



TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME: PHENOBARBITAL VS CIWA-AR PROTOCOL

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Background Benzodiazepine-based therapy for alcohol withdrawal is associated with agitation and respiratory depression. Treatment can be complicated by a need for adjunctive therapy to control these symptoms and in patients requiring mechanical ventilation. Strong evidence for the effectiveness of alternative treatment modalities is lacking, despite the availability of promising pharmacological agents such as phenobarbital.

Objective To compare the standard of care for the treatment of alcohol withdrawal—a symptom-triggered benzodiazepine protocol used in conjunction with the revised Clinical Institute Withdrawal Assessment of Alcohol (CIWA-Ar) scale—with a phenobarbital protocol.

Methods Retrospective cohort study conducted from January 2016 through June 2017 at a 42-bed medical intensive care unit in a private teaching hospital in Nashville, Tennessee. The primary outcome was intensive care unit length of stay. Secondary outcomes included hospital length of stay, incidence of invasive mechanical ventilation, and use of adjunctive pharmacotherapy.

Results Patients who received phenobarbital had significantly shorter stays in the intensive care unit than did those who received therapy based on the CIWA-Ar scale (mean [SD], 2.4 [1.5] vs 4.4 [3.9] days; $P < .001$). Those who received phenobarbital also had significantly shorter hospital stays (4.3 [3.4] vs 6.9 [6.6] days; $P = .004$). The incidence of invasive mechanical ventilation was lower in the phenobarbital group (1 [2%] vs 14 [23%] patients; $P < .001$), as was use of adjunctive agents for symptom control, including dexmedetomidine (4 [7%] vs 17 [28%] patients; $P = .002$).

Conclusion A phenobarbital protocol for the treatment of alcohol withdrawal is an effective alternative to the standard-of-care protocol of symptom-triggered benzodiazepine therapy. (*American Journal of Critical Care*. 2018;27:454-460)

CE 1.0 Hour

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doi:<https://doi.org/10.4037/ajcc2018745>

Alcohol withdrawal syndrome (AWS) is a life-threatening medical condition characterized by dysregulation of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) and the excitatory neurotransmitter glutamate.^{1,2} Historically, this syndrome has been managed with standardized administration of benzodiazepines, supportive care, and continuous evaluation using a validated clinical scale, such as the revised Clinical Institute Withdrawal Assessment of Alcohol scale (CIWA-Ar).³ However, with alcohol use disorder remaining a highly prevalent problem nationwide, several limitations of this approach have become apparent.⁴

The standard of care for AWS revolves around CIWA-Ar-based administration of benzodiazepines. This protocol places a heavy burden on the nursing staff, as it requires frequent reassessment of the patient beyond traditional clinical monitoring. Additionally, patients receiving large cumulative doses of lorazepam are at risk for development of both delirium and respiratory depression.⁵ Other pharmacological agents, such as dexmedetomidine and propofol, can be used adjunctively to reduce the total amount of benzodiazepines given or to control refractory symptoms. This approach, however, may increase cost (in the case of dexmedetomidine) or require mechanical ventilation (in the case of propofol).⁶ Little has been published in support of the use of alternative strategies for treating AWS. Thus, clinicians are left with few options for the management of these complex patients.

Phenobarbital is a promising therapeutic option for management of AWS because of its potentiating activity on GABA receptors and its antagonizing activity on NMDA (*N*-methyl-*D*-aspartate) and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors.^{7,8} This mechanism of action differs from that of benzodiazepines, which act solely to

potentiate GABA without affecting the increased activity of glutamate on neuronal receptors. The long half-life of phenobarbital eases the burden of administration compared with benzodiazepines, which may need to be given more than once per hour. Phenobarbital's long half-life also allows for a gradual transition off of therapy after the last dose is provided. Previous studies on the use of phenobarbital for the treatment of AWS have relied on weight-based dosing (10 mg/kg) or a strategy of escalating or de-escalating doses, beginning at 60 mg or 260 mg, respectively.⁹⁻¹² However, a simple and practical phenobarbital protocol has yet to be established.

