Review Article | Writing Club

Efficacy and Safety of Phenobarbital in Alcohol Withdrawal Syndrome Management: a Focused Literature Review

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Alcohol withdrawal syndrome (AWS) is a potentially life-threatening clinical complication in patients who misuse alcohol.[1] In the United States, clinical treatment is required for approximately 500,000 episodes of AWS annually.[2] Protocols and guidelines are often utilized in hospital settings for the treatment of AWS.[3] However, severe and treatment-resistant cases are more likely to rely on clinician input and professional judgment for symptom management. Currently there are multiple dosing strategies used to manage AWS, including fixed dose, loading dose, symptom-triggered, and symptom-monitored loading dose regimens.[4]

The Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar) is used to measure the severity of symptoms associated with alcohol withdrawal syndrome.[4] Higher scores indicate greater potential for life-threatening complications, such as seizures and delirium tremens. Benzodiazepines are commonly used in symptom-triggered therapy protocols, which are often guided by CIWA-Ar. Benzodiazepines (BZD) mimic alcohol's depressive effects on the central nervous system (CNS) by increasing the opening frequency of gamma-aminobutyric acid (GABA) chloride channels.[5] Large doses of benzodiazepines can put patients at an additional risk of oversedation, delirium, and/or respiratory depression. Chronic alcohol users can develop a cross-tolerance to benzodiazepines and become unresponsive or require more frequent dosing.[6] Thus, there is a need for alternate AWS treatment strategies.

Barbiturates, like phenobarbital (PB), may be considered an alternative therapeutic option to benzodiazepines in the management of AWS due to the differing mechanism of action. Phenobarbital directly stimulates GABA receptors and reduces glutamate transmission by antagonism of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid (AMPA) receptors.[5] Cross tolerance between phenobarbital and alcohol is noted to be less than that of benzodiazepines and alcohol due to the difference in binding properties and receptor affinity.[1]

The long half-life associated with phenobarbital in comparison to benzodiazepines like lorazepam (LZ) (79 hours and 14 hours, respectively) is advantageous in treating withdrawal in the setting of adverse events, like seizures and delirium tremens.[7-9] Phenobarbital's tapering effect is an added benefit, reducing the need for additional supportive medications upon discharge.[5] However, this medication has historically been less preferred in the treatment of AWS due to its narrow therapeutic index in comparison to benzodiazepines.[6] Recent literature and studies evaluate phenobarbital as a safe and effective therapeutic option for the treatment of AWS.

This article reviews evidence for various phenobarbital dosing regimens both as monotherapy and as an adjunct to benzodiazepines in treating AWS within emergency departments (EDs) and intensive care units (ICUs).

Methods

A search of the PubMed and SCOPUS databases was performed, targeting publication dates between January 1, 1950, and February 18, 2022, using the following search terms: phenobarbital, barbiturates, alcohol withdrawal, alcohol withdrawal syndrome, emergency department, emergency room, intensive care unit, ICU, and critical care. Meta-analyses, randomized controlled trials (RCTs), and cohort studies were included. After removing duplicate articles, a total of 186 articles were identified. Abstracts were reviewed by the authors and were excluded if the full article was not freely accessible, not written in the English language, only discussed benzodiazepine use, included patients with seizure disorders, included patients with anxiety disorders, or lacked an objective association with phenobarbital use in AWS. Together, the authors identified 17 articles that met the above criteria. Articles were subsequently reviewed in full and pertinent results were summarized. Results were organized by dosing regimens, benzodiazepine requirements, mechanical ventilation, and severe complications, like seizures, hallucinations, and delirium.

