Benzodiazepines vs barbiturates for alcohol withdrawal: Analysis of 3 different treatment protocols

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ABSTRACT

Introduction: Alcohol withdrawal treatment varies widely. Benzodiazepines are the standard of care, with rapid onset and long durations of action. Recent drug shortages involving IV benzodiazepines have required incorporation of alternative agents into treatment protocols. Phenobarbital has similar pharmacokinetics to select benzodiazepines frequently used for alcohol withdrawal. The objective of this study is to describe the effectiveness and safety of our institutional protocols during three time periods utilizing benzodiazepines and barbiturates for the acute treatment of alcohol withdrawal in the emergency department.
Methods: Adult patients presenting to the ED for acute alcohol withdrawal from April 1st, 2016 to January 31st, 2018 were reviewed. Patients who received at least one dose of treatment were included. Treatments were based on availability of medication and given protocol at time of presentation. The primary outcome was the rate of ICU admission.
Results: 300 patient encounters were included. Overall baseline characteristics were equal across groups, except for age. There was no difference in rate of ICU admission from the ED between groups (D:8, L&P:11, P:13 patients, p = 0.99). Rate of mechanical ventilation was no different across all groups (D:1, L&P:3, P:3 patients, p = 0.55).
Conclusion: During benzodiazepine shortages, phenobarbital is a safe and effective treatment alternative for alcohol withdrawal. Incorporating phenobarbital into a benzodiazepine based protocol or as sole agent led to similar rates of ICU admission, length of stay, and need for mechanical ventilation in patients treated for alcohol withdrawal in the emergency department.

1. Introduction

Alcohol withdrawal is a significant problem in the United States with more than half of the 8 million people dependent on alcohol expected to suffer from withdrawal symptoms after a decrease in alcohol intake [1]. Roughly half of those will experience moderate to severe withdrawal symptoms and 5% will require treatment for their withdrawal in an emergency department [2-4]. The burden to the healthcare system is potentially significant. At our institution in 2009, in-hospital charges for alcohol withdrawal exceeded twenty eight million dollars [5].

The assessment and management of patients with alcohol withdrawal in the emergency department (ED) is variable across institutions [6]. With respect to assessment, the most widely used means of alcohol withdrawal assessment is the employment of the Clinical Institute Withdrawal Assessment (CIWA) and more recently the Clinical Institute Withdrawal Assessment of Alcohol Revised (CIWA-Ar) Scales. However,

as we have reported previously, neither of these scales are ideal for use in the clinical setting and especially in the ED [5]. The Minnesota Detoxification Scale (MINDS), a shorter alcohol withdrawal assessment tool developed to lessen the time spent doing each scheduled assessment (~3–5 min), has shown efficacy in the intensive care unit (ICU) population thus implemented in many ED's and ICU's [7].

Benzodiazepines, long considered the standard of care for the treatment of alcohol withdrawal syndromes, have a proven efficacy record. However, no consensus regarding what specific benzodiazepine is best, how it should be administered, or at what dosages has been established [1,8-12]. Intravenous regimens typically include those with a rapid onset and longer durations of action, such as diazepam or lorazepam, to utilize the self-tapering effect of the drug to its advantage.

Faced with the aforementioned uncertainty in management and a continued increase in the number of patients treated at our urban, safety-net hospital for alcohol related problems including withdrawal, we developed a new assessment and treatment protocol. Due to the lack of validation in ED patients and time constraints of the available assessment scales, we internally validated a new alcohol withdrawal severity assessment score, the Severity of Ethanol Withdrawal

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Symptoms Score (SEWS) [13] and developed an aggressive protocol for managing patients using diazepam in frequently administered, front-loaded doses. However, recent drug shortages involving most IV benzodiazepines have left institutions such as ours scrambling to incorporate alternative agents into their protocols [14,15].

The objective of this retrospective cohort study is to describe the effectiveness of three alcohol withdrawal protocols during three time periods utilizing benzodiazepines and barbiturates for the acute treatment of alcohol withdrawal in the emergency department.

2. Methods

2.1. Setting

This single center, retrospective observational cohort study was conducted at Denver Health Medical Center (DHMC), a vertically integrated, public safety-net institution, with 525 inpatient beds, and Level 1 trauma center in Denver, Colorado. Our emergency department sees roughly 100,000 patients annually. This study was approved by the Colorado Institutional Review Board.

