Evaluation of phenobarbital for prevention of alcohol withdrawal in trauma patients

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BACKGROUND: Up to 30% of trauma patients experience alcohol withdrawal syndrome (AWS) during their hospital admission, which is associated with worse outcomes. While benzodiazepines and phenobarbital are the mainstay of AWS management, there are limited data on the prevention of AWS. The objective was to evaluate the safety and efficacy of phenobarbital for the prevention of AWS.

METHODS: Adult patients admitted to a level 1 trauma center who received at least one dose of phenobarbital for the prevention of AWS between January 2019 and August 2021 were included. Patients were case matched to a control group managed with symptom-triggered therapy based on risk of AWS. Risk factors included sex, age, history of AWS/delirium tremens or withdrawal seizures, selected laboratory values, and screening questionnaires. The primary endpoint was the need for rescue therapy. Secondary endpoints included the time to rescue therapy, intensive care unit (ICU) length of stay (LOS), and hospital LOS.

RESULTS: Overall, 110 patients were included with 55 patients in each group. The phenobarbital group had higher baseline Injury Severity Scores ($p = 0.03$) and were more likely to be admitted to the ICU (44% vs. 24%; $p = 0.03$). The phenobarbital group required less rescue therapy (16% vs. 62%; $p < 0.001$) with a longer time to rescue therapy administration (26 vs. 11 hours; $p = 0.01$). The phenobarbital group had a longer hospital LOS (216 vs. 87 hours; $p = 0.0001$) but no difference in ICU LOS ($p = 0.36$). There was no incidence of delirium tremens or seizures and no difference in intubation rates ($p = 0.68$). There was no incidence of hypotension associated with phenobarbital.

CONCLUSION: Patients managed with phenobarbital had a lower need for rescue therapy for AWS with no increased adverse effects. Further studies should evaluate a protocol to prevent alcohol withdrawal in the trauma population. (*J Trauma Acute Care Surg.* 2023;95: 573–576.

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Pharmacotherapy; alcohol withdrawal syndrome; phenobarbital; trauma; benzodiazepine.

Alcohol is one of the most commonly used substances in the United States with 51.7% of adults consuming it recreationally at least once a month and 23.3% of adults engaging in binge drinking.[1] Traumatic injuries are one of the leading causes of mortality in patients with alcohol use disorder and up to 50% of surgical trauma patients present with a positive blood alcohol concentration (BAC).[2] In addition, it has been estimated that up to 30% of those patients will experience alcohol withdrawal syndrome (AWS) during their hospital admission.[3] The diagnosis and management of AWS in trauma patients may be delayed because of the similarity between AWS symptoms and the physiological response to traumatic injury.[4] Alcohol withdrawal syndrome is a potentially life-threatening illness and is a hospital complication, which is reported in the National Trauma Databank. Given the severity of the complication, efforts should target its prevention.[5]

Alcohol is a central nervous system depressant, and its abrupt cessation leads to generalized hyperexcitability of the brain through multiple pathways.[6] Prolonged alcohol consumption leads to a downregulation of γ-aminobutyric acid (GABA-A) receptors, resulting in a decreased GABA inhibitory activity. Simultaneously, *N*-methyl-D-aspartate receptors are inhibited, which result in an upregulation of the *N*-methyl-D-aspartate receptors with a subsequent increased responsiveness to the excitatory effects of glutamate. In addition, α-2 receptors are desensitized, which leads to an increased norepinephrine concentration. The combination of these mechanisms will result in the development of alcohol withdrawal symptoms such as anxiety, irritability, agitation, delirium, and seizures. If left untreated, complicated AWS is associated with a mortality rate of up to 20% compared with a mortality rate of 2% when patients are appropriately treated.[7,8]

Benzodiazepines are the mainstay treatment for AWS and have been shown to reduce the risk of recurrent alcohol withdrawal seizures and decrease withdrawal symptoms.[9,10] Benzodiazepines bind on the GABA-A receptor and increase the frequency of chloride channel opening, which results in the inhibition of neuronal excitability.[11]

Recent literature suggests that phenobarbital may provide a safe and effective alternative to benzodiazepines for the management of AWS.[12,13] Contrary to benzodiazepines, phenobarbital prolongs the chloride channel opening at the GABA-A receptor, thereby increasing the inhibitory effects upregulating GABA

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activity.[11] However, limited data support the use of phenobarbital for prophylaxis of AWS in trauma patients.[4,14,15] The objective of this study was to evaluate the safety and efficacy of phenobarbital for the prevention of AWS in the trauma population.

