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ORIGINAL ARTICLE

Comparison of Alcohol Withdrawal Outcomes in Patients Treated with Benzodiazepines Alone versus Adjunctive Phenobarbital: a Retrospective Cohort Study

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Abstract

Background: For treatment of severe alcohol withdrawal syndrome, high dose benzodiazepines (BZDs) may cause delirium and over-sedation. Phenobarbital (PBT) is a long-acting barbiturate effective for the treatment of alcohol withdrawal. Given the potential benefits of PBT, we sought to investigate the effectiveness of PBT as adjunctive treatment for alcohol withdrawal.
Methods: This was a retrospective cohort study on patients with a diagnosis of alcohol withdrawal who had a CIWA-Ar score > 10 treated with either BZDs alone (BZD alone group) or BZDs with adjunctive PBT (PBT-adjunct group). The patients received at least one dose of PBT in addition to BZDs (variable doses) in the PBT-adjunct group, and three doses of 20 mg diazepam equivalents within 6 hours in the BZD alone group. The primary endpoint was the proportion of patients with a CIWA-Ar score < 10 at 24 hours after initial treatment. Duration of withdrawal and cumulative dose of BZDs were also assessed.
Results: Seven subjects in the adjunctive phenobarbital and 21 in the benzodiazepine group were included in the final analysis. Two patients (28.6%) in the PBT-adjunct group and 5 patients (23.8%) in the BZD only group achieved the primary endpoint, though the difference between the two groups was not statistically significant (P = 0.588). The median (IQR) duration of withdrawal symptoms was 44 (12-62) hours in the PBT-adjunct group compared to 53 (37-87) hours in the BZD only group, with no significant difference between the groups (P = 0.249). The median (IQR) cumulative BZD dose requirement (diazepam equivalent) in the PBT-adjunct group was significantly lower than BZD alone group (25 (20-226) vs. 326 (160-550) mg, P = 0.02).
Conclusion: PBT appears to be a safe and effective alternative to BZDs for the treatment of alcohol withdrawal in non-critically ill patients and may be BZD sparing.

Keywords: Alcohol Withdrawal Delirium; Alcoholism; Benzodiazepines; Comparative Effectiveness Research; Phenobarbital

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INTRODUCTION

Alcohol use disorders (AUDs) are prevalent worldwide. According to the recent report by World Health Organization (WHO), in 2010, the global AUD prevalence was 4.1% among people 15 years of age and older (1). In the United States, the 2010 National Survey on Drug Use and Health, conducted by the Substance Abuse and Mental Health Services Administration, found that 17.9 million people (7% of the US general population) were dependent on or abused alcohol (2). It has been estimated that 1.8 million annual hospital admissions meet the definition of an AUD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (3). The overall incidence of symptomatic alcohol withdrawal is reported to be 8% among all hospitalized patients in the United States (4).

The severity of alcohol withdrawal symptoms is variable. Not all patients with AUDs will develop life-threatening signs and symptoms; however, untreated patients may develop hallucinations, seizures, and approximately 5% of patients will progress to delirium tremens (DT) which can lead to cardiovascular collapse and death (3). Risk factors for the development of DT include past history of DT, history of heavy daily alcohol consumption (defined as greater than the equivalent of 10 standard drinks per day in the two weeks prior to admission), higher level of blood alcohol, cirrhosis or enlarged liver, electrolyte disturbances, structural brain damages, older ages and/or early onset withdrawal symptoms (4,5). Treatment of alcohol withdrawal is indicated when the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) score, a validated monitoring tool for severity of alcohol withdrawal, is greater than 10 (Figure 1) (6). The current standard of care is symptom-triggered therapy with benzodiazepines (BZDs) as opposed to fixed dose strategies which have been shown to result in higher drug requirements and over-sedation (3,4,7).