2.2. Selection of participants

Adult patients presenting to the emergency department requiring medical treatment for acute alcohol withdrawal syndrome from April 1st, 2016 to January 31st, 2018 were reviewed for study inclusion. Patients were included if they were 18 years or older and received at least one dose of treatment according to documented SEWS symptom severity score as identified by querying the electronic medical record system. Patients were excluded if they were <18 years old, pregnant, incarcerated, did not have documented SEWS score, or did not receive treatment as part of our institutional protocol.

2.3. Interventions

All study participants were placed on the ED Alcohol Withdrawal SEWS Protocol, our symptom-triggered treatment protocol for acute alcohol withdrawal. Dependent on availability of IV benzodiazepines and barbiturates over the time period analyzed, 3 separate protocols were developed to account for product availability. Patients were treated according to the specific protocol that was implemented during those 3 separate time periods. These included intravenous diazepam alone (D), intravenous lorazepam & intravenous phenobarbital (L + P), or intravenous phenobarbital alone (P). See Fig. 1 for the phenobarbital based protocols.

2.4. Data collection methods

Data was collected from April 2016 to January 2017 for diazepam only protocol, June 2017 to July 2017 for lorazepam & phenobarbital protocol, and December 2017 to January 2018 for phenobarbital only protocol. These time frames correlated with the use of each individual protocol. Convenience sampling of consecutive patients was used to obtain data for each cohort. The electronic medical record was queried for all data points and endpoints of interest.

2.5. Outcome measures

The primary outcome measure was the rate of ICU admission from the ED. Secondary outcomes included rate of mechanical ventilation, overall rate of hospitalization, length of hospital stay, length of ICU stay, total dose of benzodiazepines in diazepam equivalents, total dose of phenobarbital, and number of protocol violations.

2.6. Statistical analysis

All data were recorded on a standardized data collection instrument. Continuous and categorical data were characterized with Mann-Whitney U test and chi-square tests, respectively. A p-value of ≤0.05 was considered to be statistically significant.
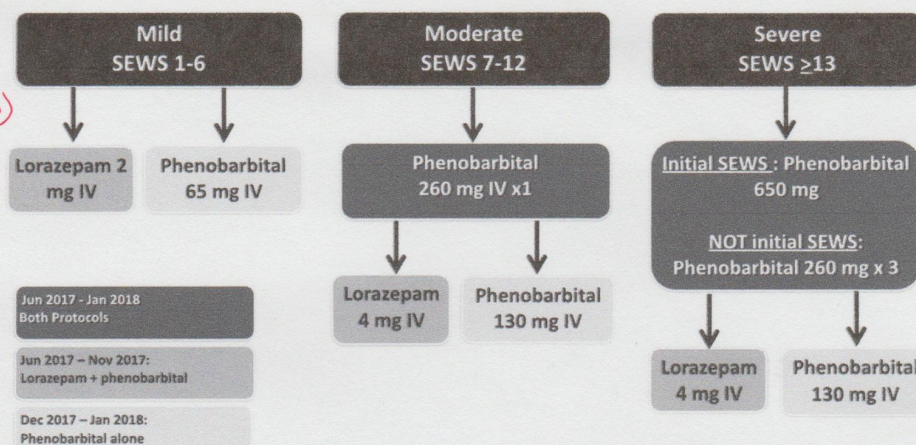
3. Results

Our 75-bed emergency department saw over 320 patients in the lorazepam & phenobarbital period, and 299 patients in the phenobarbital only period for alcohol withdrawal and treated according to our SEWS protocol. These patients were compared to our previous SEWS protocol utilizing diazepam which treated over 500 patients in that period. A convenience sample of 100 patients was obtained from each group and included for study analysis. Patients were excluded if documentation of SEWS scores were missing or incomplete or did not receive treatment according to the protocol in place at the time.