PATIENTS AND METHODS

A single center, case-matched, retrospective study was conducted for adults older than 18 years admitted to the trauma service at an academic level I trauma center who received at least one dose of phenobarbital for the prevention of AWS between January 1, 2019, and August 20, 2021. Institutional review board approval (H00023186) was obtained from the local institution. This study conforms with the STrengthening the Reporting of OBservational studies in Epidemiology guidelines, and a complete checklist has been uploaded as Supplemental Digital Content (Supplementary Data 1, http://links.lww.com/TA/D109).

The primary endpoint was the need for rescue therapy for AWS. Secondary endpoints included the time to rescue therapy, intensive care unit (ICU) length of stay (LOS), and hospital LOS. Patients were matched based on sex, age, history of AWS/delirium tremens (DT) or prior withdrawal seizures, BAC upon presentation, elevated laboratory values of aspartate aminotransferase and/or mean corpuscular volume, and screening questionnaires including the Binge Drinking Question; Screening, Brief Intervention, and Referral to Treatment; and Cut down, Annoyed, Guilty, and Eye-opener (CAGE). Additional data points included type and severity of injury, admission unit, Clinical Institute for Withdrawal of Alcohol (CIWA) score, phenobarbital regimen and duration of treatment, adjunctive therapy for AWS, and the incidence of new onset DT or seizures during hospitalization, as well as the rates of intubation and hypotension within 1 hour of phenobarbital administration. Hypotension was defined as systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or the use of vasopressor(s). Patients were identified from the local institution's trauma registry and the electronic medical record database. Patients were screened for alcohol abuse in three ways: Binge Drinking Question, BAC upon presentation, and CAGE questionnaire. If patients screened positive, then a Screening, Brief Intervention, and Referral to Treatment was performed. Patients were initiated on phenobarbital based on provider preference.

TABLE 1. Baseline Characteristics

Characteristic	Phenobarbital (n = 55)	Control Group (n = 55)	*p*
Sex, male, n (%)	44 (80)	43 (78)	0.81
Age, mean (SD), y	54 (15)	54 (15)	0.83
Weight, mean (SD), kg	77 (20)	77 (15)	0.86
History of AWS, n (%)	26 (47)	25 (45)	0.85
History of alcohol withdrawal complications, n (%)	5 (9.1)	2 (3.7)	0.44
Classification of injury, n (%)			0.27
Blunt trauma	49 (89)	53 (96)	
Penetrating trauma	6 (11)	2 (3.6)	
ISS, n (%)			0.03
≤15	33 (60)	45 (82)	
16–25	15 (27)	8 (15)	
>25	7 (13)	2 (3.6)	
Admission unit, n (%)			0.03
ICU	24 (44)	13 (24)	
General acute care floor	31 (56)	42 (76)	
Baseline laboratory values			
AST, median (IQR), U/L	40 (30–60)	35 (25–87)	0.66
MCV, mean (SD), fL	93 (6.5)	95 (5.4)	0.07
BAC, mean (SD), mg/dL	222 (116)	254 (112)	0.14
Screening survey, n (%)			
SBIRT	55 (100)	55 (100)	—

AST, aspartate transaminase; IQR, interquartile range; MCV, mean corpuscular volume; SBIRT, Screening, Brief Intervention, and Referral to Treatment.

TABLE 2. Primary Outcome

Outcome	Phenobarbital (n = 55)	Control Group (n = 55)	*p*
Rescue therapy for AWS administered, n (%)	9 (16)	34 (62)	<0.0001
Type of medication administered, n (%)			0.001
Benzodiazepine	4 (44)	33 (97.1)	
Phenobarbital	5 (56)	1 (2.9)	
CIWA score at time of rescue therapy, n (%)			0.01
>8: Mild-moderate	5 (56)	23 (96)	
>20: Severe	4 (44)	1 (4.2)	
Duration of AWS treatment (rescue doses only), median (IQR), h	0 (0–0)	5.6 (0–43)	0.0003
Total duration of phenobarbital for AWS prophylaxis and rescue doses, mean (SD), h	70 (56)	n/a	—

IQR, interquartile range; n/a, not applicable.

Percentages were presented for discrete variables. Standard deviations and mean were calculated for normally distributed continuous variables. Interquartile ranges and median were reported for skewed continuous variables. χ^2 Tests were performed to test for differences between medication groups for discrete variables, and Fisher's exact test was used when expected cell sizes were less than 5. The *t* test was used for comparing means between the two groups, while the Wilcoxon rank-sum test was used for skewed continuous variables. An α level of 0.05 was used as a criterion to determine statistical significance. All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC). Assuming an incidence of 30% of AWS and an anticipated reduction by 70% if treated with phenobarbital as prophylactic therapy, a sample size of 110 patients was calculated with 80% power.