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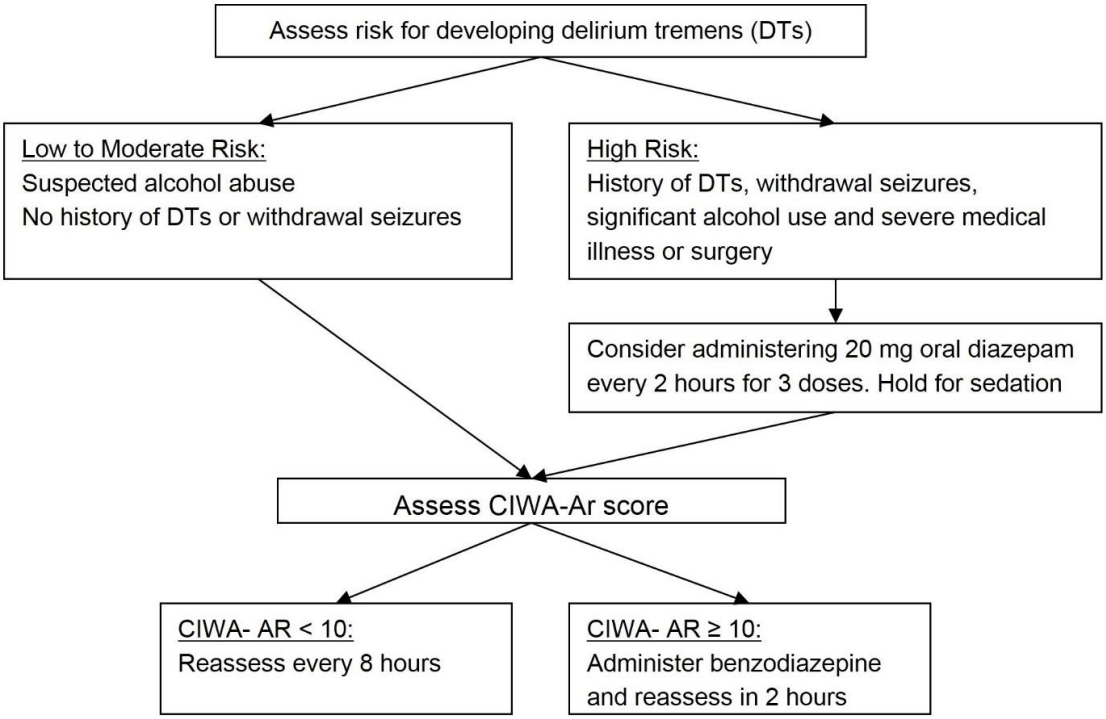

Figure 1. URMC Alcohol Withdrawal Guideline (Choice of benzodiazepine: Diazepam 20 mg orally is the preferred choice. In cirrhosis or severe liver dysfunction diazepam 10 mg or lorazepam 4 mg is recommended. If aged 60 or older diazepam 10 mg or lorazepam 2 mg is recommended.)
- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-revised

Phenobarbital (PBT) is an alternative agent with limited data on its use in the management of alcohol withdrawal. Small studies have indicated that it may improve symptom control in progressed DTs, reduce the need for intensive care unit (ICU) admission and mechanical ventilation, decrease BZD dose requirements, and it has been used successfully in detoxification programs (8-14). Local guidelines for PBT use recommend a starting dose of 65 mg intravenously with reassessment of CIWA-Ar every 15 minutes, increasing the dose by two-fold up to 260 mg per dose until symptoms are controlled. Given the potential benefits of PBT and increased use at our institution, we sought to investigate the effectiveness of PBT as adjunctive treatment for alcohol withdrawal.

METHODS

Study design and subjects

This was a retrospective cohort study of patients admitted to the University of Rochester Medical Center (URMC) from March, 1st 2011 through October 31st, 2012 who were treated for alcohol withdrawal with either BZDs alone (BZD alone group) or BZDs with adjunctive PBT (PBT-adjunct group). This study was approved by the institutional review board. Subjects were identified through electronic medical record reports which queried the database for orders for intravenous PBT or intravenous and oral diazepam or lorazepam in addition to ICD-9 codes related to alcohol withdrawal or an administration instruction containing "CIWA." Subjects were included if they: (a) were 18 years old or older, (b) received a diagnosis of alcohol withdrawal, had at least one documented CIWA-Ar score greater than 10, (c) received at least one dose of intravenous PBT in addition to BZDs (variable doses) in the PBT-adjunct group, and (d) received at least 3 doses of 20 mg oral diazepam or equivalent in a six hour period in the BZD alone group. These criteria were based on institutional guidelines for the treatment of patients at risk for moderate to severe alcohol withdrawal (Figure 1). Subjects were excluded from the analysis: if they received BZDs or PBT therapy for any indication other than alcohol withdrawal, primidone (which can be metabolized to PBT), an intravenous ethanol infusion, if they were directly admitted to the ICU when alcohol withdrawal treatment was initiated, or if they had a positive urine toxicology screen for BZDs (unless given for the treatment of alcohol withdrawal), barbiturates, opiates (unless administered at URMC prior to sampling), or other illegal substances.

