Bringing Back Barbiturates:
Phenobarbital Use in Alcohol Withdrawal Syndrome

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Pharmacy Grand Rounds
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Alcohol Use: The Facts

- 15.1 million adults ages 18 and older had an alcohol use disorder (AUD) in 2015
- 3rd leading preventable cause of death in the United States
- ~20% of men and ~10% of women will suffer from an AUD

National Institute on Alcohol Abuse and Alcoholism. 2017
Objectives

• Review the pathophysiology of alcohol withdrawal syndrome (AWS)
• Discuss literature evaluating the use of phenobarbital for the treatment of AWS
• Outline general recommendations for phenobarbital use in refractory AWS
Review the pathophysiology of alcohol withdrawal syndrome (AWS)
Acute Alcohol Ingestion

- Ethanol
- Glutamate
- GABA
- GABA<sub>A</sub> receptor
- NMDA receptor

Decreased excitatory effects
Increased inhibitory effects

GABA: gamma-aminobutyric acid
NMDA: N-methyl-D-aspartate
Chronic Alcohol Ingestion

Ethanol
Glutamate
GABA

Increased excitatory effects
Decreased inhibitory effects

NMDA receptor
GABA_A receptor

Ca^{2+}
Na^+
Cl^-
Ca^{2+}
Na^+
Cl^-
Ca^{2+}
Na^+
Cl^-
Alcohol Withdrawal

Increased excitatory effects

Decreased inhibitory effects

Glutamate
GABA
GABA_A receptor
NMDA receptor
Clinical Manifestations

- Autonomic hyperactivity [6-8 hours]
- Hallucinations [12-24 hours]
- Neuronal excitation [12-48 hours]
- Delirium tremens [3 days]

Question #1

• In chronic alcohol ingestion, upregulation of which receptor is responsible for alcohol withdrawal symptoms?
  • GABA$_A$ receptor
  • GABA$_B$ receptor
  • NMDA receptor
### Screening & Assessment Tools

<table>
<thead>
<tr>
<th><strong>PAWSS</strong></th>
<th><strong>CIWA-Ar</strong></th>
<th><strong>RASS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Screening tool to identify patients at risk for complicated AWS</td>
<td>• Symptom-triggered therapy</td>
<td>• Symptom-triggered therapy</td>
</tr>
<tr>
<td>• Greater the number of positive findings, higher the risk of development of AWS</td>
<td>• Most widely used</td>
<td>• Ranges from -5 to +4</td>
</tr>
<tr>
<td>• Maximum = 10 points</td>
<td>• Effective patient communication required</td>
<td>• -5 = unarousable</td>
</tr>
<tr>
<td>• Score of ≥4 suggests high risk for moderate to severe AWS</td>
<td>• Assesses 10 domains</td>
<td>• +4 = combative</td>
</tr>
<tr>
<td></td>
<td>• Maximum = 67 points</td>
<td>• Target goal of 0 to -2</td>
</tr>
<tr>
<td></td>
<td>• Score of ≥20 indicates severe AWS</td>
<td></td>
</tr>
</tbody>
</table>

PAWSS: Prediction of Alcohol Withdrawal Severity Scale  
CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol  
RASS: Richmond Agitation-Sedation Scale  
Maldonado et al. Alcohol. 2014;48:375-90  
Duby et al. J Trauma Acute Care Surg. 2014;77:938-43
Management & Treatment Options

• **Standard of care:**
  • Supportive care
  • Benzodiazepines

Dixit et al. Pharmacotherapy. 2016;36:797-822
Benzodiazepine “Refractory” AWS

- Multifactorial mechanism
  - Altered GABA_\text{A} receptor subunits
  - Overall down-regulation of GABA_\text{A} receptors
- >40 mg diazepam in 1 hour

Management & Treatment Options

• **Standard of care:**
  - Supportive care
  - Benzodiazepines

• **Adjunctive therapies:**
  - Propofol
  - $\alpha_2$-agonists
    - Clonidine
    - Dexmedetomidine
  - Baclofen
  - Ketamine
  - $\beta$-blockers
  - Ethanol