The standard of care for AWS revolves around administration of benzodiazepines.

Methods

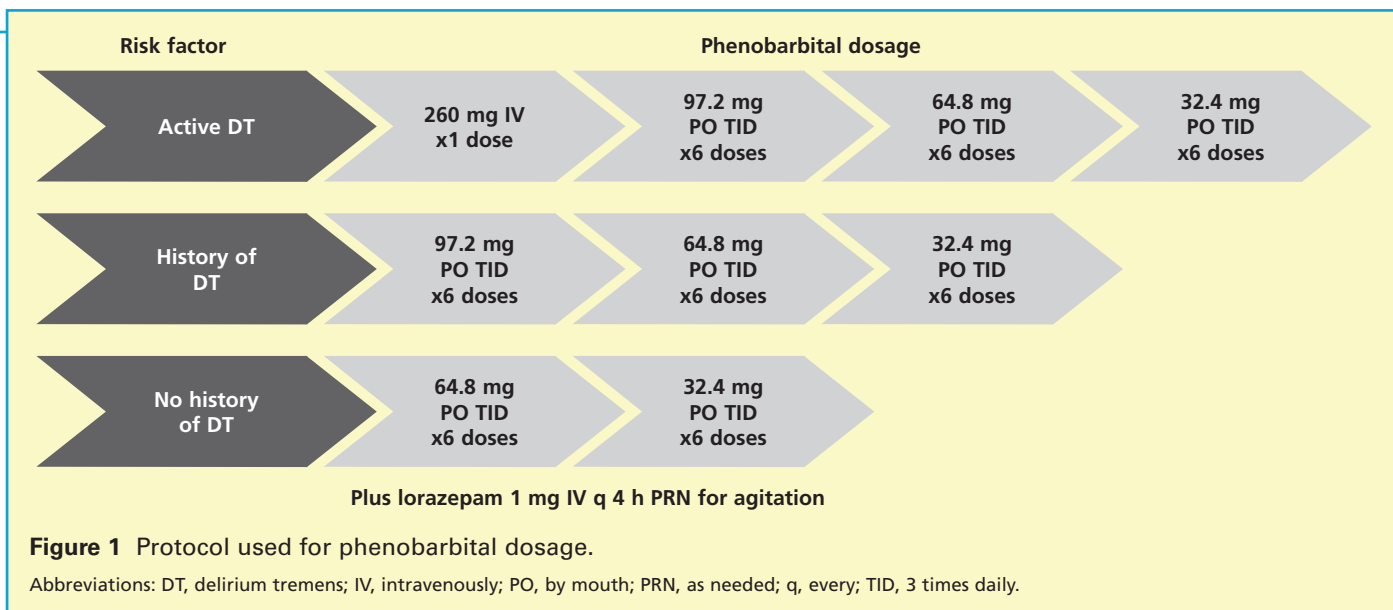
Study Design

We conducted a retrospective cohort study at a 42-bed medical intensive care unit (ICU) in a private teaching hospital in Nashville, Tennessee. The study included medical ICU patients admitted from January 1, 2016, through June 30, 2017, and treated for the onset or prevention of AWS. At the study institution, the standard of care for treating AWS had been the use of a benzodiazepine protocol in conjunction with the CIWA-Ar scale. Patients with suspected AWS receive the same treatment as those with diagnosed AWS, as long as they continue to exhibit symptoms. However, with high readmission rates for AWS and large cumulative doses of benzodiazepines given to these patients, practitioners began to explore the use of alternative agents to help prevent benzodiazepine-associated agitation and respiratory depression, as well as to help treat benzodiazepine-refractory cases. Beginning in 2017, a phenobarbital protocol was implemented as an alternative course of therapy for AWS given this agent's appealing pharmacokinetic and pharmacodynamic properties and the available literature suggesting beneficial outcomes. This study was conducted to validate a

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previously used phenobarbital protocol as compared with the historical standard of care at the study institution.