RESULTS

A total of 110 patients were identified with 55 patients in the phenobarbital group and 55 patients in a control group. The control group consisted of those treated with benzodiazepines based on CIWA scores. Regarding baseline characteristics, the majority of patients were male with a mean age of 54 years (Table 1). There was no difference between the two groups with regard to history of AWS ($p = 0.85$) or alcohol withdrawal

complications ($p = 0.44$). In the phenobarbital group, there was a higher percentage of patients admitted to the ICU (44% vs. 24%, $p = 0.03$) and presented with higher Injury Severity Scores (ISSs) ($p = 0.03$). There were no differences in baseline aminotransferase ($p = 0.66$), mean corpuscular volume ($p = 0.07$), or BAC ($p = 0.14$), or CAGE questionnaire scores ($p = 0.48$).

Patients in the phenobarbital group required significantly less rescue therapy for AWS (16% vs. 62%, $p < 0.001$) (Table 2). The most common rescue therapy varied between the two groups in that phenobarbital was more commonly administered in the phenobarbital group and benzodiazepines in the control group ($p = 0.001$). Patients in the phenobarbital group were treated for AWS for a shorter duration than the control group ($p = 0.0003$), which was defined as the time from the first dose of medication given for rescue therapy to the last dose of medication given for rescue based on their CIWA scoring.

Secondary outcomes and dosing strategies are listed in Table 3 and Table 4, respectively. If rescue therapy was required, the need for treatment was delayed in the phenobarbital group compared with the control group (26 hours vs. 11 hours, $p = 0.01$). There was no difference in ICU LOS ($p = 0.36$). However, the phenobarbital group had a longer hospital LOS (216 hours vs. 87 hours, $p = 0.0001$). Patients with an ISS of ≤15 in the phenobarbital group had longer hospital LOS (165 hours vs. 71 hours, $p = 0.001$). In addition, there were more patients in the phenobarbital group who received adjunctive therapy (71% vs. 45%, $p = 0.01$). Treatments included clonidine, dexmedetomidine, haloperidol, ketamine, olanzapine, propofol, valproic acid, and, most commonly, gabapentin. However, given the retrospective nature of this study, it is unclear whether these medications were indicated specifically for AWS or other reasons such as agitation, pain, or sedation. There was a variety of phenobarbital dosing strategies with an average initial total daily dose of 115 mg and the most common frequency being every 12 hours. A subset of patients had a dose change within the first 24 hours with 22% of them undergoing a dose reduction.

For safety outcomes, none of the patients treated with phenobarbital or the standard of care developed complications from AWS, including new onset DT or seizures (Table 5). There was no difference in rates of intubation (7.3% vs. 3.7%, $p = 0.68$), and there was no incidence of hypotension after phenobarbital administration.

TABLE 3. Secondary Outcomes

Outcome	Phenobarbital (n = 55)	Control Group (n = 55)	*p*
Time to rescue therapy, median (IQR), h	26 (20–52)	11 (4.7–21)	0.01
Hospital LOS, median (IQR), h	216 (91–357)	87 (42–155)	0.0001
Hospital LOS by ISS			
ISS ≤15	165 (91–333)	71 (41–123)	0.001
ISS 16–25	122 (86–313)	102 (70–355)	0.77
ISS >25	327 (260–432)	288 (170–405)	0.66
ICU LOS, median (IQR), h	80 (44–245)	61 (43–205)	0.36
ICU LOS by ISS			
ISS ≤ 15	48 (43–153)	44 (31–61)	0.46
ISS 16–25	74 (55–262)	53 (43–231)	0.69
ISS >25	229 (213–264)	136 (67–205)	0.33
Adjunctive therapy for AWS,* n (%)	39 (71)	22 (45)	0.01
Clonidine	7 (18)	2 (9.1)	0.47
Dexmedetomidine	7 (18)	2 (9.1)	0.47
Haloperidol	4 (10)	3 (14)	0.70
Ketamine	3 (7.7)	2 (9.1)	0.99
Olanzapine	2 (5.1)	1 (4.6)	0.99
Propofol	3 (7.7)	1 (4.6)	0.99
Valproic acid	2 (5.1)	2 (9.1)	0.61
Gabapentin	35 (90)	15 (68)	0.08

*Adjunctive medications may have been ordered for indications other than the prevention of AWS, including agitation, sedation, or as part of a multimodal pain regimen.
IQR, interquartile range.