Data collection

Demographic data collected from the subject's medical record included: age, gender, primary reason for admission, past medical history of alcohol withdrawal, alcohol withdrawal seizures or DT, blood level of hepatic transaminases, history of cirrhosis, estimated ethanol intake in the 2 weeks prior to admission (obtained via provider documentation during history taking), blood alcohol concentration (BAC) on admission, the availability of baseline CIWA-Ar score prior to treatment and baseline score, and time to start the first dose of either medications after the first documented CIWA-Ar score. The CIWA-Ar score was recorded 24 hours after the first dose of

medication (PBT or BZD). The primary endpoint was the proportion of patients who had a CIWA-Ar score less than 10 at 24 hours after treatment initiation, regardless of whether PBT or BZD was given first. If a score was not available at the 24 hour mark, the last recorded score prior to the 24 hour mark was used. All patients in both groups were included in the analysis of secondary and safety endpoints. Secondary endpoints included: mean and median discrete benzodiazepine dose, cumulative benzodiazepine dose, mean and median discrete PBT dose (mg and mg/kg), mean cumulative dose of PBT, length of stay, and the presence of BZD refractory withdrawal. BZD refractory withdrawal was defined as persistent withdrawal symptoms despite treatment with a single intravenous diazepam dose greater than or equal to 40 mg, i.e. 40 mg of intravenous diazepam (or equivalent) in one hour or 200 mg of intravenous diazepam in 4 hours (13,15,16). All BZD doses were reported in diazepam equivalents; for example 1 mg lorazepam = 5 mg diazepam (17). Safety endpoints included aspiration events (witnessed or defined as new radiographic infiltrate due to probable aspiration), need for intubation, need for ICU admission, seizures, need for rapid response call (call for rapid emergency response team composed of critical care clinicians, ICU nurses nad respiratory therapists), hemodynamic instability, and mortality.

Statistical analysis

The results are presented with frequency (percentage) for dichotomous variables and mean ± standard deviation (SD) for continuous variables with normal distribution or median and interquartile range (IQR) for continuous variables with non-normal distribution. The effect of the treatment on dichotomous endpoints, including the primary endpoint, was analyzed using Fisher's exact test, while continuous secondary endpoints were analyzed by Mann-Whitney U test. Because most alcohol withdrawal patients admitted to our institution received only BZDs, in order to ensure heterogeneity of the BZD only group, up to three times the number of patients enrolled in PBT-adjunct groupwere enrolled into the BZD only group. A power calculation was performed based upon a previous study comparing symptom triggered versus fixed doses of oxazepam (18). In that study, 45% of subjects treated with a BZD were symptomatic 24 hours after commencement of the treatment. We hypothesized that the addition of PBT would decrease the proportion of subjects who were symptomatic at 24 hours to 25%.

RESULTS

From March 1st, 2011 through October 31st, 2012, 28 patients received PBT for alcohol withdrawal in URMC. Seven patients met inclusion criteria and were enrolled in the PBT-adjunct group. A total of 21 patients were excluded due to: direct admission to the ICU (n = 11), CIWA-Ar criteria not met (n = 6), and positive toxicology screening or concomitant drug overdose (n = 4). During the same time period, 3083 patients received BZDs for alcohol withdrawal. Per the study protocol, 89 patients were screened for enrollment via random number generator to enroll 21 patients into the benzodiazepine group. A total of 68 patients were excluded due to: dose criteria not met (n = 29), direct admission to the ICU (n = 12), CIWA-Ar criteria not met (n = 11), positive toxicology screening of concomitant drug overdose (n = 11), treatment with an ethanol infusion (n = 2), treatment with PBT during hospital admission (n = 2) and seizure of unknown origin (n = 1).

The baseline characteristics of subjects are shown in table 1.

