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Evaluation and Implementation of a New Phenobarbital Protocol for Alcohol Withdrawal Management in the Emergency Department

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PROVIDENCE Health & Services

Background

- Alcohol withdrawal syndrome can lead to substantial health care costs and mortality.
- Although historically benzodiazepines (BZDs) are considered the mainstay treatment for alcohol withdrawal, some studies have shown that phenobarbital may be the safer and preferred alternative option.
- Advantages of phenobarbital are its mechanism of action, more predictable pharmacokinetics, and greater therapeutic index.
- A prospective study by Rosenson et al. 2012 found that a single 10 mg/kg IV dose of phenobarbital versus standardized lorazepam protocol resulted in decreased ICU admissions (8% vs. 25%).
- A retrospective study by Tidewell et al. 2018 demonstrated shorter hospital stays, less incidence of mechanical ventilation and less use of adjunctive agents with phenobarbital compared to that of BZDs.
- The phenobarbital protocol was approved by the Oregon Region P&T in October 2020.

Purpose

- The purpose is to evaluate the safety and efficacy of phenobarbital use compared to BZDs use for the management of alcohol withdrawal in the emergency department (ED) at two large tertiary medical centers.

Objectives

- Evaluate the safety and efficacy of phenobarbital in alcohol withdrawal compared to BZDs.
- Discuss the new phenobarbital protocol that was implemented in this study.
- Assess protocol compliance and areas of improvement.

Methodology

- Institutional Review Board (IRB)-approved
- Electronic health record (EHR)-based retrospective chart review of patients in the ED at two large tertiary medical centers
- Study population:
  - Patients ≥ 18 years admitted to the ED with the primary diagnosis of 'alcohol withdrawal' with a presenting CIWA/PAWSS scores and received phenobarbital or BZD therapy (based on CIWA scores ranging from 9 to ≥25)
  - Patients were stratified according to presenting CIWA/PAWSS scores (see protocol for complete scale)
- Study period:
  - Jan 1, 2020– Mar 31, 2021
- Included first 60 patients that met inclusion criteria between determined study period
- Exclusion criteria:
  - Allergy or hypersensitivity to phenobarbital or BZDs
  - Pregnancy
  - Documented history of acute intermittent porphyria, hepatic encephalopathy
  - Use of phenobarbital prior to admission as an anti- epileptic
  - Concomitant HIV medication use contraindicated with phenobarbital (Evotaz, Prezcobix, Tivicay, Doravirine, Genvoya, Stribild
- Primary Outcome: ICU admission for alcohol withdrawal from the ED
- Secondary Outcomes: Incidence of mechanical ventilation, use of restraints, use of adjunctive agents, and protocol compliance
- Evaluation of phenobarbital protocol compliance based on three factors: appropriate CIWA/PAWSS risk stratification, correct weight for loading dose and met safety parameters

Preliminary Results

Table 1. Patient Baseline Characteristics

Characteristic	Phenobarbital Group (n=30)	BZD Group (n=30)
Age, Years (Mean)	47 (range 25-75)	45 (range 29-70)
Sex, Male, No. (%)	20 (66.7)	19 (63)
Weight, Kg (Mean)	79.2 (range 45.4-117.9)	82.4 (range 48.5-113.4)
Race, No. (%)		
White or Caucasian	26 (86.7)	27 (90)
Black or African American	2 (6.7)	0
Hispanic	1 (3.3)	1 (3.3)
American Indian or Alaska Native	1 (3.3)	2 (6.7)
Comorbidities, No. (%)		
Liver Disease	10 (33.3)	7 (23.3)
Seizure Disorder	4 (13.3)	1 (3.33)
Psychiatric Disorder	12 (40)	10 (33.3)
Polysubstance Use	4 (13.3)	1 (3.3)
History of Delirium Tremens	0	1 (3.3)
Hospital Day 1 Laboratory Values, No. (Mean)		
Baseline ALT	103.4 (range 9-417)	77 (range 8-241)
Baseline AST	135.4 (range 21-611)	107.1 (range 21-520)
CIWA-Ar score	13.6 (range 1-35)	12.7 (range 3-33)
Hospital Course, Mg (Mean)		
Average phenobarbital loading dose	520.5 (range 0-790)	-
Average cumulative phenobarbital dose	862.2 (range 130-4820)	-
Total lorazepam equivalents	18 (range 0-89.7)	15 (range 2-61)

Abbreviations: ED = Emergency Department; ICU = Intensive Care Unit; CIWA = Clinical Institute Withdrawal Assessment for Alcohol; PAWSS = Prediction of Alcohol Withdrawal Severity Scale; No = Number; ALT = Alanine Transaminase; AST = Aspartate Aminotransferase; BZD = Benzodiazepines

Table 2. Clinical Outcomes

Outcome, No. (%)	Phenobarbital Group (n=13)	BZD Group (n=30)	Phenobarbital and BZD Group (n= 17)
Discharge from ED	13 (100)	8 (26.7)	4 (23.5)
ED to ICU admission	0	2 (6.6)	4 (23.5)
ED to floor admission	0	15 (50)	9 (52.9)
Use of restraints	2 (15.4)	5 (16.7)	10 (58.8)
Use of adjunctive agents	1 (7.7)	8 (26.7)	3 (17.6)
Mechanical ventilation	0	0	0

