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Original Contribution

Single dose phenobarbital in addition to symptom-triggered lorazepam in alcohol withdrawal☆

Francisco Ibarra Jr, PharmD, BCCCP

Community Regional Medical Center, P.O. Box 1232, Fresno, CA 93715, United States of America

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ABSTRACT

Objective: The purpose of this study was to evaluate the safety and efficacy of a single parenteral dose of phenobarbital in addition to symptom-triggered lorazepam for the acute management of alcohol withdrawal syndrome (AWS).

Methods: This was a retrospective chart review of adult patients who presented to the Emergency Department with moderate or severe symptoms of alcohol withdrawal. Patients were included if they received at least 4 mg of lorazepam through the hospital's Alcohol Withdrawal Order Set on hospital day one. Patients who received a single parenteral dose of phenobarbital on hospital day one were compared to those who did not.

Results: Forty patients received phenobarbital and 38 patients received lorazepam only. Median daily lorazepam requirements, disposition, hospital length of stay, and median maximum daily CIWA-Ar scores were not statistically significant different between the groups. Significantly more patients in the phenobarbital group were discharged within three days in comparison to the lorazepam only group (9 patients vs. 2 patients, respectively, $p < 0.05$). In the lorazepam only group, two patients were intubated, one patient had delirium tremens, and no patients seized. In the phenobarbital group no adverse events were observed.

Conclusions: More patients were discharged within three days if they received a single parenteral dose of phenobarbital on hospital day one, in addition to symptom-triggered lorazepam for the acute management of AWS. Emergency Medicine physicians should consider ordering one parenteral phenobarbital dose on hospital day one to patients presenting with AWS.

1. Introduction

Acute alcohol withdrawal syndrome (AWS) is a common disease state encountered in the Emergency Department. In the United States, alcohol use disorder is among the leading causes of mortality and morbidity and is associated with significant health care resource utilization [1,2]. According to the 2015 National Survey on Drug Use and Health, 15.1 million adults had alcohol use disorder and the reported economic burden of alcohol misuse exceeded $200 billion [3,4].

The standard of care for managing AWS is symptom-triggered therapy with benzodiazepines (BZDs) [5-8]. Benzodiazepines reduce central nervous system excitability and the incidence of alcohol cessation related seizures through the enhancement of gamma-aminobutyric acid (GABA) at its receptors. Patients requiring high doses of BZDs or with refractory symptoms are often admitted to the intensive care unit for close monitoring and mechanical ventilation. In select patients, adjuvant therapy with anticonvulsants, antipsychotics, and alpha-2-agonists is warranted [9,10].

Phenobarbital, a barbiturate, has been used successfully in the management of AWS [8,11]. Phenobarbital increases the duration of GABA-A channel opening through directly binding to GABA-A receptors, whereas BZDs increase the frequency of channel opening through inducing a conformational change in GABA-A receptors and increasing GABA's affinity for GABA-A receptors [12]. Researchers have proposed that the two agents may work synergistically in the management of AWS due to differences in their GABA-A channel mediated processes. Studies evaluating this combination to date are limited, but have demonstrated a potential role for the addition of phenobarbital to standard care [8,13-15]. In the Rosenson J et al. study, a single dose of intravenous phenobarbital was associated with lower intensive care unit admission rates and was not associated with increased adverse events [14]. These findings have not been replicated and this approach to managing AWS is not recognized as standard care. Additional studies are warranted to confirm this approach to patient care. The purpose of this study was to evaluate the safety and efficacy of a single parenteral dose of phenobarbital in addition to symptom-triggered lorazepam for the acute management of AWS.

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E-mail address: fibarra@communitymedical.org.

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2. Methods

This was a retrospective chart review of adult patients at an academic medical center in Fresno, California who presented to the Emergency Department with a principal diagnosis of AWS during September 2015 to December 2017. The sole author performed a manual chart review of a system generated report of patients who received lorazepam through the institution's Alcohol Withdrawal Order Set. Patients were included if they were 18 years of age or older, presented with moderate or severe symptoms of alcohol withdrawal, and received at least 4 mg of lorazepam through the hospital's Alcohol Withdrawal Order Set on hospital day one. Moderate symptoms were defined as a Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) score of 9–15. Severe symptoms were defined as a CIWA-Ar score >15. Patients who received a single parenteral dose of phenobarbital on hospital day one were compared to those who did not.

