Phenobarbital for Moderate to Severe Alcohol Withdrawal in the Acute Care Setting

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Today’s presenters have nothing to disclose
Objectives

- Explain patient management and treatment goals when treating moderate to severe alcohol withdrawal symptoms with phenobarbital.

- Describe the mechanism of action of phenobarbital in treating patients with alcohol withdrawal symptoms.

- Describe potential protocols to decrease the amount of dexmedetomidine and benzodiazepines that are used in their institutional settings for treating patients with alcohol withdrawal symptoms.
Approximately 7% of US population abuses or is dependent on alcohol.
- 10% of patients will experience seizures
- 5% experience delirium tremens
20% of patients admitted to the in-patient units
- Patients often seek medical attention in Emergency departments for complications directly related to alcohol use.
  - 16% surgical patients
  - 31% of trauma patients
    - 25-35% MVAs
Effects of Alcohol Exposure and Withdrawal

- Short term alcohol intake
- Long term alcohol intake
- Withdrawal
- Tolerance
- Cessation of alcohol

Adapted from: McKinley MG. Crit Care Nurse. 2005 Jun;25(3):40-2, 44-8
## Symptoms of Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor symptoms: Insomnia, tremulousness, mild anxiety, GI upset, headache, diaphoresis, palpitations, anorexia</td>
<td>6 – 12 hours</td>
</tr>
<tr>
<td>Alcoholic hallucinosis: visual, auditory, or tactile hallucinations</td>
<td>12 – 24 hours</td>
</tr>
<tr>
<td>Withdrawal seizures: generalized tonic-clonic seizures</td>
<td>24 – 48 hours</td>
</tr>
<tr>
<td>Alcohol withdrawal delirium (delirium tremens): hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis</td>
<td>48 – 72 hours</td>
</tr>
</tbody>
</table>
Two major types of neurotransmitter systems in the CNS:
- γ-aminobutyric acid (GABA) → inhibitory of electrical activity
- Glutamate → Excitatory impact on electrical activity

> 80% of neurons in the brain use GABA or glutamate

Alcohol agonizes GABA receptors and blocks glutamate receptors
CNS Alcohol Withdrawal Physiology: GABA vs. Glutamate

GABA and Glutamate – Chronic Alcohol Use

Ethanol acting on GABA receptor

GABA activity

Glutamate activity

Baseline Activity

Nejad, unpublished
CNS Alcohol Withdrawal Physiology: GABA vs. Glutamate

GABA and Glutamate – Abrupt Cessation of Alcohol

Amount of GABA agonism needed to override glutamate activity

Baseline Activity

GABA activity

Glutamate activity

Nejad, unpublished
Effects of Alcohol Exposure and Withdrawal

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Adapted from: McKinley MG. Crit Care Nurse. 2005 Jun;25(3):40-2, 44-8
16 different GABA\textsubscript{A} receptors $\rightarrow$ 9 in brain based upon subunit composition

GABA related symptoms:
- Sweating, tremors, anxiety and sleep alternations

1-4 Benzodiazepines
- Require GABA to bind
- Increase the frequency Cl channel opening
- Affinity guided by $\alpha$ unit selectivity

Barbiturates
- Does NOT require GABA to bind
- Increase time Cl channel is open
- Attenuate BZD and GABA binding

Sankar R. *CNS Drugs.* 2012 Mar 1;26(3):229-44.
Krystal JH, et al. *Arch Gen Psychiatry.* 2006 Sep;63(9):957-68.
### Select GABA agonists for Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Variable</th>
<th>Midazolam</th>
<th>Lorazepam</th>
<th>Phenobarbital</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area of Use</strong></td>
<td>ICU</td>
<td>All</td>
<td>All</td>
<td>ICU</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>IV</td>
<td>IV/PO</td>
<td>IV/IM/PO</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Typical Dose</strong></td>
<td>1-3 mg q1hr</td>
<td>1-4 mg q4hrs</td>
<td>65-320 mg Q6hrs</td>
<td>0-5 mg/kg/hr</td>
</tr>
<tr>
<td><strong>IV onset (min)</strong></td>
<td>1-5</td>
<td>5-20</td>
<td>5</td>
<td>10-50 seconds</td>
</tr>
<tr>
<td><strong>IM onset (min)</strong></td>
<td>15</td>
<td>30</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Short</td>
<td>Medium</td>
<td>Long</td>
<td>Really Short</td>
</tr>
<tr>
<td><strong>Prolonged in renal failure</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prolonged in hepatic failure</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Elimination T1/2</strong></td>
<td>1-4 hrs</td>
<td>12-14 hrs</td>
<td>1.5-4.9 days</td>
<td>1.5-12.4 hrs</td>
</tr>
<tr>
<td><strong>Active Metabolite</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>IV formulation toxicity</strong></td>
<td>None</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Lipid elimination</td>
</tr>
</tbody>
</table>
## Prophylene Glycol Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Amount of propylene glycol (mg/ml)</th>
<th>Daily propylene glycol exposure (g)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>4</td>
<td>830</td>
<td>99.6</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>130</td>
<td>702.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Based on a lorazepam infusion of 20 mg/hr and phenobarbital dosage of 130 mg 3 times a day*
Phenobarbital’s Mechanism of Action

