Evaluation of Phenobarbital in the Treatment of Alcohol Withdrawal in the Intensive Care Unit

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Introduction

Alcohol withdrawal syndrome (AWS) is characterized by an imbalance of inhibitory γ-Aminobutyric acid (GABA) and excitatory N-methyl-D-aspartic acid (NMDA) receptors due to chronic ethanol use. Symptoms can range from mild to severe and can lead to life threatening delirium tremens and/or require intensive care unit (ICU) admission as well as increase health care costs.

The standard of care for AWS is the Clinical Institute Withdrawal Assessment (CIWA) protocol, which includes treatment with benzodiazepines, supportive care, and close clinical monitoring. However, large cumulative doses of benzodiazepines may lead to development of delirium or respiratory depression requiring mechanical ventilation. Phenobarbital provides several advantages over benzodiazepines in the treatment of AWS. Its longer half-life and tapering effect provide better control of symptoms and eases burden of administration. Both phenobarbital and benzodiazepines inhibit GABA receptors, but phenobarbital has an additional benefit of suppressing the excitatory glutamate receptors[1]. Therefore, the addition of phenobarbital to traditional benzodiazepine-based AWS treatment may confer better clinical management and outcomes as well as limit adverse effects.

Aims and Objectives

This project sought to evaluate different alcohol withdrawal treatments used in the Intensive Care Unit at Beaumont Hospital, Royal Oak. Specifically, we sought to identify whether the addition of phenobarbital to the CIWA protocol improves outcomes in patients with AWS.

I. The primary aim was to compare rates of ICU length of stay in patients diagnosed with AWS that were treated with phenobarbital compared to those who were treated without.
II. The secondary aim was to also compare hospital length of stay, need for mechanical ventilation, and all-cause mortality in these patients.

Methods

A total of 492 subjects diagnosed with alcohol withdrawal and/or delirium tremens were included for analysis. The electronic medical record was queried for adults age 18-75 years admitted to William Beaumont Hospital, Royal Oak between 2017 and 2021. Subjects were divided into two groups: those who received phenobarbital [N=181] and those who did not [N=311]. ICU length of stay (LOS) and hospital LOS were compared using two-sample *t*-tests. Need for mechanical ventilation and all-cause mortality were analyzed using chi-squared tests. Differences in baseline CIWA scores were controlled for by utilizing regression models. ICU LOS and hospital LOS were compared using linear regressions, while need for mechanical ventilation and all-cause mortality were compared using logistic regressions. All statistical analysis was completed using Python's pandas and statsmodels libraries.

Results

There was not a statistically significant difference in ICU LOS, hospital LOS, and need for mechanical ventilation for subjects who received phenobarbital compared to those who did not. There was a statistically significant difference in all-cause mortality (0.55% mortality in those who received phenobarbital vs 8.68% mortality in those who did not; p=0.000174). (Table 1). However, when controlling for initial CIWA scores this difference was no longer statistically significant (p=0.085) (Table 2). The group of subjects who received phenobarbital had a higher average CIWA score on admission (13.296 vs 9.850 with p=0.0000139).

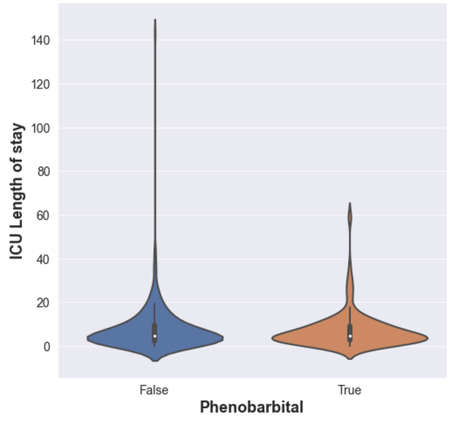

Figure 1. Violin plot illustrating the ICU LOS in days for subjects that did [True] and did not [False] receive phenobarbital.

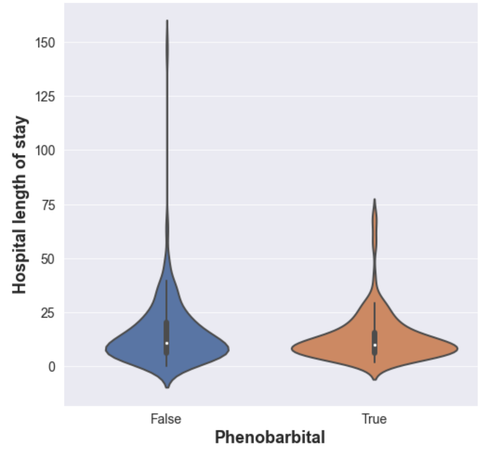

Figure 2. Violin plot illustrating the hospital LOS in days for subjects that did [True] and did not [False] receive phenobarbital.

Outcome	True Average (± standard deviation)	False Average (± standard deviation)	P value
ICU LOS	7.293 days (± 8.290)	7.630 days (± 10.484)	p=0.711
Hospital LOS	13.385 days (± 11.200)	15.244 days (± 15.678)	p=0.162
Mechanical Ventilation	11.0%	16.4%	p=0.103
All-Cause Mortality	0.55%	8.68%	p=0.000174

Table 1. Table comparing the average values for ICU LOS, hospital LOS, need for mechanical ventilation, and all-cause mortality with the 'True' representing those who received phenobarbital (N=181) and 'False' representing those who did not (N=311).

Outcome	Regression Type	Coefficient (standard error)	P value
ICU LOS	Linear	1.019 (0.712)	0.153
Hospital LOS	Linear	-0.874 (1.166)	0.454
Mechanical Ventilation	Logistic	-0.377 (0.375)	0.315
Mortality	Logistic	-1.895 (1.099)	0.085

Table 2. Results of regression models used to analyze the four principle outcomes and correcting for their difference in initial CIWA scores.

Conclusions

The results do not suggest that the addition of phenobarbital to the standard of care CIWA protocol provides a significant decrease in ICU length of stay, hospital length of stay, or need for mechanical ventilation by using phenobarbital in the treatment of AWS. There was a statistically significant difference in all-cause mortality between the two groups, with phenobarbital being associated with a lower likelihood of mortality. However, there was only one mortality in the group that received phenobarbital. Additionally, when controlling for initial CIWA score, this difference was no longer statistically significant. The effect of phenobarbital on outcomes associated with AWS may be better studied in the future using larger sample sizes, matched groups, additional outcome measures, and more delineation of specific benzodiazepine and barbiturate treatment regimens.

References

1. Parthvi R, Agne P. Update on Phenobarbital for Alcohol Withdrawal Syndrome in Intensive Care. *J Clin Intensive Care Med*. 2019;4(1):036-039. doi:10.29328/journal.jcicm.1001023

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