TABLE 4. Phenobarbital Dosing

	Phenobarbital (n = 55)
Total initial daily dose, mean (SD), mg	115 (53)
Loading dose only, n (%)	7 (13)
Loading dose followed by scheduled, n (%)	5 (9.1)
Every 8 h,* n (%)	7 (13)
Every 12 h,* n (%)	41 (75)
Every 24 h,* n (%)	1 (1.8)
Duration, mean (SD), h	88 (105)
Route, n (%)	
Intravenous	28 (51)
Oral	27 (49)
Dose change in <24 h, n (%)	
Titration	3 (5.5)
<20%	—
20–50%	1 (33)
>50%	2 (67)
Taper	12 (22)
<20%	—
20–50%	6 (50)
>50%	6 (50)

*These regimens were given scheduled without a loading dose.

TABLE 5. Safety Outcomes

Outcome	Phenobarbital (n = 55)	Control Group (n = 55)	*p*
New onset DT, n (%)	0	0	
New onset of seizures, n (%)	0	0	
Intubation, n (%)	4 (7.3)	2 (3.7)	0.68
Reason for intubation, n (%)			0.99
Respiratory failure	1 (25)	1 (50)	
Procedural sedation	—	—	
Operating room	1 (25)	0 (0)	
Other	2 (50)	1 (50)	
Hypotension* within 1 h of phenobarbital administration, n (%)	0	0	

*Hypotension defined as systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or the use of vasopressor(s).

DISCUSSION

Phenobarbital was effective in preventing AWS in adult trauma patients who were at risk for AWS. This study adds to the existing literature supporting the use of fixed dose phenobarbital to manage AWS and suggests that it may prevent AWS.[14–16] Previous studies used fixed dose phenobarbital for the treatment of AWS in the medical ICU and general medicine patients.[14–16] To date, Ammar et al.[15] is the only available published literature on the use of phenobarbital for AWS management in the surgical-trauma population. However, one of the limitations of Ammar et al.[15] is the lack of a comparator group. In our study, 16% of patients managed to phenobarbital, and 62% of patients managed with standard care required symptom-triggered treatment; however, none of these patients developed severe alcohol withdrawal-related complications such as DT or seizures. These findings suggest the potential benefit of phenobarbital to prevent AWS.

The optimal dosing strategy for phenobarbital to prevent AWS is unknown, and there is no standard dosing protocol in place. As such, there was variability with the dosing regimens used in this study. Patients who required rescue therapy had received suboptimal dosing of phenobarbital, either omitting a loading dose or potentially tapering a scheduled regimen too quickly.

Regarding the safety profile of phenobarbital, there is a potential risk of respiratory depression. There were four intubated patients in the phenobarbital group; however, intubation was not related to an adverse effect of the phenobarbital. Two patients required intubation because of severe agitation, one intubation occurred in the operating room, and one patient was intubated for respiratory failure related to a chest wall injury. In the control group, one patient was intubated for respiratory failure and had a pulmonary injury complicated by a chronic obstructive lung disease exacerbation, and the other patient was intubated for airway protection with suspicion of aspiration.

There were several limitations to this study. First, this was a retrospective analysis with inherent limitations to the study design and patient selection. Second, while an attempt was made to minimize confounding variable through case matching, there was a significant difference in severity and level of care needed between the two groups. While there was a longer hospital LOS in the phenobarbital group, specifically those with an ISS of ≤15, this may be attributed to the higher risk of AWS in that group. Prescribers may have initiated phenobarbital if they had a strong suspicion that their patient may develop AWS, which could have resulted in a longer hospital LOS. In addition, more patients received other adjunctive treatments in the phenobarbital group. Of note, while the most common adjunctive therapy was gabapentin, this may have been primarily ordered as a part of multimodal pain regimens instead of used for AWS. While CIWA scores were collected at the time of rescue therapy and subsequent scores were not trended, the significantly shorter treatment time for AWS suggests that phenobarbital may have helped prevent further AWS. Furthermore, this institution did not have a standard dosing algorithm based on risk factors, which led to a variety of dosing strategies.

In summary, this study provides insight into a novel approach using phenobarbital to prevent AWS in the adult trauma population. Phenobarbital was associated with significantly less symptom-triggered treatments when compared with the standard of care. These findings may be used to help implement a protocolized approach to use phenobarbital to prevent AWS in this population.

AUTHORSHIP

L.M.K. and I.L. conducted the literature search. L.M.K., I.L., A.F., and J.D. D. acquired, analyzed, or interpreted the data and were responsible for the study concept and design. L.M.K. drafted the article, and I.L., A.F., and J.D.D. assisted in revising it for important intellectual content. All authors approved the final version of the article.

DISCLOSURE

The authors declare no conflicts of interest.

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