Patients were excluded from the study if they had received CIWA-Ar–based treatment for more than 24 hours before starting the phenobarbital protocol, had received no doses of either protocol, were currently pregnant or had a positive pregnancy test, left against medical advice within 24 hours of presentation, died within 24 hours of presentation, or had phenobarbital as a documented outpatient maintenance medication. Patients who had received either therapy protocol during the study period were identified by a report run in the electronic medical records system. An initial record search was conducted to identify patients who received the phenobarbital protocol, which began in 2017. At the time of collection, data through June 2017 were available. Patients with confirmed or suspected AWS were identified

by the attending or admitting physician. Cases were screened and included in the study based on inclusion and exclusion criteria and sorted into 1 of 2 groups according to patient management, with the goal of having equal numbers in each group. Data collection and analysis occurred

after all patient cases meeting the inclusion criteria were identified. The Sterling Institutional Review Board approved the study and waived the requirement to obtain informed consent.

Baseline characteristics and patient demographics were collected by retrospective manual review of patient records. For the purpose of the study, a patient was counted as having abnormal liver laboratory

values on admission if his or her initial laboratory testing included any of the following: aspartate aminotransferase or alanine aminotransferase level 3 times the upper limit of normal, platelet count less than $150 \times 10^3/\mu\text{L}$, total bilirubin level less than 0.3 mg/dL or greater than 1.1 mg/dL (to convert to micromoles per liter, multiply by 17.104), direct bilirubin level greater than 0.2 mg/dL (to convert to micromoles per liter, multiply by 17.104), or an albumin level less than 3.8 g/dL or greater than 5 g/dL. The primary efficacy outcome was the difference in ICU length of stay (LOS) between the 2 protocols. Secondary outcomes measured included hospital LOS, use of invasive mechanical ventilation, and use of adjunctive and sedating agents to control AWS symptoms. The primary and secondary efficacy end points of ICU and hospital LOS were measured in days, defined as the patient's location at midnight. The secondary end points of invasive mechanical ventilation and adjunctive or sedative agent use were measured in number of occurrences and frequency in each group and were not present at the time of group assignment.

In the phenobarbital protocol, patients received a tapered regimen of phenobarbital, with the starting dose dependent on assessment of risk factors by the admitting physician, as shown in Figure 1. As this was a retrospective study of a previously implemented protocol, each stage of the phenobarbital taper was allowed to be extended by the attending physician as clinically warranted. Duration of therapy was also guided by the attending provider. The doses used in the protocol were extrapolated from previous publications, with consideration given to commercially available dosage forms and ease of administration. Lorazepam was included in the phenobarbital protocol as an as-needed adjunctive agent if the provider deemed it clinically necessary. Patients receiving

ICU length of stay was compared between the standard treatment protocol and the phenobarbital protocol.

CIWA-Ar-based lorazepam were evaluated on the CIWA-Ar scale as described in previous publications and treated with the regimen depicted in Figure 2.

Evaluation of adjunctive medications for control of symptoms related to alcohol withdrawal included the use of haloperidol, quetiapine, olanzapine, and dexmedetomidine. For comparison, all benzodiazepines that were administered to the patient in the ICU were converted to lorazepam equivalents based on previously published conversion scales, as shown in Table 1.^{13,14}

Data Analysis

The primary outcome of ICU LOS was analyzed using a *t* test for continuous data. Secondary outcomes and background characteristics were analyzed using appropriate statistical tests: *t* test for continuous variables and χ^2 test for nominal variables. *P* less than .05 was considered statistically significant. We completed statistical analyses using JMP Pro, version 11.2.0 (SAS Institute Inc).