Table 1. Baseline characteristics of subjects

	Study groups		P value
	Phenobarbital-adjunct (n = 7)	Benzodiazepine alone (n = 21)	
Male gender, n (%)	6 (85.7)	18 (85.7)	≃ 1.000
Age (year), mean (range)	46.1 (33-58)	49.9 (30-77)	0.756
Alanine aminotransferase (U/L), mean ± SD	50.5 ± 34	66.2 ± 48	0.316
Aspartate aminotransferase (U/L), mean ± SD	61.3 ± 28	114.4 ± 110	0.408
On-admission BAC measured, n (%)	6 (85.7)	15 (71.4)	0.639
On-admission BAC (mg/dL), mean ± SD	203.4 ± 145	204.4 ± 78	0.205
Undetectable BAC on admission, n (%)	1/6 (16.7)	8/15 (53.3)	0.178
Documented history of cirrhosis, n (%)	0 (0.0)	0 (0.0)	-
Past medical history of alcohol withdrawal, n (%)	3 (42.9)	12 (57.1)	0.670
Past medical history of delirium tremens, n (%)	1 (14.3)	2 (9.5)	≃ 1.000
Past medical history of withdrawal seizures, n (%)	2 (28.6)	10 (47.6)	0.662
CIWA-Ar recorded prior to treatment, n (%)	2 (28.6)	11 (52.4)	0.385
CIWA-Ar prior to treatment, median (range)	13.5 (13-14)	15 (4-34)	0.641
Highest recorded CIWA-Ar, median (IQR)	22 (17-23.5)	24 (18-31)	0.321
Estimated ethanol use more than 8 standard drinks per day, n (%)	4 (57.1)	14 (66.7)	0.674

- BAC: Blood alcohol concentration
- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-revised

Aspartate aminotransferase (AST) appeared to be numerically higher at baseline in the BZD alone group; however, the difference did not reach statistical significance. The percentage of subjects with an undetectable BAC on admission was also observed to be numerically higher in the BZD alone group versus PBT-adjunct group; however, this difference also did not reach statistical significance. A past medical history of alcohol withdrawal syndromes, defined as alcohol withdrawal, DT, or withdrawal seizures, was documented in 57.1% of subjects in the PBT-adjunct group and 66.7% of subjects in the BZD alone group. Two patients (28.6%) in the PBT-adjunct group and 5 patients (23.8%) in the BZD only group achieved the primary endpoint, though the difference between the two groups was not statistically significant (P = 0.588). The median (IQR) duration of withdrawal symptoms was 44 (12-62) hours in the PBT-adjunct group compared to 53 (37-87) hours in the BZD only group, despite no significant difference between the groups (P = 0.249). The median (IQR) cumulative BZD dose requirement (diazepam equivalent) in the PBT-adjunct group was significantly lower than BZD alone group (25 (20-226) vs. 326 (160-550) mg, P = 0.02). BZDs were the first medication administered for alcohol withdrawal in all cases except one. One subject (14.3%) in the PBT-adjunct group met criteria for BZD-resistant withdrawal compared to 12 subjects (57.1%) in the BZD alone group, which shows the difference was close to level of significance (P = 0.08). The safety endpoints are displayed in table 3. There were no statistically significant differences in the incidence of adverse events observed. One subject died in the PBT-adjunct group due to pulseless electrical activity arrest shortly after being transferred to the ICU where he was intubated for hypoxemia. It is unclear whether this was directly linked to severity of poisoning or the adverse effect of treatments he received or other comorbidities as he had a past medical history notable for chronic obstructive pulmonary disease and aspiration pneumonia with a significant chest radiograph.

DISCUSSION

Despite the use of symptom-triggered BZD therapy, alcohol withdrawal has remained difficult to treat. BZD requirements may vary significantly between patients and long-acting agents with active metabolites may accumulate in the elderly and those with hepatic disease leading to over-sedation (4). Patients with refractory symptoms or high BZD requirements are often admitted to the ICU and may require

Table 2. Primary and secondary endpoints

	Study groups		P value
	Phenobarbital-adjunct (n = 7)	Benzodiazepine alone (n = 21)	
Primary Endpoint			
CIWA-Ar less than 10 at 24 hours, n (%)	2 (28.6)	5 (23.8)	0.588
Secondary Endpoints			
Duration of withdrawal symptoms (hour), median (IQR)	44 (12-62)	53 (37-87)	0.249
Length of hospital stay (day), median (IQR)	4 (1-4.5)	5 (3-9)	0.189
Discrete benzodiazepine dose* (mg), median (IQR)	10 (9-16)	20 (15-20)	0.080
Cumulative benzodiazepine dose* (mg), median (IQR)	25 (20-226)	326 (160-550)	0.020
Discrete phenobarbital dose (mg), median (IQR)	130 (106-195)	-	-
Cumulative phenobarbital dose (mg), median (IQR)	455 (309-618)	-	-
Cumulative phenobarbital dose (mg/kg), median (IQR)	6.3 (3.5-10.3)	-	-

* Benzodiazepine doses are reported in diazepam equivalents
- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-revised

Table 3. Safety endpoints

	Study groups		P value
	Phenobarbital-adjunct (n = 7)	Benzodiazepine alone (n = 21)	
Aspiration event, n (%)	1 (14.3)	1 (4.8)	0.440
Intubation requirement, n (%)	1 (14.3)	1 (4.8)	0.440
ICU admission, n (%)	1 (14.3)	4 (19)	≈ 1.000
Seizures, n (%)	0 (0.0)	1 (4.8)	≈ 1.000
Hemodynamic instability, n (%)	1 (14.3)	1 (4.8)	0.440
Mortality, n (%)	1 (14.3)	0 (0.0)	0.250

mechanical ventilation increasing length of hospital stay and potential complications (10,13).