All patients received symptom-triggered lorazepam through the institution's Alcohol Withdrawal Order Set during the study time period. The order set does not include phenobarbital; it was given at the discretion of the physician. Per protocol, patients received 2 mg of oral or intravenous lorazepam for moderate symptoms and 4 mg of intravenous lorazepam for severe symptoms. Per the order set, nurses could only administer lorazepam. Lorazepam doses other than 2 mg or 4 mg or administration of a BZD other than lorazepam required new orders. Patients who received a BZD other than lorazepam or received lorazepam outside of the Alcohol Withdrawal Order Set once the order set was placed were excluded as their care was not standardized and would be difficult to replicate in future studies. Additional exclusion criteria included: received dexmedetomidine, discharged within 24 h, received multiple doses of phenobarbital, and intubated on hospital day one.

The primary outcome measure was the total daily lorazepam dose administered in milligrams. Secondary outcomes included patient disposition and rates of intubation, seizures, and delirium tremens. Safety and efficacy data was collected through hospital day three. Patients' electronic medical records, including the physicians' progress notes and discharge summaries, were reviewed to determine past medical history and if an adverse event occurred. Total daily lorazepam dose requirements were obtained from the patients' medication administration record.

Non-normally distributed and normally distributed continuous variables were compared using the Mann-Whitney *U* test and Student's *t*-test, respectively. Dichotomous variables were compared using the Chi-Square test. A priori p-value of < 0.05 was used to determine statistical significance. All study measures and procedures were approved by the local Institutional Review Board. There are no conflicts of interest to report.

3. Results

Of the 400 patient charts reviewed, 322 were excluded. Forty patients received phenobarbital and 38 patients received lorazepam only. The most common met exclusion criterion were: received < 4 mg of lorazepam through the hospital's Alcohol Withdrawal Order Set on hospital day one ($n = 125$, 38.8%), received multiple phenobarbital doses ($n = 80$, 24.8%), and received a BZD other than lorazepam ($n = 51$, 15.8%). Past medical histories were not statistically significant different between the groups (Table 1). The phenobarbital group's median blood alcohol concentrations (BAC) on admission was 0.0 g/dL (interquartile range (IQR): 0.0–0.067), whereas the lorazepam only group's median BAC was 0.11 g/dL (IQR: 0.0–0.23). This finding was statistically significant (95% confidence interval (CI): 0.0–0.14). The median maximum daily CIWA-Ar scores were not statistically significant different on any day between the groups (Table 2). In the phenobarbital group, 24 (60%) patients received 260 mg, 14 (35%) received 130 mg, and 30 (75%) received the medication as a slow intravenous push.

Table 1
Patient characteristics.

	Lorazepam only ($n = 38$)	Phenobarbital ($n = 40$)	p-value
Median age, yr (IQR)	46 (39–58)	49 (39–56)	0.95
Males, n (%)	34 (90)	38 (95)	0.36
Past medical history, n (%)			
Alcohol withdrawal syndrome	15 (39.5)	23 (57.5)	0.11
Delirium tremens	2 (5.3)	4 (10)	0.43
Seizures	14 (36.8)	11 (27.5)	0.38

IQR: interquartile range.

Daily median lorazepam requirements were not statistically significant different between the groups on any day (Fig. 1). The lorazepam only group's median hospital length of stay was four days (IQR: 3–5), whereas the phenobarbital group's median hospital length of stay was five days (IQR: 3–6). This finding was not statistically significant. The number of patients discharged from the Emergency Department or admitted to the intensive care unit or general wards was not statistically significant different between the groups (Table 3). The phenobarbital group had significantly more patients discharged within three days compared to the lorazepam only group (9 patients vs. 2 patients, respectively, $p < 0.05$). In the lorazepam only group, two patients were intubated, one patient had delirium tremens, and no patients seized. In the phenobarbital group no adverse events were observed.