Results

Phenobarbital Monotherapy

Six studies, including 5 retrospective studies and 1 prospective RCT, evaluated the use of phenobarbital monotherapy compared to benzodiazepine monotherapy when treating patients with AWS.[5,6,10-13] Bosch and colleagues used a quasi-experimental study design with mixed methods that reviewed changes in workflow with phenobarbital-based monotherapy to determine if noninferior outcomes were possible in medical ICU patients with severe AWS.[10] This study (n = 485) demonstrated a decrease in hospital length of stay (LOS) when patients were treated with phenobarbital (10 mg/kg bolus with rescue doses of 2.5-5 mg/kg) in the ICU (mean difference 1.8 days, 95% CI: −3.4 to −0.2 d). One retrospective chart review notably compared phenobarbital monotherapy (6-15 mg/kg) to the current benzodiazepine protocol.[6] ICU admissions and ICU LOS rates were found to be similar between benzodiazepine and phenobarbital protocol use in patients. Notably, there was a statistically significant increase in ICU admissions for patients who switched from benzodiazepines to phenobarbital when they did not show improvement (44% vs 11%, p < 0.001). Conversely, another retrospective chart review that used similar protocols found a non-statistically significant increase in ICU admission rates in patients treated with benzodiazepines compared to phenobarbital (11.5% vs 0%, p = 0.078).[11] This same study showed no difference in hospital LOS between the two treatment groups.

A previously completed study in critically ill patients used physician clinical judgment to determine weight-based dosing relative to the risk for alcohol withdrawal delirium and risk of sedation.[12] The more recent study, by Goodberlet and colleagues, exhibited an increase in medical ICU LOS (2 [1:2] vs 2 [2:5], p = 0.002) and hospital LOS (4.5 [3:6] vs 8 [6:12], p < 0.001) for phenobarbital monotherapy protocol compared to the original regimen. Tidwell and colleagues assessed how outcomes differed when phenobarbital doses were determined using physician-directed risk factor assessment of active delirium tremens (DT), history of DT, and no history of DT.[5] This method of dosing phenobarbital showed statistically significant decreases in total hospital LOS (4.3 vs 6.9 d; p = 0.004) and mean ICU LOS (2.4 vs 4.4 d; p < 0.001) compared to benzodiazepine protocols.

One study assessed CIWA-Ar scores at baseline, at discharge from the ED, and at 48 hours post-discharge for patients who received either lorazepam 2 mg doses as needed or one dose of phenobarbital 260 mg followed by subsequent doses of 130 mg phenobarbital as needed.[13] Both groups demonstrated statistically significantly decreased CIWA-Ar scores from baseline to discharge from the ED (PB: 15.0-5.4, p < 0.0001; LZ: 16.8-4.2, p < 0.0001). Additionally, there was not a statistically significant difference between the use of lorazepam monotherapy and phenobarbital monotherapy with regard to hospital admission rates (12% vs 16%, p = 0.8), relapse rates, or compliance with medication between groups upon follow-up (p > 0.05).

Phenobarbital Adjunct to Benzodiazepines

One retrospective cohort study was a pre-post assessment of protocol revision that looked at the use of intermittent boluses of diazepam (D) (n = 54) versus escalating diazepam doses with adjunctive phenobarbital after one hour of continued agitation (n = 41) to treat AWS.[14] This study found that after implementation of the new protocol, patients received less diazepam in the first 24 hours (120 mg vs 280 mg, p = 0.01) and had significantly reduced rates of mechanical ventilation (47% vs 22%, p = 0.008) compared to patients treated prior to protocol implementation. A second retrospective cohort study that looked into symptom-triggered lorazepam plus phenobarbital (n = 36) compared to lorazepam monotherapy (n = 36) found similar median ICU LOS between the two arms [4.1 days (IQR = 2.4-8.4) vs 4.5 days (IQR = 2.8-6.1), p = 0.727].[15] Additionally, the average change in CIWA-Ar score from baseline to 24 hours was statistically significantly lower in the adjunctive phenobarbital arm (1.8 ± 9.0 vs. 6.5 ± 8.5, p = 0.0275).