• **Antipsychotics**
• **Antiepileptics**
  - Carbamazepine
  - Gabapentin
  - Valproic acid
  - Phenobarbital

Dixit et al. Pharmacotherapy. 2016;36:797-822
Phenobarbital: Mechanism of Action

• Dual activity to oppose AWS effects
  - Increases the duration of $\text{GABA}_A$ receptor opening
  - Inhibits NMDA receptor activity

• Can be GABA mimetic and directly activate the chloride channel at high concentrations

Basicmedical Key. 2017
Phenobarbital: Pharmacokinetics & Dosing

- **Onset of action**
  - Oral: ≥60 min
  - IV: 5 min

- **Duration of action**
  - Oral: 10-12 hrs
  - IV: ~6 hrs

- **Half-life**
  - ~79 hrs
  - (53-118 hrs)

- **Weight-based dosing**
  - 10-15 mg/kg IV infusion

- **Fixed dosing**
  - 65, 130, or 260 mg IV boluses

- **Adverse effects**
  - Hypotension, respiratory depression

Drug Facts and Comparisons. 2017
Discuss literature evaluating the use of phenobarbital for the treatment of AWS
Gold et al: Adjunctive Phenobarbital

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective pre-post</th>
</tr>
</thead>
</table>
| Population     | • Patients admitted to the medical intensive care unit (ICU) for treatment of severe AWS  
                  - Preguideline (n = 54)  
                  - Postguideline (n = 41) |
| Goals          | • Describe outcomes of patients  
                  • Determine whether a strategy of escalating doses of diazepam in combination with phenobarbital would improve outcomes |
| Intervention   | Symptom-triggered therapy with escalating doses of diazepam in combination with phenobarbital |
Diazepam 10 mg IV

Significant agitation within 1 hr

Escalating doses of diazepam up to 100-150 mg/dose

Agitation controlled for at least 1 hr

Continue diazepam at max dose

Significant agitation within 1 hr

Escalating doses of IV phenobarbital (65, 130, 260 mg) + diazepam at max dose

Agitation controlled for at least 1 hr

Continue diazepam at max dose
Use phenobarbital if necessary

Significant agitation within 1 hr

Consider propofol 20 mg boluses or infusion with mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>Preguideline</th>
<th>Postguideline</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average 24-hr diazepam dose</td>
<td>248</td>
<td>562</td>
<td>0.001</td>
</tr>
<tr>
<td>requirement (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average maximal individual</td>
<td>32</td>
<td>86</td>
<td>0.001</td>
</tr>
<tr>
<td>diazepam dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital use (%)</td>
<td>17</td>
<td>58</td>
<td>0.01</td>
</tr>
<tr>
<td>Need for mechanical</td>
<td>47</td>
<td>22</td>
<td>0.008</td>
</tr>
<tr>
<td>ventilation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gold et al: Adjunctive Phenobarbital

Conclusions

• Significant reduction in mechanical ventilation
• Reduced ICU length of stay and incidence of nosocomial infections

Limitations

• Systematic changes in ICU care could have confounded results
• Treatment decisions left up to practitioner

### Duby et al: Adjunctive Phenobarbital

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective pre-post</th>
</tr>
</thead>
</table>
| Population     | • Patients with AWS admitted to an ICU  
                              - PRE (n = 60)  
                              - POST (n = 75) |
| Primary Outcome| ICU length of stay     |
| Intervention   | • PRE  
                              - Nonprotocolized treatment with continuous infusions or scheduled doses of benzodiazepines  
                              • POST  
                              - Escalating doses of diazepam and phenobarbital according to an AWS protocol |

Duby et al. J Trauma Acute Care Surg. 2014;77:938-43
Inadequate sedation (RASS ≥ 1)

Determine effective dose

Diazepam IV (reassess after 15 min)

Max diazepam and RASS ≥ 1

Phenobarbital 60 mg IV (reassess after 30 min)

60 → 120 → 240 mg (repeat or escalate)

Diazepam IV (mg)

