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Parenteral Phenobarbital Monotherapy for Non-Severe Alcohol Withdrawal in Emergency Department Patients Managed and Discharged from a Provider at Triage Zone

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Abstract

Background: Few studies have assessed the safety and efficacy of discharging emergency department patients with alcohol withdrawal after receiving parenteral phenobarbital. This study aimed to validate this practice and delineate the role of intramuscular phenobarbital for this indication. Methods: This single-center retrospective chart review included adult patients with non-severe alcohol withdrawal, as diagnosed by treating providers based on clinical judgment, who were managed in the emergency department's low-acuity provider at triage zone, received parenteral phenobarbital, and were discharged within 12 h of arrival. The primary safety and efficacy endpoints were the percentages of patients who expired or re-presented to the emergency department for an alcohol-related diagnosis within seven days of the initial presentation, respectively. A subgroup analysis was performed to compare outcomes between those who only received intramuscular or intravenous phenobarbital. Results: Of the 192 patient encounters included, no deaths were reported. Twenty-one (10.9%) patients re-presented after the initial visit, received treatment, and were discharged home. One (0.52%) patient was admitted following re-presentation. The percentages of patients who re-presented in the intramuscular-only and intravenous-only groups were 8% and 13.5%, respectively (p = 0.25). The total and weight-based doses received were not significantly different between those who did and did not re-present in both the intramuscular-only and intravenous-only groups. The median length of stay in the intramuscular-only and intravenous-only groups was 3.97 h and 5.87 h, respectively ($p < 0.001$). Conclusions: Our findings suggest that patients presenting with non-severe alcohol withdrawal symptoms may be discharged from the emergency department following receipt of parenteral phenobarbital, without requiring additional outpatient alcohol withdrawal medications. Intramuscular phenobarbital appears to be a viable alternative route of administration and warrants further investigation.

Keywords: alcohol withdrawal syndrome; phenobarbital; emergency department

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1. Introduction

Ethanol is the most commonly abused drug in the world [1]. In the United States (US), alcohol abuse is the third leading cause of preventable death, and an estimated 95,000 individuals die annually from alcohol-related illnesses. Between 2006 and 2014, the rate of alcohol-related emergency department (ED) visits increased 47%, representing an annual

increase of 210,000 visits [2]. An estimated 18.5% of all US ED visits are alcohol-related. The US annual cost of alcohol misuse was $249 billion in 2010 [3]. Approximately one-third of patients presenting to the ED for an alcohol-related complaint experience moderate to severe alcohol withdrawal (AW) symptoms, including tachycardia, hypertension, tremors, seizures, and hallucinations [4]. Alcohol withdrawal is associated with increased utilization of institutional resources [5]. When AW progresses to delirium tremens, mortality rates approach 4% [6].

Phenobarbital and benzodiazepines are commonly utilized in the management of AW [7]. Both agents enhance inhibitory neurotransmission via GABA-A receptors, but through different mechanisms. Phenobarbital increases the duration of GABA-A channel opening through directly binding to GABA-A receptors independent of GABA, whereas benzodiazepines increase the frequency of channel opening in the presence of GABA [8]. In addition to enhancing inhibitory neurotransmission, phenobarbital suppresses excitatory neurotransmission [9].

Studies to date have primarily evaluated the role of phenobarbital in the inpatient setting, with few studies evaluating its role in the ED [10–14]. Due to phenobarbital's long half-life (50–140 h) resulting in a tapering effect, its pharmacological profile may permit providers to discharge patients from the ED after receiving treatment [15]. To our knowledge, only three studies have evaluated this approach [16–18]. In these studies, patients were discharged from the ED after receiving phenobarbital intravenously (IV) without additional outpatient prescriptions or increased risk for adverse effects. Despite these findings, this approach is not recognized as an option in the American Society of Addiction Medicine (ASAM) guidelines, possibly due to a limited number of studies evaluating this approach [7]. Therefore, this study aimed to validate this approach by evaluating re-presentation and mortality rates within seven days of the index visit and comparing outcomes between IV and intramuscular (IM) phenobarbital.

2. Materials and Methods

2.1. Study Setting

This was a single-center, retrospective chart review conducted at a 685-bed, academic-affiliated tertiary-level-one trauma center with an annual census of approximately 120,000 visits. All study measures and procedures were approved by the local Institutional Review Board, and there are no conflicts of interest to report. The waiver of consent was approved under 45 CFR 46.117 (c)(1)(i, ii, or iii)/21 CFR 56.109(c)1. This study was determined to involve no more than minimal risk and met all criteria for IRB approval under 45 CFR 46.111 and 21 CFR 56.111.