Phenobarbital Monotherapy vs Adjunctive Therapy

In a randomized, double-blind, controlled trial (n = 102), the primary outcome of "initial level of hospital admission (ICU vs. telemetry vs. floor ward) from the emergency department" was analyzed for a single dose of phenobarbital (10 mg/kg) in adjunct to a symptom-guided lorazepam protocol compared to placebo. The former had decreased ICU admission rates directly from the emergency department (difference: 17%, 95% CI 4–32%).[16] However, there was no difference in admission rates to non-intensive care inpatient units. In a retrospective chart review, a single dose of parenteral phenobarbital (options of 260 mg IV, 130 mg IV, or 20 mg slow IV push) in conjunction with a symptom-triggered lorazepam protocol (ranging from 2 to 4 mg per dose) was compared to the same lorazepam protocol alone.[17] The addition of the bolus dose of phenobarbital resulted in a greater number of patients discharged within three days compared to those who received lorazepam alone (9 vs. 2 patients, p < 0.05). Despite this, the review found that changes in both CIWA-Ar scores and hospital admission rates were not significantly different.

Another retrospective cohort study that evaluated phenobarbital 260 mg IV with or without benzodiazepines (n = 97) compared to a symptom-triggered benzodiazepine protocol (n = 112) in the ED found similar ICU and hospital admission rates.[18] Additionally, there were similar lengths of stay in the ED and ICU between the groups but a statistically significant decrease in hospital LOS for the phenobarbital monotherapy group (3 vs. 4 days, p = 0.048). An observational study compared three treatment groups (D [n = 100], LZ + PB [n = 100], and PB alone [n = 100]) for management of AWS in adults in the ED.[19] The rate of ICU admissions was not statistically significantly different between groups (D: 8, LZ & PB: 11, PB: 13 patients, p = 0.99). The average length of stay was the lowest for the lorazepam plus phenobarbital group (D: 59 h, LZ + PB: 51 h, P: 70 h, p = 0.04).

Benzodiazepine Requirements

Across multiple studies, including one prospective RCT, two retrospective cohorts, and one observational study (n = 1088), it has been shown that phenobarbital used as monotherapy following failed benzodiazepine treatment, or as an adjunct to benzodiazepines, decreases

benzodiazepine requirements in treating AWS.[5,17,19,20] Notably, researchers have found a correlation between higher ICU LOS and the total amount of benzodiazepines administered (r = 0.48; p = 0.008).[14] Rosenson and colleagues demonstrated a mean 23 mg decrease in lorazepam use when patients were given a single dose of phenobarbital (26 vs. 49 mg; difference 23 mg [95% CI 7–40]).[17] Lebin and colleagues demonstrated a median decrease in benzodiazepines of 2 mg lorazepam equivalent (benzodiazepine 6 mg vs. 4 mg equivalent lorazepam, p < 0.001).[20] When assessing the need for adjunctive medications for treatment of alcohol withdrawal-related agitation (n = 205), it was found that phenobarbital compared to benzodiazepines required less quetiapine, haloperidol, and dexmedetomidine as supportive therapies.[5,11] Murphy and colleagues assessed the role of adjunctive phenobarbital in AWS by evaluating three studies that took place in the ED.[21] There was a lack of consistent dosing between each study, however, the benzodiazepine-sparing effect was consistent. An RCT (n = 44) found that patients who were given phenobarbital followed by placebo at discharge did not demonstrate a statistically significant decrease in CIWA-Ar scores after 48 hours compared to those treated with lorazepam followed by chlordiazepoxide at discharge (PB: 5.8 vs. LZ: 7.2, p = 0.6).[13]