4. Discussion

More patients were discharged within three days if they received a single parenteral dose of phenobarbital on hospital day one, in addition to symptom-triggered lorazepam for the acute management of AWS. Lorazepam and phenobarbital are proven mono-therapies for AWS, but there is insufficient data to recommend combining the two [5-8,11,13-15]. This study adds support for the use of combination phenobarbital and symptom-triggered lorazepam for the management of AWS.

In the Rosenson J et al. study, patients were randomized to receive a single dose of intravenous phenobarbital (10 mg/kg) or normal saline, in addition to symptom-triggered lorazepam. Phenobarbital use was associated with lower intensive care unit admission rates and was not associated with increased adverse events [14]. In comparison to the Rosenson J et al. study, this study was not a prospective, controlled, randomized trial. Despite these notable limitations in methodology, this study was designed to assess the same intervention, single dose parenteral phenobarbital in addition to symptom-triggered lorazepam, on patient outcomes. Several studies have assessed the safety and efficacy of combination phenobarbital and BZDs, but were not designed to specifically evaluate patient outcomes following a single dose of phenobarbital on hospital day one [10,13,15]. This study positively contributes to the limited literature demonstrating favorable patient outcomes with this novel approach to managing alcohol withdrawal.

In the Rosenson J et al. study patients were randomized to receive a weight based phenobarbital dose (10 mg/kg) administered as an intravenous piggy-back infusion. In comparison, phenobarbital dosing was not standardized and given at the discretion of the physician in this study. This study found that a single dose, not to exceed 260 mg, given

Table 2
Median maximum daily CIWA-Ar scores.

	Lorazepam only	Phenobarbital	p-value
Score (IQR)			
Day 1	16 (12−20)	18 (12−21)	0.25
Day 2	11 (9–15)	11 (9–18)	0.89
Day 3	9 (3−12)	11 (4–17)	0.18

IQR: interquartile range.

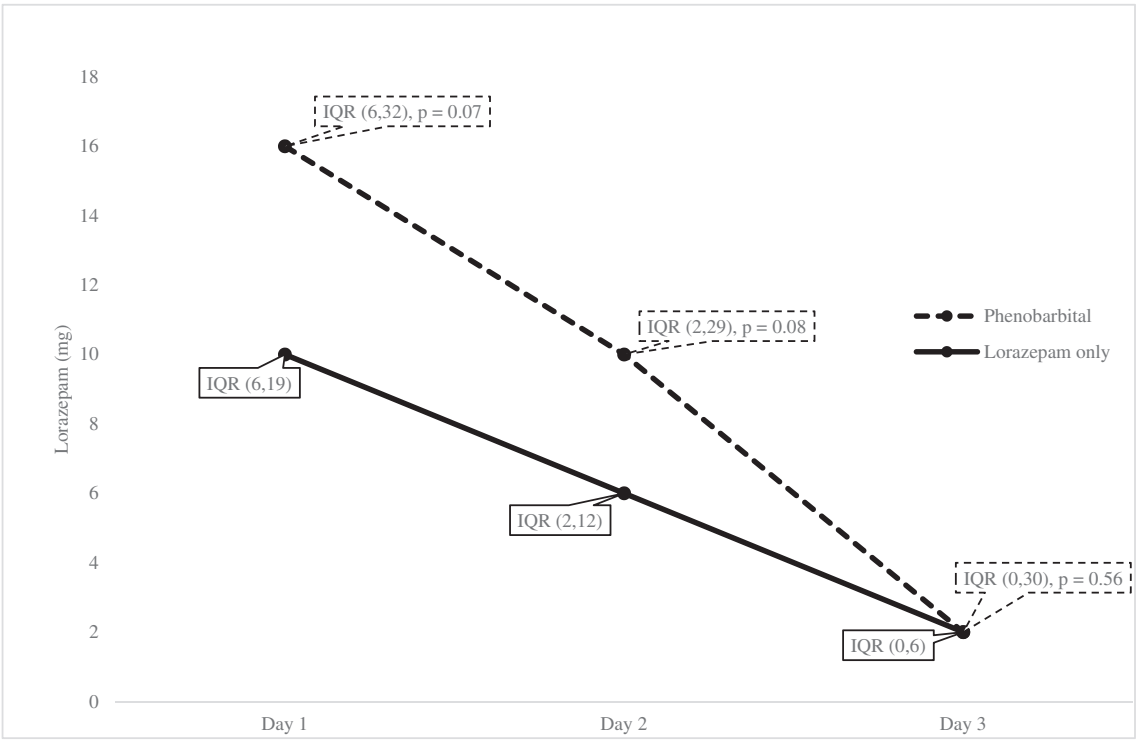

Fig. 1. Daily median lorazepam requirements. IQR: interquartile range.

as a slow intravenous push produced similar patient outcomes. The optimal dosing and administration of single-dose phenobarbital when given in addition to symptom triggered lorazepam remains unknown.

