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