Mechanical Ventilation

Bosch and colleagues found a decrease in mechanical ventilation rates, from 17.1% to 12.9%, after the implementation of a phenobarbital protocol.[10] Similarly, Tidwell and colleagues reported a statistically significantly lower rate of mechanical ventilation in the phenobarbital group (n = 60) compared to the benzodiazepine group (n = 60) when using physician-directed phenobarbital dosing compared to benzodiazepine protocols (2% vs. 23%, p < 0.001).[11] A study by Rosenson and colleagues looked into the use of a single dose of IV phenobarbital compared to placebo of 100 mL of normal saline in the ED infused over 30 minutes.[17] Another study by Nelson and colleagues compared three patient groups presenting to the ED following separate protocols: benzodiazepines only, benzodiazepines with phenobarbital adjunct, and phenobarbital only.[19] When phenobarbital was used as monotherapy or as an adjunct to benzodiazepines, there was no statistically significant difference in the rate of intubation for patients presenting to the ED between groups. Goodberlet and colleagues compared two populations, patients who received benzodiazepines versus those who received phenobarbital, and found that there was no difference in duration of intubation once mechanical ventilation was started in both the ED and ICU when assessing these populations pre- and post-implementation of a protocol that included phenobarbital for AWS.[12,19]

Adverse Effects

Across two retrospective studies and one RCT (n = 102), no significant differences in adverse effects, such as bradycardia, oversedation, and respiratory depression, were reported when phenobarbital protocols were utilized compared to benzodiazepines.[6,17,18] Another retrospective chart review (n = 85) compared alcohol withdrawal delirium (AWD) risk-based protocols for phenobarbital and benzodiazepines.[11] The study found phenobarbital had a statistically significantly lower incidence of side effects such as aspiration, oversedation, rash, and hypotension compared to benzodiazepines (PB = 0, BZD = 19.2, p = 0.006). Conversely, when Ammar and colleagues conducted a retrospective case series (n = 31) evaluating the use of phenobarbital monotherapy for AWS management, it was found that 10% of patients (n = 3) experienced hypotension following use of phenobarbital.[22]

Severe Complications

Five studies, which included four retrospective chart reviews and one prospective, double-blind, RCT (n = 1,132) found no significant difference in alcohol withdrawal-induced seizures between phenobarbital and benzodiazepines.[6,11,16-18] One retrospective chart review found no incidences of complicated AWS in the phenobarbital group when comparing phenobarbital-fixed dosing with oral taper up to seven days versus benzodiazepine-fixed dosing, using a lorazepam taper (n = 85).[11] Specifically, a statistically significant decrease in delirium was confirmed for the phenobarbital group. Uncomplicated AWS symptoms, including tremors, anxiety, gastrointestinal upset, headaches, diaphoresis, palpitations, and anorexia were not observed in the phenobarbital group (n = 33) and were statistically significantly lower compared to the benzodiazepine group (n = 52) (0 vs 73.1%, p = 0.001). One retrospective case series in a surgical ICU study (n = 31) assessed phenobarbital as monotherapy followed by a taper regimen and reported that no patients developed severe AWS-related complications, including seizures, hallucinations, or delirium.[22] Three retrospective studies assessed phenobarbital use both as monotherapy and as an adjunct to benzodiazepines in AWS (n = 362) and found that phenobarbital had no significant differences in mortality compared to when benzodiazepines were used alone.[11,12,18]

Discussion

Phenobarbital use is currently not the standard of care for AWS. As a result, the majority of phenobarbital protocols identified had varied dosing, routes, frequencies, and durations of treatment tailored to the specific healthcare institutions. Protocols were adapted to each institution based on severity of symptoms, medication availability, and provider preference. While this complicates comparison of phenobarbital use between studies, this may have been a beneficial approach to designing phenobarbital protocols specific to institutional demands. Similarities between protocols may be due to the narrow therapeutic index associated with phenobarbital. Given the risks of phenobarbital overdose and overall lower clinical experience with phenobarbital by many providers, it is possible that an increased level of caution and surveillance was exercised with phenobarbital dosing compared to the more frequently used benzodiazepines. This could account for the similar, and sometimes lower, number of adverse events seen with phenobarbital compared to benzodiazepines.[6,11,17,18] Although various dosing strategies were identified in this article, there is little data to suggest any overall "best" dosing regimen when utilizing phenobarbital in AWS. Both phenobarbital as monotherapy and as an adjunct to benzodiazepine treatment have evidence for comparable and, in some cases superior, outcomes to benzodiazepines alone.[5,10,11,14-16,19]

Many studies demonstrated a decrease or no difference in admission rates and/or LOS across general floors and ICU with phenobarbital treatment, suggesting that inclusion of phenobarbital in some manner may result in improvements in these outcomes. [5,6,10,15,18,19] In the single study where the phenobarbital group demonstrated an increase in hospital and ICU LOS, the authors noted a higher APACHE II score, a general measure of increased disease severity, in the phenobarbital group.[12] This suggests that patients in the phenobarbital group had a higher baseline illness severity when compared to the patients in the benzodiazepine protocol, a probable confounding factor.