A system-generated report identified patients who were discharged with a diagnosis of AW from 1 January 2019 through 31 December 2019. Included in the study were patients $\geq$ 18 years of age who were discharged or left against medical advice from the ED within 12 h of presentation, had a diagnosis of AW, and received a parenteral (IV or IM) dose of phenobarbital (130 mg/mL) in the provider-at-triage (PAT) area. In the PAT area, providers diagnose and manage AW using their own clinical judgment as recommended in the ASAM guidelines [7]. Patients diagnosed with severe AW symptoms are transferred from the PAT area to the main ED to be managed. Patients were excluded if they were managed outside of the PAT area, transferred to another facility, received a benzodiazepine during their ED visit, or were prescribed a barbiturate or benzodiazepine on discharge.

2.2. Study Outcomes

The primary safety and efficacy endpoints were the percentages of patients who expired or re-presented to the ED for an alcohol-related diagnosis within seven days of the

initial presentation, respectively. Patients who re-presented were categorized into one of the following groups: (1) did not receive treatment, (2) received treatment, or (3) were admitted. Patients who did not re-present within seven days of the index visit but had a subsequent hospital encounter occurring after the 7-day index period were classified as surviving. Through the Care Everywhere function within EPIC, outside local hospital records were reviewed to determine if patients presented to an outside facility's ED. Secondary endpoints included the number of patients who, after receiving phenobarbital, developed hypotension requiring vasopressor support or experienced respiratory compromise necessitating non-invasive ventilation. A subgroup analysis was performed to compare outcomes between those who only received IM or IV phenobarbital.

2.3. Data Analysis

A system-generated report identified all phenobarbital recipients, who were then screened for eligibility. All data was obtained from the electronic medical record and collected by the study investigators using a standardized data collection tool. Interrater agreement was assessed across all collected variables, yielding a Cohen's kappa coefficient of 0.9. The diagnosis of AW was confirmed by reviewing providers' progress notes, phenobarbital dosing information was obtained from the medication administration record, and rates of hypotension and respiratory compromise were obtained from the patients' vitals flow sheet, which documents the use of vasopressors as well as oxygen support. Additional data manually obtained from the medical record included patient demographics, history of liver disease (cirrhosis, hepatitis, ascites) as noted in the patient's problem list, and length of stay. Patients who returned more than seven days after their previous visit were included and counted as a new, separate encounter. Descriptive statistics were used to summarize patient demographics and outcomes. Continuous data was assessed using the Mann–Whitney U test, and nominal data was assessed using the Pearson's chi-squared test. Statistical significance was determined with a p-value < 0.05.

3. Results

Of the 673 patient encounters reviewed, 192 met the inclusion criteria, of which 148 were unique patient encounters. Patients were excluded for the following reasons: having received a benzodiazepine during their ED visit (n = 462), having been prescribed a barbiturate or benzodiazepine on discharge (n = 12), and having been transferred to another facility (n = 7). The study cohort was primarily male, middle-aged, and White/Caucasian (Table 1). The majority of patients (70.8%) received a single phenobarbital dose and most often received their dose IV (Table 2). The median (interquartile range, IQR) dose received in the total population was 260 mg (130–260). The majority of patients were discharged home (87.5%), with the remainder leaving against medical advice.

There were no deaths reported in the cohort, and all patients who did not re-present within seven days of the index visit had at least one subsequent healthcare encounter documented after the initial presentation. Twenty-one (10.9%) patients in the total population re-presented after the initial visit, received treatment, and were discharged home. One (0.52%) patient was admitted on re-presentation. No patients required vasopressors or non-invasive ventilation. The median (IQR) length of stay in the total population was 5.19 h (3.53–6.88). Within the IM-only phenobarbital group, the total and weight-based doses received were not significantly different between those who did and did not re-present (Table 3). A similar finding was observed within the IV-only phenobarbital group.

Table 1. Patient demographics.