<table>
<thead>
<tr>
<th>Repeat x 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 10</td>
</tr>
<tr>
<td>20 20</td>
</tr>
<tr>
<td>30 30</td>
</tr>
<tr>
<td>40 40</td>
</tr>
<tr>
<td>60 60</td>
</tr>
<tr>
<td>80 80</td>
</tr>
</tbody>
</table>

Max: 120 mg

Duby et al. J Trauma Acute Care Surg. 2014;77:938-43
Mean Benzodiazepine & Phenobarbital Use

Mean benzodiazepine use: PRE = 320 mg, POST = 95 mg, \( p = 0.0002 \)

Mean phenobarbital use: PRE = 52 mg, POST = 90 mg, \( p = 0.04 \)

Duby et al. J Trauma Acute Care Surg. 2014;77:938-43
<table>
<thead>
<tr>
<th></th>
<th>PRE (n = 60)</th>
<th>POST (n = 75)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ICU length of stay (days)</td>
<td>9.6</td>
<td>5.2</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mean time on ventilator (days)</td>
<td>5.6</td>
<td>1.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intubation due to AWS (%)</td>
<td>22</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Continuous sedation (%)</td>
<td>55</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death (%)</td>
<td>12</td>
<td>3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Duby et al. J Trauma Acute Care Surg. 2014;77:938-43
Duby et al: Adjunctive Phenobarbital

Conclusions

- Decreased:
  - Need for mechanical ventilation
  - Time on mechanical ventilation
  - ICU length of stay
  - Benzodiazepine exposure
  - Mortality

Limitations

- Differences in ICU management
- Varied AWS management strategies in PRE group
**Hendey et al: Fixed Dosing**

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, randomized, double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Emergency department (ED) patients (n = 44) with known or suspected acute AWS</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Change in AWS scores from the ED baseline score to discharge or admission score</td>
</tr>
<tr>
<td>Intervention</td>
<td>• Lorazepam 2 mg IV per dose &lt;br&gt;• Phenobarbital 260 mg IV load, followed by 130 mg IV subsequent doses (Number and timing of doses at discretion of practitioner)</td>
</tr>
</tbody>
</table>

CIWA Scores

- Baseline: Phenobarbital = 15, Lorazepam = 16.8, \( p = 0.3 \)
- Emergency department discharge: Phenobarbital = 5.4, Lorazepam = 4.2, \( p = 0.4 \)
- 48 hours: Phenobarbital = 5.8, Lorazepam = 7.2, \( p = 0.6 \)

Hendey et al: Fixed Dosing

Conclusions

- Phenobarbital and lorazepam similarly effective in treatment of mild to moderate AWS
  - Symptom control
  - Length of stay
  - Treatment failures
  - Symptoms at 48 hours

Limitations

- Only enrolled patients with mild to moderate AWS
- No protocol utilized

### Rosenson et al: Weight-Based Dosing

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, randomized, double-blind, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td></td>
</tr>
<tr>
<td>• ED patients (n = 102) with:</td>
<td></td>
</tr>
<tr>
<td>- Acute AWS</td>
<td></td>
</tr>
<tr>
<td>- Hospital admission with primary diagnosis of AWS</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>• Initial level of hospital admission from ED</td>
<td></td>
</tr>
<tr>
<td>- ICU vs telemetry vs floor ward</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
</tr>
<tr>
<td>• Symptom-guided lorazepam-based AWS protocol</td>
<td></td>
</tr>
<tr>
<td>- Single dose of IV phenobarbital (10 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>- Placebo</td>
<td></td>
</tr>
</tbody>
</table>
Rosenson et al: Weight-Based Dosing

Conclusions

• Decreased use of continuous lorazepam infusion and ICU admission
• Did not cause increased adverse outcomes

Limitations

• Patient weight estimated
• Unvalidated institutional AWS protocol
• Enrollment decisions left to practitioner

Question #2

• Based on the literature discussed, which of the following limitations do you feel is most important regarding phenobarbital use in AWS?
  • Poor study design
  • Lack of consistent benzodiazepine dosing protocols
  • Variability of AWS severity and threshold to give phenobarbital
  • Lack of consistent phenobarbital dosing protocols
Outline general recommendations for phenobarbital use in refractory AWS
Candidates for Phenobarbital Therapy