Similar to BZDs, PBT enhances the effect of GABA at its receptor, a chloride channel. PBT increases the duration of channel openings versus the BZDs which increase the frequency of channel openings (19). This difference may explain the observed synergy with both agents in previous reports, and the effectiveness of PBT in BZD refractory alcohol withdrawal (13).

In this study, we found that adjunctive PBT therapy significantly reduced the BZD dose requirement for patients with alcohol withdrawal syndrome. However, there were no statistically significant differences in adverse events between patients receiving PBT + BZDs and BZD alone, although as mentioned previously there was one death in the PBT-adjunct group. There are few studies evaluating the use of PBT in alcohol withdrawal while their study designs and endpoints are highly variable. A recent prospective study in the emergency department included 102 patients and compared a single dose of PBT 10 mg/kg to placebo in addition to symptom-triggered BZDs. The findings included decreased transfer to the ICU and decreased BZD requirements (14). Another prospective trial on 44 patients in an emergency department compared 48 hours of treatment with PBT or lorazepam (9). After 48 hours, the patients in the PBT arm received placebo while the patients in the lorazepam arm received chlordiazepoxide. The mean cumulative PBT dose was 509 mg. Both agents significantly decreased CIWA-Ar score from baseline to the last visit, while there was no statistically significant difference in discharge or 48 hour follow-up scores, suggesting that the effects of PBT on alcohol withdrawal symptoms persist without the need for additional doses (9). A third study conducted in an emergency department on 62 patients found that 92% were safely discharged with no re-admission in seven days after receiving a mean total dose of 598 mg of intravenous PBT or 8.4 mg/kg body weight (12). A retrospective study on patients admitted to the ICU for the treatment of alcohol withdrawal which compared a treatment plan of escalating doses of BZDs and PBT with another treatment plan of symptom-triggered BZDs alone showed that the use of escalating doses of BZDs and PBT significantly reduced the need for mechanical ventilation and showed trends towards reduced length of hospital stay and nosocomial infection (10). Patients received a median cumulative PBT dose of 390 mg, although the range was quite broad (10).

In the present study, there was no statistically significant difference between PBT adjunct-group and BZDs alone for reducing the proportion of patients with withdrawal symptoms requiring treatment at 24 hours. The median cumulative PBT requirement of 455 mg in this study was consistent with previous studies (9-11)

LIMITATIONS

There were several limitations of our study. It was designed as a retrospective cohort which increases the risk of selection bias. In an effort to control for the possibility of higher severity patients in the PBT-adjunct group, patients were only included in the BZD only group if they met the minimum BZD dose requirements (3 or more equivalent doses of diazepam) specified in the inclusion criteria. This criterion was chosen based on the recommended doses in our local guideline for patients at high risk for DTs (Figure 1). The groups appeared comparable based on history of alcohol withdrawal syndromes and other demographics, however there was a numerically higher, although not statistically significant, mean AST in the BZD only group which may indicate a higher incidence of alcoholic hepatitis in this group. Furthermore, there were more patients in the BZD alone group who had an undetectable BAC on admission, although the difference did not reach statistical significance, which may indicate that these patients were actively withdrawing from alcohol to a greater extent than those who received PBT, although pre-treatment CIWA-Ar scores were comparable. We also specifically excluded patients who were admitted to ICU for inception of alcohol withdrawal treatment or PBT in order to evaluate if there was a difference in ICU admission or intubation rate between the groups. This significantly decreased the population of patients available to enroll in the PBT-adjunct group and we were not able to demonstrate a significant difference in the number of subjects requiring ICU admission or intubation. An important limitation was the small sample size which could not adequately power the primary endpoint to detect a statistical difference in resolution of withdrawal. This study was too small to show statistically significant differences in the duration of alcohol withdrawal with the use of PBT.

CONCLUSION

PBT appears to be as safe as BZDs in treatment of alcohol withdrawal while it is effective on reducing the BZD dose requirement especially for non-critically ill patients and may be BZD sparing. Larger, prospective studies are necessary to be conducted to fully clarify the effectiveness of PBT on alcohol withdrawal patients.

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