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Use of Propofol-Containing Versus Benzodiazepine Regimens for Alcohol Withdrawal Requiring Mechanical Ventilation

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Abstract

Background: When chronic, excessive alcohol intake is abruptly halted, patients are at risk for developing life-threatening alcohol withdrawal syndrome (AWS). Benzodiazepines have established efficacy, yet some patients' symptoms persist despite treatment with high doses. **Objectives:** The study objective was to compare time to resolution of AWS symptoms in mechanically ventilated patients receiving propofol-containing versus benzodiazepine infusions. **Methods:** This study was a retrospective cohort analysis of adult patients with ICD-9 codes for AWS who required mechanical ventilation for AWS symptoms. **Results:** A total of 1637 records were reviewed, and 64 were included. Propofol-containing regimens were used in 46 cases (72%), whereas benzodiazepine infusion monotherapy accounted for 18 cases (28%). Patients were predominantly male (97%), with a mean age of 45 years. Lorazepam-equivalent benzodiazepine doses given prior to intubation were greater in patients receiving propofol infusion (56 vs 15 mg, $P = .03$). Time to resolution of AWS symptoms for propofol- and benzodiazepine-treated patients was 8 and 7 days, respectively ($P = .34$). Median hospital and intensive care unit lengths of stay were similar (9 vs 10 days and 4 vs 4 days, respectively; $P > .05$ for both comparisons), as were days of mechanical ventilation (4 vs 3 days, $P = .98$). Patients in the benzodiazepine infusion monotherapy group required numerically increased amounts of benzodiazepine bolus doses while on continuous sedation, compared with patients receiving propofol infusion (36 vs 10 mg, $P = .06$). **Conclusions:** Propofol and Benzodiazepine-treated patients with AWS requiring mechanical ventilation experienced similar days of AWS symptoms, length of stay, and mechanical ventilation.

Keywords

alcohol withdrawal syndrome, propofol, benzodiazepines, resolution of symptoms, intensive care unit, mechanically ventilated, delirium tremens

Introduction

Alcohol is the most widely abused drug in the world.[1] According to the 2011 National Survey on Drug Use and Health, 51.8% of Americans aged 12 years or older reported being active consumers of alcohol; 22.6% reported participation in binge drinking (defined as having 5 or more drinks on the same occasion on at least 1 day in the last 30 days); and 6.2% reported heavy drinking (defined as binge drinking on at least 5 days in the past 30 days).[2] Approximately 500 000 episodes of withdrawal severe enough to require pharmacological treatment occur in the United States each year.[3]

As a result of alcohol's exogenous inhibitory effects, chronic use causes neurological changes in order to maintain equilibrium. These changes include upregulation of excitatory glutaminergic neuroreceptors, such as *N*-methyl-D-aspartate (NMDA), and downregulation of inhibitory neuroreceptors, including γ-aminobutyric acid (GABA).

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Following abrupt discontinuation of alcohol use, neuronal hyperactivity results, characterized as alcohol withdrawal syndrome (AWS).[4,5] AWS is a compilation of physiological manifestations that can range from mild jitteriness to seizures and death.[4] Diagnostic criteria for AWS are outlined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) and include at least 2 or more of the following symptoms after the cessation of or reduction in heavy or prolonged alcohol use: autonomic hyperactivity; increased hand tremor; insomnia; nausea or vomiting; visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; and grand mal seizures. Symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and should be such that they cannot be explained by a general condition or other mental disorder.[6] Approximately 5% of patients suffering from AWS will also experience delirium tremens, which is defined as hallucinations, disorientation, tachycardia, hypertension, fever, agitation, and diaphoresis. Delirium tremens begins between 48 and 96 hours after the last alcohol consumption and may last for up to 7 days.[7]

Benzodiazepines have been shown to alleviate autonomic hyperactivity and agitation seen in AWS by potentiating the effects of GABA and are currently accepted as the standard of practice in the treatment of AWS.[5] However, a significant portion of the population experiences refractory AWS despite treatment with high-dose benzodiazepines.[8] Published case reports and case series demonstrate anecdotal success using propofol to alleviate symptoms of AWS in benzodiazepine-refractory patients.[9-13] Propofol is thought to have a mechanism of action similar to that of alcohol on the central nervous system. Both agents bind to the GABA-A receptor, causing an influx of chloride ions; the resulting activation of the GABA-A receptor causes anxiolysis, sedation, and impaired motor coordination. Both propofol and ethanol also inhibit the excitatory NMDA receptor, intervening with the postsynaptic excitatory effects of glutamate. Of note, NMDA receptors seem to play a central role in alcohol and other substance dependence, withdrawal states, and alcohol-induced neurological disorders, and it has been postulated that severe AWS not controlled with benzodiazepines results from lack of effect on the glutamate neurotransmitters. In addition, propofol is associated with less cross-tolerance with ethanol than benzodiazepines and is easily titrated.[5,9,14]

Although published case reports have demonstrated safe and effective use of propofol in severe AWS refractory to benzodiazepines, there are currently no comparative studies evaluating propofol-containing versus benzodiazepine regimens. The objective of this retrospective study was to compare time to resolution of AWS symptoms in patients receiving propofol-containing infusions versus benzodiazepine infusions in the management of AWS requiring mechanical ventilation.