Results

A total of 147 patients were screened for eligibility, and 120 patients met inclusion criteria for participation in the study, with 60 receiving treatment with the phenobarbital protocol and 60 receiving treatment with the CIWA-Ar protocol. The most common reason for exclusion was overlapping of ordered protocols that exceeded 24 hours, which affected 18 patients. Three patients were excluded for not starting treatment for AWS within 24 hours after admission to the medical ICU, 3 were excluded for having phenobarbital listed as a documented home medication, and 3 were excluded for leaving against medical advice within the first 24 hours after presentation. A post hoc power analysis revealed the study to have 96% power with an α of .05 and the effect size seen between groups for the primary outcome.

Baseline demographics (Table 2) of the 2 cohorts were similar with regard to sex and ethnicity. A statistically significant difference was found between the 2 groups in mean age (45 years in the phenobarbital group vs 52 years in the CIWA-Ar group). The 2 groups had similar incidences of comorbid medical conditions potentially affecting alcohol withdrawal as documented in the patient record, including psychiatric disorder, seizure disorder, reactive airway disorder, liver disease, and polysubstance abuse. The incidence of abnormal liver laboratory values on admission was also similar in the 2 groups. No difference between groups was found in documented history of delirium tremens (DT) or withdrawal seizures, or in number of patients presenting in active withdrawal.

Initial or rising CIWA-Ar score

5-9: lorazepam 1 mg IV q 4 h
10-14: lorazepam 2 mg IV q 2 h
15-19: lorazepam 3 mg IV q 1 h
20-24: lorazepam 4 mg IV q 30 min
25-29: lorazepam 5 mg IV q 15 min
30-34: lorazepam 6 mg IV q 10 min

Stable or falling CIWA-Ar score

5-9: lorazepam 1 mg IV q 8 h
10-14: lorazepam 2 mg IV q 4 h
15-19: lorazepam 3 mg IV q 2 h
20-24: lorazepam 4 mg IV q 1 h
25-29: lorazepam 5 mg IV q 30 min
30-34: lorazepam 6 mg IV q 10 min

≥35: lorazepam 6 mg IV x 1 dose, lorazepam infusion at 4 mg/h, increase by 2 mg/h q 30 min until score stabilizes or falls

Figure 2 CIWA-Ar protocol.

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; IV, intravenously; q, every.

Table 1
Lorazepam equivalents

Benzodiazepine	Dose to equal 1 mg of lorazepam, mg
Alprazolam, tablet	0.5
Chlordiazepoxide, capsule	12.5
Clonazepam, tablet	2
Diazepam, tablet or intravenous injection	5
Midazolam, intravenous injection	2

Table 2
Baseline patient demographics

Demographics	CIWA-Ar arm (n=60)	Phenobarbital arm (n=60)	<i>P</i>
Age, mean (SD), y	52 (15.5)	45 (11.4)	.003
Race, No. (%) of patients			>.99
White	57 (95)	57 (95)	
Black or African American	2 (3)	1 (2)	
Other	1 (2)	2 (3)	
Male sex, No. (%) of patients	43 (72)	44 (73)	.84
Left against medical advice, No. (%) of patients	1 (2)	3 (5)	
Comorbid conditions			
Psychiatric disorder	29	29	>.99
Polysubstance abuse	10	10	>.99
Seizure disorder	5	8	.41
Reactive airway disorder	8	6	.59
Liver disease	14	16	.68
Previous delirium tremens or withdrawal seizures	27	32	.92
Clinical presentation on admission			
Abnormal liver laboratory values	30	38	.17
Active alcohol withdrawal/delirium tremens	20	28	.46

Abbreviation: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised.