The studies in this review demonstrate phenobarbital as a safe therapy in various dosing strategies. Some studies found patients who were treated with phenobarbital experienced fewer side effects than those treated with benzodiazepines.[11] None of the studies using phenobarbital experienced life-threatening complications or differences in mortality rates when compared to benzodiazepines.[6,17,18] Mechanical ventilation rates were decreased or comparable to benzodiazepine protocols when phenobarbital was utilized across studies.[5,10,12,17,19] Another interesting result is the overall decrease in benzodiazepine dose requirements seen in protocols which utilized benzodiazepines with or prior to phenobarbital.[5,17,19,20] A possible explanation for this outcome could be the efficacy of phenobarbital in those patients who are resistant to benzodiazepine treatment. Including phenobarbital in treatment regimens may expedite an ultimately necessary escalation of care, where previously, patients would receive excessive additional benzodiazepine doses with marginal additional benefit. In addition to decreased benzodiazepine requirements, phenobarbital therapy decreased the need for other sedatives, antipsychotics, and discharge medications.[5,11] Overall, these results indicate that phenobarbital reduces the use of acute therapies and hospital resources.

A number of studies in this review were retrospective, leaving an opportunity for bias.[1,6,11,14-18] Three of the studies reviewed were cohorts, which typically consist of small patient populations.[14,15,18] Larger studies are needed to support consistent guidelines with more coherent dosing protocols. In addition to the data presented in this article, future research on dosing regimens and head-to-head comparisons between phenobarbital and benzodiazepines is warranted to provide a more comprehensive comparison between phenobarbital and benzodiazepines in the setting of AWS.

While there are many potential benefits to the addition of phenobarbital demonstrated within these studies, it is important to note that overall, benzodiazepines have more evidence for efficacy and clinical experience as they are still recommended as first-line therapy for the treatment of AWS, according to the American Society of Addiction Medicine 2020 Clinical Practice Guideline on Alcohol Withdrawal Management.[23] Additionally, other factors aside from the treatments themselves could have contributed to the results seen in these data. Incomplete assessment of withdrawal risk or symptom severity may contribute to under- or over-prescribing of benzodiazepines in facilities that utilize CIWA-Ar assessments of AWS.[24] This could result from a lack of access to patient histories, overburden on the healthcare system, or, possibly, a lack of training in the use of CIWA-Ar-based benzodiazepine dosing. It is unclear if these factors played a role in the difference in outcomes between benzodiazepines and phenobarbital, or if addressing these issues would confer similar, or even superior, outcomes to the addition of phenobarbital. Nevertheless, the above data suggest that there is a place for phenobarbital in the treatment of AWS.

Conclusion

Phenobarbital is a safe and effective alternative to benzodiazepines for treatment of AWS when used in a supervised clinical setting. Phenobarbital use resulted in similar and, in some cases, improved rates of hospital/ICU admission and hospital/ICU LOS. Phenobarbital utilization also demonstrated decreased rates of mechanical ventilation, total benzodiazepine requirements, and requirements for other supportive medications. There were similar rates of adverse effects between phenobarbital and benzodiazepines.

It is reasonable for institutions to tailor a phenobarbital protocol that best suits the institutional resources and capabilities, as well as provider preference. Additional education may be appropriate to support providers in making clinical decisions regarding the use of phenobarbital in AWS treatment.

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Disclosure: The author(s) declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria..

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

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