Enhanced GABA Activity

GABA receptor complex

- Barbiturates
- Steroids
- BZ = Benzodiazepines
- ETOH = Ethanol (Alcohol)

GABA recognition site

- Benzodiazepines
- Barbiturates

GABA-T
- Succinic semialdehyde dehydrogenase
- Metabolites

Vigabatin
Pharmacokinetics of Phenobarbital

- Available in parenteral, intramuscular and enteral formulations
- Bioavailability of IM, IV and PO formulations is almost 100% complete
- Time to maximum plasma concentration
  - IV: 15 to 30 minutes
  - PO: 0.5 to 4 hours
  - IM: 2 to 8 hours
- Half-life is 1 to 4 days
- Possible induction of cytochrome 2B6 and 3A4
## Side Effects

- CNS excitation or depression
- Respiratory depression
- Dermatitis
- Facial edema
- Headache
- Hypotension
- Nausea
- Bradycardia
- Agitation
- Confusion
- Insomnia
- Somnolence
- Hallucinations
- Vertigo
Contraindications

- History of SJS/TEN
- History of acute intermittent porphyria
- History of rash with an AED
- History of cirrhosis

Adverse Reactions

- Sedation
- Respiratory depression
- Rash/SJS/TEN
- Exacerbation of acute or intermittent porphyria

Chronic Use

- Bone loss
- Hematologic
Published Literature About Phenobarbital Dosing
51 patients were randomized to receive phenobarbital versus 51 placebo. Patients received a single dose of i.v. phenobarbital had a decreased ICU admission rate:

- Phenobarbital vs. placebo, 8% vs. 25%, difference 17% [95% confidence interval (CI) 4–32%]

Phenobarbital resulted in decrease in:

- Use of continuous lorazepam infusion
  - 4% vs. 31%; difference 27% [95% CI 14–41%]
  - Decreased total lorazepam required
    - 26 vs. 49 mg; difference 23 mg [95% CI 7–40]

There were no differences in:

- Telemetry admission
- Floor ward admission
- Median ICU
- Total hospital LOS

Use of Phenobarbital as an Adjunctive Therapy

- **Advantages**
  - A single dose of 10 mg/kg IV phenobarbital resulted in decreased:
    - ICU admission rate
    - Use of continuous lorazepam infusion
    - Not associated with increased adverse events

- **Disadvantages**
  - Predominantly males
  - Single center study
Addition of Phenobarbital to Benzodiazepines in ICU Patients With DTs

- Diazepam 10mg iv
  - Significant agitation within 1hr.
    - Escalating doses of Diazepam up to 100-150mg/dose
      - Agitation controlled for at least 1hr.
        - Continue Diazepam at maximal dose
      - Significant agitation within 1hr.
        - Escalating doses of iv Phenobarbital (65, 130, 260mg).
          - Continue to administer Diazepam at maximal dose
          - Agitation controlled for at least 1hr.
            - Continue Diazepam at maximal dose.
            - Use Phenobarbital if necessary
          - Significant agitation within 1hr.
            - Consider the Following:
              - Propofol in 20mg boluses
              - Propofol infusion with mechanical ventilation

Crit Care Med 2007;35:724-730
Addition of Phenobarbital to Benzodiazepines in ICU Patients With DTs

<table>
<thead>
<tr>
<th>Significant patient characteristics/metrics/outcomes</th>
<th>Benzo alone (n = 54)</th>
<th>Benzo+Barb (n = 41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperdol use</td>
<td>2 (4%)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Phenobarbital use</td>
<td>9 (17%)</td>
<td>24 (58%)</td>
<td>(p &lt;0.01)</td>
</tr>
<tr>
<td>Intubation requirement</td>
<td>26 (47.3%)</td>
<td>9 (21.9%)</td>
<td>(p &lt;0.01)</td>
</tr>
<tr>
<td>Days intubated</td>
<td>6.4 ± 1.6</td>
<td>3.1 ± 1.3</td>
<td>(p = 0.01)</td>
</tr>
<tr>
<td>Nosocomial Pneumonia intubated (%)</td>
<td>55.5</td>
<td>12.5</td>
<td>(p = 0.02)</td>
</tr>
</tbody>
</table>