N	192
Male, n (%)	146 (76)
Age, years	46 (36–55)
Weight, kg	80.9 (68.2–90.9)
Race, n (%)	
American Indian and Alaska Native	2 (1.0)
Asian	8 (4.2)
Black or African American	10 (5.2)
Eastern Indian	8 (4.2)
White or Caucasian	158 (82.3)
Other	6 (3.1)
Liver disease, n (%)	32 (16.7)

Liver disease: cirrhosis, hepatitis, ascites. Values are reported as medians (interquartile ranges) unless stated otherwise.

Table 2. Phenobarbital dosing in the total population.

Number of doses administered per patient, n (%)	
1	136 (70.8)
2	49 (25.5)
3	7 (3.7)
Route of administration, n (%)	
IM-only	75 (39.1)
IV-only	104 (54.1)
IV and IM	13 (6.8)
Total dose received, mg	
All	260 (130–260)
IM-only	130 (130–260)
IV-only	260 (260–390)
IV and IM	390 (260–390)

IM: intramuscular; IV: intravenous. Values are reported as medians (interquartile ranges) unless stated otherwise.

In comparison to the IV-only phenobarbital group, the total and weight-based doses received were significantly lower in the IM-only phenobarbital group (Table 4). Sixty-eight (91%) patients who only received IM phenobarbital received a single dose, whereas 65% of patients who only received IV phenobarbital received a single dose ($p < 0.001$). The percentages of patients who re-presented after only receiving IM or IV phenobarbital were 8% and 13.5%, respectively ($p = 0.25$). The total and weight-based doses received in those who re-presented were not significantly different between those who only received IM or IV phenobarbital. The median length of stay in those who only received IM or IV phenobarbital was 3.97 h and 5.87 h, respectively ($p < 0.001$). In comparison to those who only received IV phenobarbital, the median time from ED presentation to when phenobarbital was given was significantly shorter in those who only received IM phenobarbital (104 min vs. 57 min, respectively).

Table 3. Within-group re-presentation rates.

	Yes	No	*p*-Value
IM-only, n (%)	6 (8)	69 (92)	-
Total dose, mg	195 (130–260)	130 (130–260)	0.84
Total weight-based dose, mg/kg	2.5 (1.4–3.3)	1.9 (1.5–3.4)	0.95
IV-only, n (%)	14 (13.5)	90 (86.5)	-
Total dose, mg	260 (228–293)	260 (260–390)	0.70
Weight-based dose, mg/kg	3.1 (2.3–4.1)	3.5 (2.5–4.6)	0.32

IM: intramuscular; IV: intravenous. Values are reported as medians (interquartile ranges) unless stated otherwise.

Table 4. Subgroup analysis of outcomes between those who only received intramuscular or intravenous phenobarbital.

	Intramuscular	Intravenous	*p*-Value
N	75	104	-
Male, n (%)	59 (79)	80 (77)	0.78
Age, years	46 (37–53)	47 (36–57)	0.75
Weight, kg	81.8 (70.5–95.5)	79.4 (68.2–90.9)	0.13
Liver disease, n (%)	11 (15)	17 (16)	0.76
Total dose, mg	130 (130–260)	260 (260–390)	<0.001
Total weight-based dose, mg/kg	1.9 (1.4–3.4)	3.4 (2.5–4.5)	<0.001
Re-presented, n (%)	6 (8)	14 (13.5)	0.25
Total dose, mg	195 (130–260)	260 (228–293)	0.19
Total weight-based dose, mg/kg	2.5 (1.4–3.3)	3.1 (2.3–4.1)	0.20
Length of stay, h	3.97 (2.57–5.78)	5.87 (4.02–7.59)	<0.001
Time from ED presentation to dose given, min	57 (35–147)	104 (54–163)	0.009
Time from dose given to discharge, min	133 (52–201)	225 (135–329)	<0.001

Values are reported as medians (interquartile ranges) unless stated otherwise.

4. Discussion

In this study evaluating the practice of discharging patients within 12 h of presenting to the ED with non-severe AW symptoms following the administration of parenteral phenobarbital, re-presentation rates were low, and no deaths were observed. Our findings suggest that phenobarbital's pharmacological profile may permit patients to be discharged from the ED without additional medications.