Primary and secondary outcomes are reported in Table 3. Use of the phenobarbital protocol was associated with a statistically significant reduction

Table 3
Outcomes and clinical characteristics

Outcome or clinical characteristic	CIWA-Ar arm (n=60)	Phenobarbital arm (n=60)	P
ICU stay (midnights), mean (SD)	4.4 (3.9)	2.4 (1.5)	<.001
Hospital stay (midnights), mean (SD)	6.9 (6.6)	4.3 (3.4)	.004
Total lorazepam equivalents, mean (SD), mg	35.2 (48.5)	11.3 (18)	<.001
Ventilator use, No. of patients	14	1	<.001
Dexmedetomidine use, No. of patients	17	4	.002
Olanzapine use, No. of patients	7	5	.54
Haloperidol use, No. of patients	10	4	.08
Quetiapine use, No. of patients	5	2	.24

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; ICU, intensive care unit.

in ICU LOS of 2 days (mean [SD], 2.4 [1.5] vs 4.4 [3.9] days; $P < .001$). The phenobarbital protocol was also associated with a statistically significant reduction in total hospital LOS of 2.6 days (4.3 [3.4] vs 6.9 [6.6] days; $P = .004$). The incidence of mechanical ventilation was lower in patients treated with the phenobarbital protocol than in those treated with the CIWA-Ar protocol (1 [2%] vs 14 [23%] patients). Additionally, use of adjunctive medications to control alcohol withdrawal symptoms was markedly

lower in patients treated with phenobarbital. Specifically, the number of patients receiving dexmedetomidine was much lower in the phenobarbital group than in the CIWA-Ar group (4 [7%] vs 17 [28%]; $P = .002$), with most patients receiving dexmedetomidine for symptom control while not receiving mechanical

ventilation. Only 4 patients in the CIWA-Ar cohort and 1 patient in the phenobarbital cohort were receiving both mechanical ventilation and dexmedetomidine. This trend of decreased use was also seen with other adjunctive agents, including haloperidol and quetiapine. Olanzapine use was similar between the 2 groups. The average cumulative lorazepam equivalents were significantly lower in patients treated with phenobarbital than in patients treated with the CIWA-Ar protocol (11.3 [18] vs 35.2 [48.5] mg; $P < .001$).

Discussion

In this retrospective cohort study, we found that use of a phenobarbital protocol for AWS was associated with a significant reduction in ICU LOS. Other

studies using phenobarbital have shown a decrease in ICU admission rate and a trend toward reduction of ICU LOS.^{11,12} Our study corroborates these results and provides further evidence that phenobarbital is an effective treatment for AWS. We also found phenobarbital use to be associated with reduced hospital LOS, indicating that patients are not requiring additional hospital days once they are transferred out of the ICU. Patients receiving phenobarbital also had less use of adjunctive agents for control of AWS symptoms, such as quetiapine, haloperidol, and olanzapine. A significant decrease in the use of dexmedetomidine was found. In most cases requiring dexmedetomidine, the agent was used for behavioral control, and propofol was the most commonly used ventilator sedative. This reduction in sedation needs for patients being treated with phenobarbital has been reported previously,¹⁰ as has our observed reduction in the incidence of invasive mechanical ventilation.² Average cumulative lorazepam equivalents were significantly lower in patients receiving the phenobarbital protocol.

The patients included in this study had similar baseline characteristics as well as a similar incidence of comorbid conditions, which may have affected clinical course such as need for mechanical ventilation due to preexisting respiratory disorder or avoidance of hepatotoxic medications in advanced liver failure. There were no extreme examples of abnormal laboratory values in either group. On average, patients receiving the phenobarbital protocol were significantly younger than those receiving the CIWA-Ar protocol; however, this difference is probably not clinically meaningful. Most patients in both cohorts were white and male, which is consistent with national trends for patients seeking treatment for alcohol use disorders.¹⁵ Many clinicians' reservations about using phenobarbital include concerns about respiratory depression, drug interactions, and the medication's long half-life. In this study, no patients in either cohort underwent early cessation of therapy due to onset of adverse effects, such as respiratory depression or unmanageable agitation or delirium. This finding is supported by the limited literature available suggesting that respiratory depression associated with phenobarbital use in AWS is a rare complication of treatment, even with large loading doses.^{9,16,17}