Median daily lorazepam requirements, disposition, hospital length of stay, and median maximum daily CIWA-Ar scores were not statistically significant different between the groups. However, significantly more patients in the phenobarbital group were discharged within three days in comparison to the lorazepam only group (9 patients vs. 2 patients, respectively). These findings may be attributed to phenobarbital's mechanism of action and pharmacokinetics. Phenobarbital increases the duration of GABA-A channel opening through directly binding to GABA-A receptors, whereas BZDs increase the frequency of channel opening through inducing a conformational change in GABA-A receptors and increasing GABA's affinity for GABA-A receptors. Phenobarbital has a half-life of 80–120 h, while lorazepam has a half-life of 14–20 h [12,16]. The positive results observed in the phenobarbital group are likely accredited to synergism and phenobarbital's long half-life yielding sustainable effects following a single dose.

This study was designed to identify the effects of the interventions on the initial management of AWS and a standardized process for managing AWS. In the Hendey et al. study, administration of phenobarbital on hospital day one was associated with control of alcohol withdrawal symptoms at the 48-h follow-up [8]. Based on Hendey et al.'s findings and phenobarbital's long half-life, any beneficial or harmful effects observed in this study were expected to be limited to 72 h. Therefore, safety and efficacy data was collected through hospital day three only.

Table 3
Patient disposition.

	Lorazepam only	Phenobarbital	p-value
n (%)			
Discharged from the Emergency Department	2 (5.3)	4 (10)	0.43
Admitted to the intensive care unit	4 (11)	2 (5.0)	0.36
Admitted to the general wards	32 (84)	34 (85)	0.92

Careful selection of inclusion criteria minimized the number of confounding variables and permitted the evaluation of a standardized approach to managing AWS. The study findings support a non-standardized approach to managing AWS.

Patients who received phenobarbital had lower median BAC on admission than those in the lorazepam only group. Due to variations in alcohol consumption and physiologic dependence, the impact of baseline BAC differences in this study cannot be confirmed. Blood alcohol concentrations vary significantly between patients and are affected by many factors such as sex, weight, comorbidities, and medications [17,18]. Although this finding was statistically significant, study findings were not expected to be influenced by differences in baseline BAC for the aforementioned reasons.

This study has several limitations. This was a small, single center, retrospective chart review. Author bias cannot be excluded given the author of this study performed data collection and analyses. Although no statistically significant differences were observed between the groups with regards to adverse events, this study was not powered to detect these differences. Since not all patients received the same phenobarbital dose, the optimal phenobarbital dose is unknown. This study excluded patients who received a BZD other than lorazepam or dexmedetomidine, which limits the generalizability of the study results. A sub-group analysis of patients who received dexmedetomidine or a BZD other than lorazepam is an area for future research. This study did not evaluate which patients received adjuvant therapies and cannot exclude the potential impact of these agents on the study findings. Given this study was a retrospective chart review, the patients' medical record was used as the primary source of data. Study findings are based on the assumption that documentation in the medical record was complete. Lastly, patients' length of hospital stay can be affected by many factors and this study did not account for competing principal diagnoses.

5. Conclusions

This study highlights the additive benefit of combining a single parenteral dose of phenobarbital with symptom-triggered lorazepam in

the management of AWS. Within the limitations of this study, no significant differences with respect to intubation, seizures, and delirium tremens were observed between the groups. Phenobarbital use was associated with significantly higher rates of patients being discharged within three days. Emergency Medicine physicians should consider ordering one parenteral phenobarbital dose on hospital day one to patients presenting with moderate or severe AWS, in addition to symptom-triggered lorazepam.

Meetings

N/A.

Declarations of interest

None.

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