Table 3. Adjunctive Agents Utilized

Medication, No. (%)	Phenobarbital Group (n=13)	BZD Group (n=30)	Phenobarbital and BZD Group (n= 17)
Dexmedetomidine	0	1 (3.3)	2 (11.8)
Propofol	0	0	0
Ketamine	0	0	0
Quetiapine	0	1 (3.3)	3 (17.6)
Haloperidol	0	2 (6.7)	0
Olanzapine	0	3 (10)	0
Droperidol	1 (7.7)	2 (6.7)	0

Protocol and Education Materials

Figure 3. Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

PART A: THRESHOLD CRITERIA: ("Y" or "N", no point)
Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days? _____
OR did the patient have a "+" blood alcohol level (BAL) on admission? _____
IF the answer to either is YES, proceed with test:

PART B: BASED ON PATIENT INTERVIEW: (1 point each)
1. Have you been recently intoxicated/drunk within the last 30 days? _____
2. Have you ever undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism? (i.e., inpatient or outpatient treatment programs or AA attendance) _____
3. Have you ever experienced any previous episodes of alcohol withdrawal, regardless of severity? _____
4. Have you ever experienced blackouts? _____
5. Have you ever experienced alcohol withdrawal seizures? _____
6. Have you ever experienced delirium tremens, or DT? _____
7. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates during the last 90 days? _____
8. Have you combined alcohol with any other substance of abuse during the last 90 days? _____

PART C: BASED ON CLINICAL EVIDENCE: (1 point each)
9. Was the patient's BAL on presentation ≥ 200? _____
10. Is there evidence of increased autonomic activity? (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea) _____
TOTAL SCORE: _____

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of AWS. A score of ≥ 4 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or treatment may be indicated.

Source: Adapted **Source:** Adapted from Hakkinodo JR, Sher Y, Ashouri JF, et al. The "prediction of alcohol withdrawal severity scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol.* 2014;48(4):379-390.

Figure 1. Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens to voice (eye opening/contact) >10 sec
- 2	light sedation, briefly awakens to voice (eye opening/contact) <10 sec
- 3	moderate sedation, movement or eye opening. No eye contact
- 4	deep sedation, no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable, no response to voice or physical stimulation

Figure 2. Richmond Agitation Sedation Scale (RASS)

QR Code 1. Oregon Region Phenobarbital for Alcohol Withdrawal in ED Protocol

Protocol

QR Code 2. Nursing Education Video for the Phenobarbital Protocol

Education Video Link

Discussion

Patient Population

- At baseline, patients were similar in age, sex, race.
- The mean age was 47 years (range 25-75 years) in the phenobarbital group and 45 years (range 29-70 years) in the BZD group.
- Majority of patients were White or Caucasian.

Clinical Outcomes

- Patients who were treated with phenobarbital monotherapy did not require further ICU admission.
- Overall rates of further hospital admission were lower in the phenobarbital +/- BZD group compared to the BZD group (43.3% vs. 56.7%, respectively).
- Use of adjunctive agents were lower in the phenobarbital +/- BZD group compared to the BZD group (13.3% vs. 26.7%, respectively).
- Higher use of restraints noted in phenobarbital +/- BZD group compared to BZD (40% vs. 16.7%, respectively).
- Protocol compliance was noted in 60% of patients.

Study Limitations

- This is a retrospective, non-randomized study.
- Given recent protocol implementation, limitation of time post implementation
- Insufficient sample size required for adequate power to assess the primary and secondary outcomes
- Treatment bias due to patients in phenobarbital group also receiving BZDs and other adjunctive agents.
- Protocol compliance is difficult to assess.
- The baseline severity of alcohol withdrawal varied.

Preliminary Conclusions

- This study was performed to evaluate the safety and efficacy of phenobarbital for alcohol withdrawal compared to benzodiazepines in patients admitted to the ED at two large tertiary medical centers.
- Doses of phenobarbital and use of adjunctive sedative agents varied in patients due to individual provider prescribing practices.
- Statistical analysis is still underway but descriptive data suggest that phenobarbital may be a safe and effective treatment alternative to BZDs.
- Based on preliminary results, it appears that treatment with phenobarbital may result in reduced hospital admissions compared to standard BZD based regimens.
- Phenobarbital use may result in a reduction in the use of restraints or adjunctive agents.
- Many patients in the phenobarbital group were started on BZDs after receiving a dose of phenobarbital, which could lead to bias of results.
- Data should continue to be collected in a retrospective manner in order to adequately power this study and decrease the level of bias.
- Cost benefit analysis was not conducted in this study but the implications of phenobarbital in preventing further hospital admission, incidence of mechanical ventilation, and use of other adjunctive agents may result in cost savings that may be analyzed in the future.

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