Baseline characteristics of patients included in the analysis are listed in Table 1. No statistically significant differences were found in the rates of primary diagnosis of AWS between the groups or initial severity scores. The median initial SEWS scores for the diazepam, lorazepam &

Mild SEWS 1-6	Moderate SEWS 7-12	Severe SEWS ≥13

Mild SEWS 1-6:
- Lorazepam 2 mg IV
- Phenobarbital 65 mg IV

Moderate SEWS 7-12:
- Phenobarbital 260 mg IV x1
  - Lorazepam 4 mg IV
  - Phenobarbital 130 mg IV

Severe SEWS ≥13:
- Initial SEWS : Phenobarbital 650 mg
- NOT initial SEWS: Phenobarbital 260 mg x 3
  - Lorazepam 4 mg IV
  - Phenobarbital 130 mg IV

Jun 2017 - Jan 2018 Both Protocols

Jun 2017 – Nov 2017: Lorazepam + phenobarbital

Dec 2017 – Jan 2018: Phenobarbital alone

Fig. 1. Institutional algorithms for AWS treatment utilizing phenobarbital in the Emergency Department at Denver Health Medical Center

Table 1
Baseline characteristics

Baseline characteristics	Diazepam alone (N = 100)	Lorazepam + phenobarbital (N = 100)	Phenobarbital alone (N = 100)	p-Value
Mean age (yrs)[a]	49	46	46	p = 0.07
Male (%)	76 (76%)	81 (81%)	75 (75%)	p = 0.55
Initial SEWS score (median)	7	8	8	p = 0.88
Initial severity of AWS				
Mild (n)	44	33	33	p = 0.76
Moderate (n)	48	48	51	p = 0.87
Severe (n)	8	19	16	p = 0.08
Primary diagnosis of AWS n (%)	29 (83%)	27 (83%)	34 (63%)	p = 0.07

[a] Range 25–74 years of age.

phenobarbital, and phenobarbital alone groups was 7, 8, and 8 respectively (p = 0.88). This represents moderate severity of withdrawal.

Table 2 represents the primary outcome, rate of ICU admission from the ED, and secondary outcomes. No differences were found in the primary outcome of ICU admission when compared against all three groups, nor individual comparison between any two groups (D: 22%, L + P: 23%, P: 24%, p = 0.99). Significant differences were found when comparing admission rates and length of stay. Admission rates were increased significantly in the phenobarbital alone group compared to the diazepam group which accounted for a 19% absolute difference in admission rates. However, the comparison between lorazepam & phenobarbital and diazepam overall admission rates were not significant when compared individually (p = 0.84). Rates of intubation (D: 1, L + P: 3, P: 3 patients, p = 0.55) and mean days intubated (D: 2, L + P: 1, P: 2 days) was similar between groups. Average length of stay in hours was overall lowest for patients treated with lorazepam + phenobarbital (D: 59, L + P: 51, P: 70 h, p = 0.04); Average ED length of stay was lowest with diazepam treated patients (D: 8, L + P: 10, P: 9 h, p = 0.01); Non-ICU floor length of stay was no different between groups (D:137, L + P:71, P:96 h, p = 0.26). Benzodiazepine equivalent requirements were significantly lower in the lorazepam & phenobarbital group vs. diazepam group, as to be expected. (D:154, L + P 97, P: 29 mg diazepam equivalents, p = 0.0001).

4. Discussion

The pharmacologic management of alcohol withdrawal has not changed much over the past few decades. Benzodiazepines, considered the standard of care for the treatment of alcohol withdrawal, enhance γ-aminobutyric acid (GABA$_A$) binding to the GABA$_A$ receptor subunit, causing hyperpolarization of the neurons producing their inhibitory effect, similarly to alcohol [16]. Over time, tolerance develops and GABA$_A$ receptors are down-regulated with chronic alcohol use therefore potentially making benzodiazepine use in this condition less effective, requiring escalating doses over time [1,16-19,21]. Alternative GABAergic agents including barbiturates, specifically phenobarbital, have been evaluated and have shown promising results in this regard but have not been accepted into widespread practice [22-24].

In this study we aimed to assess the safety and efficacy of incorporating phenobarbital into a treatment protocol for alcohol withdrawal. Given phenobarbital's pharmacokinetics, specifically its long duration of action and half-life, its self-tapering properties made it an attractive alternative during times of benzodiazepine drug shortages or benzodiazepine-resistant withdrawal. Based on studies that have evaluated the use of phenobarbital, we elected to develop our protocol with increasing doses of phenobarbital both alone and in combination with lorazepam, depending on availability.

Rosenson et al. demonstrated front-loading with phenobarbital, 10 mg/kg, reduced admission to the ICU by 17% and did not find any increase in adverse effects such as need for mechanical ventilation. Our protocols were developed with this strategy in mind but also included escalating doses of phenobarbital for all severity levels. Hendy et al., assessed the use of intravenous phenobarbital vs. lorazepam on mean ED LOS and hospitalizations and found no difference between the groups. Their analysis only included mild to moderate withdrawal patients as assessed by CIWA-Ar so results cannot be extrapolated to patients presenting in severe withdrawal.

