Implementation of phenobarbital protocol for alcohol withdrawal syndrome in critically ill patients

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Background

- Alcohol withdrawal syndrome (AWS) involves autonomic hyperactivity related to neuroadaptation from chronic alcohol consumption[1-5]
- Benzodiazepines are the current treatment of choice, but chronic alcohol use can lead to conformational changes to the GABA receptor subunit and subsequent benzodiazepine resistance[2,6-8]
- Phenobarbital is a current alternative for AWS treatment. Unlike benzodiazepines, it binds GABA receptors at a different site and decreases glutamate activity[2,5,6]
- Prior to January 2024, there was no standard protocol for AWS management in the Intensive Care Unit (ICU) at Englewood Health
- We now have a protocol that utilizes phenobarbital as the main treatment choice

Objective

- To assess patient outcomes and workflow following implementation of a low intermittent dose phenobarbital protocol in patients admitted to the ICU with AWS

Methods

- Single center, retrospective chart review of patients greater than or equal to 18 years of age admitted to the ICU with AWS
- This study is still in progress
- Demographics, pertinent baseline characteristics, time of ICU admission and discharge, medication usage and administration times, labs, AWS severity scoring, and adverse events are being collected
- Clinical outcomes of patients treated for AWS compared between those treated within 12-months of phenobarbital protocol implementation and 6 months after
- Primary endpoints: development of AWS delirium and length of ICU stay
- Secondary endpoints: use of adjunctive treatments, time from ICU admission to administration of the first dose of phenobarbital, and need for bedside sitter
- Safety endpoints: incidence of hypotension, respiratory depression, elevation of liver function tests, and mortality
- Descriptive statistics used to summarize the data
- Categorical data analyzed using Fisher's exact test
- Normally distributed continuous data analyzed using independent student t test or Mann Whitney U test

Inclusion Criteria	Exclusion Criteria
• Patients ≥ 18 years old • Admitted to the ICU with/for AWS or developed AWS during ICU stay	• < 18 years old • Pregnancy • Allergy to phenobarbital, dexmedetomidine, or benzodiazepines • History of acute intermittent porphyria

AWS: Alcohol Withdrawal Syndrome
GABA: Gamma-aminobutyric acid
ICU: Intensive Care Unit

Results

Table 1. Baseline Characteristics

Characteristics	All N=28	Before Protocol N=25	After Protocol N=3
Male, no. (%)	24 (86)	21 (84)	3 (100)
Median age, years (IQR)	54 (19)	53 (20)	54 (13)
Race/Ethnicity, no. (%) • White • Asian • Black or African American • Hispanic or Latino • Other	 8 (29) 5 (18) 3 (11) 11 (39) 1 (3)	 8 (32) 5 (20) 2 (8) 10 (40) 0 (0)	 0 (0) 0 (0) 1 (33) 1 (33) 1 (33)
History of DT with or without history of alcohol withdrawal seizures, no. (%)	6 (21)	5 (20)	1 (33)
History of AWS admission, no. (%)	12 (43)	10 (40)	2 (67)
Admitting diagnosis, no. (%) • Alcohol-related complications • Overdose • Sepsis/infection • CV-related • GI-related • Endocrine-related	 12 (43) 2 (7) 6 (22) 2 (7) 4 (14) 2 (7)	 10 (40) 2 (8) 6 (24) 2 (8) 3 (12) 2 (8)	 2 (67) 0 (0) 0 (0) 0 (0) 1 (33) 0 (0)
CIWA score, median (IQR)	11 (11)	12 (11)	8 (9)
RASS score, median (IQR)	-2 (0.75)	-2 (0.75)	N/A
Patient intubated prior to AWS treatment initiation, no. (%)	6 (22)	6 (24)	0 (0)
Median SBP, mm Hg (IQR)	120 (44)	120 (43)	132 (20)
Median HR, bpm (IQR)	99 (21)	96 (21)	112 (18)

Table 2. Patient Outcomes

Outcome	All N=28	Before Protocol N=25	After Protocol N=3	P-value
Primary Endpoints				
Development of AWS delirium, no. (%)	6 (21)	6 (24)	0 (0)	1.000
Median length of ICU stay, days (IQR)	2 (1.7)	2 (1.7)	2 (0.7)	0.882
Secondary Endpoints				
Use of adjunctive lorazepam, no. (%)	10 (35.7)	10 (40)	0 (0)	0.533
Use of adjunctive dexmedetomidine, no. (%)	10 (35.7)	10 (40)	0 (0)	0.533
Median time from ICU admission to administration of 1st dose of AWS treatment, minutes (IQR)	120 (686)	180 (731)	40 (55)	0.177
Need for bedside sitter, no. (%)	1 (3.6)	1 (4)	0 (0)	1.000
Safety Endpoints				
Incidence of hypotension, no. (%)	1 (3.6)	1 (4)	0 (0)	1.000
Incidence of respiratory depression requiring intubation, no. (%)	0 (0)	0 (0)	0 (0)	1.000
Elevation of liver function tests (LFTs), no. (%)	3 (10.7)	3 (12)	0 (0)	1.000
Mortality, no. (%)	1 (3.6)	1 (4)	0 (0)	1.000

DT: Delirium Tremens
CIWA: Clinical Institute Withdrawal Assessment for Alcohol
CV: Cardiovascular
GI: Gastrointestinal
HR: Heart rate
IQR: Interquartile range
RASS: Richmond Agitation-Sedation Scale
SBP: Systolic blood pressure

Discussion

- Current data regarding the use of fixed-dose phenobarbital in treating AWS in ICU patients is limited
- Due to the small sample size, improvements in workflow and patient outcomes were non-significant
- Lack of familiarity with the protocol has limited its optimal use after implementation
- Other limitations in addition to the small sample size were the retrospective nature of the study, suboptimal provider and pharmacist education of the protocol, subjective CIWA scoring
- Furthermore, not all adjunctive benzodiazepines included in this analysis, AWS management prior to ICU admission was not reported
- Use of vasopressors, fluids, antihypertensives, sedatives for intubation were not reported and may have confounded the results for safety analysis

Conclusion

- The preliminary results of this study show no statistically significant differences in clinical and workflow outcomes after protocol-implementation
- Future directions would require
  - A larger sample size and extended timeframe given the initial hesitancy/delay regarding the use of the protocol
  - Comprehensive training and education of providers and pharmacists prior to protocol implementation
- The final outcome of the study is expected to provide insight into the benefits of standardizing therapy for AWS in our ICU

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