Crit Care Med 2007;35:724-730
Addition of Phenobarbital to Benzodiazepines in ICU Patients With DTs

- **Advantages**
  - Appear to augment benzodiazepines’ efficacy at the $\text{GABA}_A$ receptors in the brain
  - Inhibit stimulatory glutamate receptors
  - Escalating doses of benzos + Phenobarbital reduce the need for mechanical ventilation

- **Disadvantages**
  - Single center study
  - Narrow therapeutic window
  - Potential to induce respiratory depression
Taper Dosing of Phenobarbital

- **Dosing Schedule**
  - Day 1: 60 mg PO Four times a day
  - Day 2: 60 mg PO Three times a day
  - Day 3: 60 mg PO Twice daily
  - Day 4: 30 mg PO Twice daily

Am J Addict 1998;189-197
Phenobarbital Treatment in Patients resistant to Benzodiazepines for AW

- Definition of Benzodiazepine Resistance:
  - A need for more than 10 mg of lorazepam in 1 hour
- Phenobarbital improved symptom control, minimized the potential for propylene glycol toxicity and was not associated with respiratory depression and facilitated successful weaning of benzodiazepine.

Pharmacotherapy 2009;29(7):875-878
When to Use Phenobarbital in Alcohol Withdrawal

- Patients with:
  - A history of tremors or seizures
  - Apparent non-response to benzodiazepines or history of benzodiazepine resistance
  - Active DTs or severe withdrawal symptoms
  - Altered mental status and/or high or medium risk for delirium
- Patients at risk or with respiratory compromise in which you may wish to avoid benzodiazepines
Alcohol Withdrawal Orderset
Medium Risk for Alcohol Withdrawal

- Active Alcohol dependence plus 2 of the following:
  - 2 days or more since last drink
  - Elevated BAL on admit
  - Autonomic dysfunction with Blood Alcohol Level > 0.1 g/dL
  - Elevated MCV and/or AST/ALT ratio
  - Heavier and longer drinking history
  - Burn related injuries
  - Falls, particularly with long bone fractures
High Risk for Alcohol Withdrawal

- Past DTs +/- past seizures AND
  - + recent alcohol use (≥2 weeks)
  - Active symptoms of AWS
  - Positive BAL, elevated MCV, elevated AST/ALT ratio
Risk of Sedation

- Age > 65 years old
- Hepatic dysfunction
- Narcotics
- Head injury – Neuro checks
- Recent administration of Benzodiazepines
- Current administration of sedatives
Risk of Respiratory Compromise

- Pneumonia
- Rib fractures
- Chest tube
- Pulmonary contusion
  - Caused by chest trauma => fluid accumulation
  - Leads to hypoxia
- C-collar/brace
Algorithm for Loading Dose

Risk of Alcohol Withdrawal Delirium

High
- Minimal or No of Respiratory Compromise
- + Risk of Sedation or Respiratory Compromise
- + Severe Risk of Sedation or Respiratory Compromise

Medium
- Minimal or No Risk of Respiratory Compromise
- + Risk of Sedation or Respiratory Compromise
- + Severe Risk of Sedation or Respiratory Compromise

Low: Use CIWA scale
Phenobarbital Protocol

- Weight-based dosing ranging from 6-15 mg/kg
- Dosing is broken up into 3 loading doses and a taper regimen
  - Loading Dose: 1 dose given q3h for 3 doses
    - 1\(^{st}\) dose: 40%
    - 2\(^{nd}\) dose: 30%
    - 3\(^{rd}\) dose: 30%
  - Maintenance dose (decreasing by approx. 50% every stage)
    - D#2+3: Stage 1
    - D#4+5: Stage 2
    - D#6: Stage 3
    - D#7: Stage 4
Patients were retrospectively reviewed from November 1, 2016 to April 30, 2017
28 patients were initiated on the Phenobarbital protocol
14 patients utilized Precedex for control of sedation/agitation/delirium
27 patients utilized benzodiazepines
18 patients had documented CIWA scores >15 prior to starting Phenobarbital
4 patient experienced ADRs
Pilot Study Results