• Moderate to severe AWS
  • CIWA ≥15 or RASS >1
• Benzodiazepine refractory AWS
  • >8 mg lorazepam in 1 hour
• Rapid escalation of initial withdrawal symptoms
  • E.g. Patient has received 6 mg lorazepam in 1 hour but still has RASS 3
• Known history of difficult to manage AWS
Example Phenobarbital Dosing Strategies

- **Weight-based IV load:**
  - 5-10 mg/kg

- **Fixed IV boluses:**
  - 65 mg q15-30 min PRN until adequate CIWA control; may escalate to 130-260 mg if unsatisfactory response
  - 260 mg x 1 followed by 130 mg q30 min PRN CIWA ≥15

- **Weight-based IV load + fixed IV boluses:**
  - 5 mg/kg followed by 65-260 mg q15-30 min PRN until adequate CIWA control
Patient Case

• BW is a 45 year old male who presents to the ED with severe AWS. After treatment with 10 mg lorazepam in 1 hour, BW is now considered to have benzodiazepine refractory AWS and is admitted to the ICU. The medical team decides to initiate phenobarbital therapy. BW weighs 80 kg.
Question #3

• Which of the following phenobarbital dosing regimens would you select for this patient?
  • 400 mg IV x 1
  • 800 mg IV x 1
  • 260 mg x 1 followed by 130 mg q30 min PRN CIWA >10
  • 400 mg IV x 1 followed by 65-260 mg q15-30 min PRN
Summary

• AWS results from an imbalance between GABA<sub>A</sub> and NMDA receptor activity
  • Decreased GABA<sub>A</sub> receptor activity and inhibitory effects
  • Increased NMDA receptor activity and excitatory effects

• Phenobarbital treatment may improve outcomes in patients with acute AWS

• Utilization of phenobarbital could be considered in patients with refractory AWS
Questions & Discussion
DSM-5 Diagnostic Criteria

• A. Cessation or reduction in alcohol use that has been heavy and prolonged

• B. Two (or more) of the following, developing within several hours to a few days after criterion A:
  • Autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual/auditory/tactile hallucinations or illusions, psychomotor agitation, anxiety, generalized tonic-clonic seizures

• C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

• D. The symptoms are not attributable to other causes
## Example Phenobarbital Protocol

<table>
<thead>
<tr>
<th>YES</th>
<th>Patient has received $\geq 5$ mg of lorazepam PO/IV or $\geq 25$ mg of diazepam PO/IV in the last 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Phenobarbital 65 mg IV push over 1 min x 1 dose</td>
</tr>
<tr>
<td></td>
<td>• Reassess in 15 min</td>
</tr>
<tr>
<td></td>
<td>- 65 mg IV push over 1 min if symptoms still present but improved</td>
</tr>
<tr>
<td></td>
<td>- 130 mg IV push over 2 min if symptoms persist without improvement</td>
</tr>
<tr>
<td></td>
<td>- Reassessment and redosing every 15 min until CIWA &lt;8</td>
</tr>
<tr>
<td>NO</td>
<td>• Phenobarbital load 10 mg/kg ideal body weight</td>
</tr>
<tr>
<td></td>
<td>- In 100 mL normal saline over 30 min</td>
</tr>
</tbody>
</table>
### Ongoing symptom-triggered prn dosing per CIWA score (symptom-guided every 8 hours)

- Starting 1 hour after loading dose complete
- No phenobarbital dose for CIWA <8
- Phenobarbital 65 mg IV push over 1 min every 8 hours prn CIWA 8-15
- Phenobarbital 130 mg IV push over 2 min every 8 hours prn repeat CIWA >15
- No benzodiazepines if phenobarbital ordered
Maintenance taper

- Starting ~6 hours after all loading doses complete
- Doses may be given IV if patient is unable to take oral
- **Day 1:** 64.8 mg PO 4 times daily
- **Day 2:** 64.8 mg PO 3 times daily
- **Day 3:** 64.8 mg PO 2 times daily
- **Day 4:** 32.4 mg PO 2 times daily
- **Day 5:** Discontinue