Our study findings positively contribute to the limited literature evaluating this approach. In Hendey et al., there was no significant difference in the 48 h mean follow-up Clinical Institute Withdrawal Assessment for Alcohol scores between patients discharged after receiving phenobarbital (5.8) and those treated with lorazepam in the ED plus chlordiazepoxide on discharge (7.2) [16]. In Lebin et al., patients discharged from the ED after receiving phenobarbital monotherapy (18%) or in combination with a benzodiazepine (20%) were significantly less likely to re-present to the ED in seven days than those who received benzodiazepine monotherapy (32%) [17]. Lastly, Staidle et al. did not find a significant difference in the number of patients who re-presented to the ED within 48 h after receiving phenobarbital monotherapy (17.1%), benzodiazepine monotherapy (15%), or combination phenobarbital-benzodiazepine therapy (13.5%) [18].

Although no deaths were observed in our study, administering long-acting agents such as phenobarbital to ED patients discharged home has theoretical concerns, including continued alcohol or opioid use upon discharge, which can potentiate the respiratory and central nervous system depressive effects of phenobarbital. However, patients discharged from the ED with a benzodiazepine taper are also at risk for adverse effects if taken concomitantly with central nervous system depressive substances. The true likelihood of someone experiencing an adverse event after being discharged from the ED following the receipt of phenobarbital is unknown, and this should be considered when determining disposition.

In the management of AW, timely administration of medications with a quick onset of action can prevent disease progression. Following IV phenobarbital administration, absorption is complete, and the onset of action is less than five minutes, with a peak response observed after 15 min [15]. Following IM phenobarbital administration, absorption is ~80% and the onset of action is slightly slower than IV administration, with a peak response observed within one to two hours [15,19]. Due to these pharmacokinetic differences, phenobarbital is primarily administered IV in the management of AW, and support for alternative routes of administration is scarce. In this study, the route of administration did not influence re-presentation or mortality rates, but did influence lengths of stay. Patients who only received IM phenobarbital received their dose significantly sooner after presenting to the ED, were more likely to only receive a single dose, and were discharged sooner than those who only received IV phenobarbital. Timely administration of phenobarbital through avoiding the need to place an IV line may have offset the delay in the drug's onset of action when given IM and prevented patients' symptoms from progressing to a state requiring additional doses, closer observation, and longer lengths of stay. However, differences in prescriber practices, patient severity, and nursing workflow were not evaluated and may have influenced these outcomes. Based on our findings, IM phenobarbital appears to be an acceptable alternative and should be further evaluated.

The suggested dosing of phenobarbital in the management of AW is variable, with multiple dosing schema utilized. In the present cohort, the re-presentation rate was 10.9% and the median dose administered in the total population was 260 mg. In comparison to our study, the re-presentation rate in Lebin et al. was lower (6%) and the median dose administered was higher (390 mg), suggesting that higher doses may be preferred [17]. However, in Staidle et al., the re-presentation rate was 17.1% and the mean dose administered was 424 mg [18]. Due to heterogeneity among the studies, direct comparisons cannot be made, and identification of the optimal phenobarbital dose should be evaluated in future studies.

Limitations

Several limitations must be acknowledged. This was a single-center retrospective study with a small sample size that was not powered to detect small differences. Selection bias, introduced by provider discretion in route of administration and dosing, may have influenced the study's findings. A substantial proportion of patients were excluded due to concomitantly receiving benzodiazepines or discharge medications based on provider discretion, which may limit the generalizability of our findings. Due to a lack of a comparator group, we do not know how parenteral phenobarbital compares to long-acting benzodiazepines. Since providers determined patients' symptom severity using their own clinical judgment, we are unable to objectively define symptom severity. Therefore, differences in length of stay between the IM-only and IV-only groups may have been influenced by underlying patient severity rather than solely by the route of administration. Furthermore, our findings may not be generalizable to institutions where clinicians have less experience managing patients with phenobarbital. We did not account for all factors that may impact

severity and treatment outcomes, such as blood alcohol levels. Since our study population consisted primarily of males, we are unable to determine the extent to which sex may have influenced the observed outcomes. Despite using the Care Everywhere function, visits to institutions not covered by this feature may have been missed. We did not evaluate for injection site pain with IM administration. Lastly, data abstractors were not blinded to the study hypothesis, which could have introduced bias.

5. Conclusions

Our findings suggest that patients presenting with non-severe AW symptoms may be discharged from the ED following receipt of parenteral phenobarbital without requiring additional outpatient AW medications. Additionally, intramuscular phenobarbital appears to be a viable alternative route of administration. The reported findings should be confirmed through prospective, controlled studies.

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Conflicts of Interest: The authors declare no conflicts of interest.

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