- **64%** patients had Precedex discontinued within 24h from starting Phenobarbital
  - 3 patients started Precedex after Phenobarbital was initiated
- **55%** patients discontinued benzodiazepine use upon initiation of Phenobarbital
- **94%** patients were controlled once Phenobarbital protocol was initiated
  - 7 patient continued Phenobarbital + Benzo
  - 2 Patient continue Phenobarbital + Precedex
- 3 patients received q6h dosing
  - 2 patients had therapy discontinued early
Full Course of Therapy

- **75%** patients completed the full course of therapy
- **25%** patients stopped therapy prior to protocol completion
  - 2 patients had no desire to stop drinking
  - 1 patient had therapy stopped by provider due to lack of symptoms
  - 4 were due to ADRs
    - 1 developed a rash
    - 3 were due to sedation issues
Options to Optimize Treatment

- Consider Phenobarbital therapy prior to patients becoming uncontrolled on a CIWA protocol
- Reload the patient with empiric loading doses
- Consider q6h dosing
- Increase the Phenobarbital taper length
- Continue CIWA scoring, without dosing with Lorazepam
28 y.o. male, MS, is brought to the emergency room for an altered mental status.

He called EMS reporting that someone was breaking into his house and Police and SWAT were standing outside watching.

Patient has a past medical history of alcohol abuse and reports drinking 4 glasses of vodka daily.

Patient stated that he had his last drink 3 days prior to admission as he planned to self detox.
Course of Treatment

- Started on the Hospital CIWA protocol
- Patient continue to have CIWA score >15 whose symptoms remained uncontrolled
- MS was started on the phenobarbital protocol
  - Classified as High risk of withdrawal and Severe risk of sedation/respiratory compromise
- CIWA treatment was continued throughout the time the patient was on phenobarbital
  - Continued to have CIWA scores >15
  - Received regular doses of Lorazepam
Recommendations/Improvements

- Review the Risk Assessment of the patient
- Reload the patient vs. q6 hour dosing
- Start phenobarbital earlier as the patient remained uncontrolled on high dose benzodiazepines
Patient Case #2

- 52 y.o male, GC, was shoveling snow when he arrested.
- ROSC was returned prior to arrival in the emergency room.
- Patient was rushed to the cath lab and stents were placed.
- In speaking with the patient’s wife, the patient has a significant drinking history, 30 beers per day.
- Patient’s last drink was only hours before the incident, and the last day without a drink is unknown.
Patient was started on Precedex and phenobarbital protocol 48 hours after admission
- Categorized as High risk of withdrawal, low risk for respiratory compromise
Patient was uncontrolled on both agents as the taper began
- Scheduled Lorazepam was started
- Precedex and Phenobarbital continued
Phenobarbital q6h dosing was initiated 36 hours after the loading dose
- Precedex and scheduled Lorazepam were able to be rapidly weaned
Phenobarbital q6h dosing was continued for 4 days and then patient taper off based on the protocol
Patient Case #2

- Recommendations/Improvements
  - Utilize the higher loading dose based on risk stratification
  - Reload the patient based on symptom improvement from the initial loading dose
  - Utilize phenobarbital q6h dosing before starting the taper
Patient Case #3

- 51 y.o. male, PW, was brought to the emergency room by EMS after police were called by neighbors.
- When police arrive, the patient appears to be shadow boxing in the mirror, reporting that he was fighting someone.
- While in the EMR the patient reports having auditory and visual hallucinations.
- CT of the head and CXR did not show any abnormalities.
Course of Therapy

- Patient was treated in the EMR with Lorazepam and Diazepam
  - Lorazepam was given based on CIWA in conjunction with additionally ordered doses
  - Patient’s symptoms continued and remain uncontrolled
- Patient was continued on the CIWA protocol and Precedex was added to control symptoms
- Phenobarbital Protocol was initiated
  - Precedex was rapidly tapered after the loading doses
  - CIWA was discontinued within 24 hours
- PW was controlled successfully on phenobarbital alone
- PW was completed the last 2 days of therapy as an outpatient
Recommendations/Improvements

- Start phenobarbital protocol earlier
  - Patient was uncontrolled on high dose benzodiazepines
- Utilize phenobarbital protocol instead of Precedex
Improvements

- Reviewed and revised PRH CIWA protocol
- Provided education to Providers and nursing staff
- Expanded availability of Phenobarbital Protocol Initiation
- Using PRN Phenobarbital for patients receiving high doses of benzodiazepines in non-ICU settings in addition to protocol
- Utilized RASS and CIWA scoring to monitor Phenobarbital
Questions?

If there are questions that remain unanswered please email us:

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christopher.devine2@hcahealthcare.com

Thank you