In the current study, we found no difference in the rate of admission to the ICU utilizing a phenobarbital based alcohol withdrawal protocol (Table 2). This finding varies from Rosenson's analysis, and cannot be explained other than our vastly different approaches and protocols that were utilized. However, similarly to Rosenson, we found no increase in the need for mechanical ventilation in our population and a reduction in total benzodiazepine consumption using a loading dose initially in patients with severe withdrawal. Additional findings that varied from the evidence thus far include the higher rate of overall admission and longer ED length of stays when utilizing phenobarbital based alcohol withdrawal protocol.

Given the retrospective nature of this study, there are several notable limitations. These protocols were developed in light of ongoing drug shortages causing a transition from one benzodiazepine to another, then requiring the use of phenobarbital as our sole agent. We elected to review the efficacy and safety of each protocol retrospectively but in a time frame that would allow us to change the protocol if admission or safety outcomes were increasing unexpectedly. As this was not the case, no protocol underwent any change after implementation.

Table 2
Treatment outcomes

Variable	Diazepam alone (N = 100)	Lorazepam + phenobarbital (N = 100)	Phenobarbital alone (N = 100)	p value
ICU admission n(%)	8 (22%)	11 (23%)	13 (24%)	p = 0.99
Overall admission n(%)[a]	35	47	54	p = 0.024
Total length of stay (hrs)	59.10	50.98	69.77	p = 0.04
ED LOS	8.13	10.28	9.47	p = 0.01
Floor LOS	136.5	70.7	96.2	p = 0.26
ICU LOS	74.3	63.8	91.7	p = 0.21
Intubation (n)	1	3	3	p = 0.55
Days intubated	2	1	2	p = 0.49
Total diazepam equivalents (mg)[b]	154.3	97	29	p = 0.0001
Total phenobarbital (mg)[b]	0	257.4	454	p = 0.0001

[a] Diazepam vs phenobarbital group comparison p = 0.007.
[b] mg doses expressed as mean.

Table 3
Phenobarbital characteristics

Variable	Lorazepam + phenobarbital (N = 58)	Phenobarbital alone (N = 100)
Total phenobarbital doses (median)	1	3
Total phenobarbital (mg)[a]	257.4	454
Weight based dose (mg/kg)[a]	6.06	6.27
Protocol violations (n)	22	58

[a] Expressed as mean.

Additionally, education to providers was completed prior to each protocol implementation or change, but due to the onset of shortages the phenobarbital based protocols were implemented with limited advance education. This likely reflected our observation that more protocol violations occurred with our phenobarbital based protocols. Most violations involved administration of a lower dose than the protocol dose for that level of severity, suggesting that estimation of effect cannot be determined to be caused by medication or the protocol itself. Also, provider familiarity with phenobarbital's effect may have impacted admission rates early on during our initial phase of each protocol.

Convenience sampling to identify the first 100 patients during each time frame also may introduce significant sampling bias. The differences, albeit not statistically significant, in the rates of primary diagnosis of alcohol withdrawal in the phenobarbital alone group could have impacted the admission and length of stay rates to a greater extent than the treatment with either a benzodiazepine or barbiturate (Table 1).

Costs associated with each protocol could also be significant depending on the agent used. Currently, per dose costs between phenobarbital, diazepam, and lorazepam are considerably different. Phenobarbital costs 1.5–2 times greater than diazepam, which costs 20 times greater than lorazepam, per dose. While use of phenobarbital is costly, its use was associated with reduced benzodiazepine requirements and reduced phenobarbital doses (Table 3). A cost analysis of our treatment groups was not undertaken due to the significant variances in costs for each product during our observational periods.

In summary, utilization of phenobarbital is both safe and effective in patients presenting to the emergency department in acute alcohol withdrawal. Incorporation of phenobarbital into a benzodiazepine based protocol or as sole agent led to similar rates of ICU admission, length of stay, and need for mechanical ventilation in patients treated for alcohol withdrawal in the emergency department.

Source of support

None.

Prior presentations

Poster Presentation. American College of Clinical Pharmacists (ACCP) Global Annual Meeting 2018. Seattle, WA.

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