Phenobarbital provides adequate GABA agonism and glutamate antagonism for a prolonged duration, in contrast to benzodiazepines, which affect only GABA. The more balanced inhibitory profile of phenobarbital results in an increased duration of symptom control. Thus, the provider can minimize any

Use of a phenobarbital protocol for AWS was associated with a significant reduction in ICU and hospital LOS.

intermittent periods of symptomatic activity as the patient's CIWA-Ar scores fluctuate. Similarly, the nursing burden of the phenobarbital protocol is substantially reduced, as frequent nursing assessments are not required beyond what is standard practice in critically ill patients, in contrast to the frequent monitoring required by a patient with high CIWA-Ar scores.

The financial burden of an ICU stay is significant, and minimizing a patient's length of time in the ICU can benefit both the health care system and the patient financially. Drug therapy in the ICU can also be costly for both parties, especially when patients require large cumulative doses of a medication, such as in the treatment of AWS. A full course of the phenobarbital protocol for a patient presenting with active DT has an average wholesale price of \$145.82, compared with \$16.25 for an average course of CIWA-Ar therapy as used in this study. The large disparity in cost results directly from the use of phenobarbital injection for the initial loading dose, which is substantially more expensive than phenobarbital tablets. The average wholesale price of a full course of oral phenobarbital therapy with no intravenous loading dose is \$16.26. Moreover, if phenobarbital can be used as a dexmedetomidine-sparing agent, as observed in this study, medication costs will decrease further.

Limitations of this study include the small sample size and the retrospective design. Although a larger, prospective trial would have been preferred, our study demonstrates the successful use of a simple and practical phenobarbital protocol. This protocol uses standardized, commercially available doses and does not rely on weight-based dosing or complex patient staging or numerical scales such as the CIWA-Ar. Most studies investigating alternative therapies for alcohol withdrawal have had sample sizes similar to or smaller than that of our study. The largest and most directly comparable study was reported in 2014 by Duby et al,¹⁰ who compared a historical control condition of treatment of AWS by physician preference with a protocol of escalating doses of diazepam with adjunctive phenobarbital. The results were similar to those of our study with regard to ICU LOS and incidence of mechanical ventilation. Another study reported by Hjermø et al¹⁶ involved 194 patients treated with phenobarbital or diazepam for DT in a psychiatric treatment facility. One potential source of confounding data is the initial presentation of a patient and subsequent treatment. In our study, 33% and 47% of patients in the CIWA-Ar and phenobarbital groups, respectively, presented initially in active AWS as identified by the

attending clinician. However, at the study institution, patients with a high clinical suspicion of developing AWS receive the same treatment as patients with confirmed, active AWS. A final limitation of this study is that despite no observed incidence of therapy failure or serious adverse events, a full safety analysis was not conducted.

Conclusion

As alcohol withdrawal continues to be a highly prevalent concern in critically ill patients, limitations of the current standard of care have become increasingly apparent. This situation has forced providers to seek alternative treatment modalities. The results of this study corroborate previous published reports suggesting that phenobarbital may be a promising alternative therapy for AWS, as evidenced by reduced ICU and hospital LOS, as well as less use of adjunctive agents. Moreover, invasive mechanical ventilation may not be required as often in these patients. Finally, patients treated with a phenobarbital protocol may need less attention from the nursing staff than patients treated with the CIWA-Ar protocol and may incur lower health care costs as a result of reduced ICU and hospital LOS.

ACKNOWLEDGMENTS

This study was conducted at Saint Thomas West Hospital, Nashville, Tennessee. We would like to acknowledge all medical ICU staff at this institution for their continual provision of excellent patient care.

FINANCIAL DISCLOSURES

None reported.

SEE ALSO

For more about alcohol withdrawal, visit the *Critical Care Nurse* website, www.ccnonline.org, and read the article by Sutton and Jutel, "Alcohol Withdrawal Syndrome in Critically Ill Patients: Identification, Assessment, and Management" (February 2016).

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