Methods

A retrospective cohort study was performed at University Hospital, University Health System, San Antonio, Texas, to compare propofol-containing regimens versus benzodiazepine regimens for the management of AWS requiring mechanical ventilation. Adult patients admitted between January 1, 2006, and December 31, 2011, with ICD-9 codes for AWS (291.81) were eligible for inclusion. Patients were further screened based on pharmacy charges for benzodiazepine or propofol infusion. On evaluation by the chart reviewer, patients with confirmed AWS, defined as meeting DSM-IV criteria for AWS, were included. Patients also required mechanical ventilation for symptoms of AWS to be eligible for inclusion. Patients were excluded if they failed to meet DSM-IV criteria for AWS, were not intubated, or were intubated for indications other than symptoms of AWS. They were also excluded for incomplete medical record, pregnancy, or documented allergy to propofol (including egg or soy allergy) or benzodiazepines. The study was reviewed and approved by the hospital's research department as well as the institutional review board of the University of Texas Health Science Center at San Antonio.

Data were abstracted from the medical record by a residency-trained Doctor of Pharmacy skilled in data extraction using a standardized electronic data collection form, which was stored in a password-protected electronic database (Microsoft Excel, 2010, Redmond, WA). Data collected included age, gender, race, height, weight, duration of stay, documented symptoms at time of admission meeting DSM-IV criteria for AWS, Clinical Institute Withdrawal Assessment of Alcohol (CIWA) score, duration of symptoms, study drug adverse events, duration of mechanical ventilation, reintubation, and medications (benzodiazepines and propofol) administered prior to and during propofol or benzodiazepine infusion. Intermittent lorazepam was administered prior to intubation based on CIWA score. Once the patient was intubated, sedation with propofol or benzodiazepines was assessed by either the Ramsay score or Richmond Agitation Sedation Score. Medication data collected included lorazepam equivalent dose and duration of use. Our preferred benzodiazepine infusion is midazolam, which is most commonly initiated at a dose of 0.02 to 0.1 mg/kg/h; the preferred benzodiazepine for intermittent dosing is lorazepam initiated at 1 to 4 mg intravenous push. Dosing of benzodiazepines other than lorazepam was converted to lorazepam equivalents as follows: alprazolam 0.5 mg = lorazepam 1 mg = midazolam 2 mg = diazepam 5 mg = chlordiazepoxide 25 mg.[15] Propofol is dosed from 5 to 80 μg/kg/min. Periodic meetings were held between the chart abstractor and study coordinators to address queries and clarifications. Study coordinators monitored the performance of the chart abstractor throughout the data collection period.

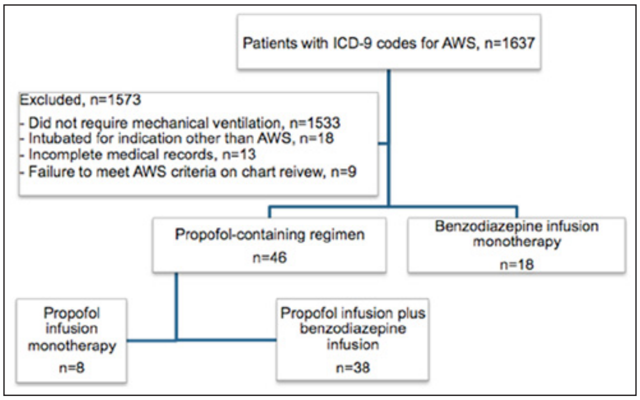

Figure 1. Patient inclusion and exclusion flow chart.
Abbreviation: AWS, alcohol withdrawal syndrome.

The primary outcome was time to resolution of AWS symptoms, defined as cessation of AWS symptoms (ie. tremor, diaphoresis, nausea, vomiting, tachycardia, hypertension, anxiety, agitation, altered mental status, seizures, and hallucinations) per documentation in the electronic medical record. Secondary outcomes included hospital and intensive care unit (ICU) length of stay, days requiring mechanical ventilation, rates of reintubation, in-hospital mortality, and adverse drug events (ADEs), including propylene glycol toxicity (serum propylene glycol level > 25 mg/dL), hypotension (SBP < 90 mm Hg), myoclonus, acute kidney injury, pancreatitis, anaphylaxis, nausea or vomiting, propofol infusion syndrome, hypertriglyceridemia (serum triglyceride level > 500 mg/dL), injection site reaction, and bradycardia (heart rate < 55 beats/min). ADEs were defined when specifically listed as ADEs in the patients' medical records.

Statistical Analysis

Data were analyzed using JMP 9.0.2 (2012 SAS Institute, Cary, NC). Descriptive statistics were used to summarize patient demographics and outcomes. Continuous variables were tested for normality using the Shapiro-Wilk W test. Normally distributed continuous data were analyzed using the Student t test, whereas non-normally distributed continuous data were analyzed using the Wilcoxon Rank Sum test. χ^2 or Fisher's exact tests were used to compare nominal data as appropriate. An *a priori* α level of less than or equal to .05 was used to determine statistical significance for all comparisons, except for multiple comparisons, where statistical significance was set at less than or equal to .025. Comparisons between the 3 groups were analyzed using the ANOVA test.

Results

Of 1637 records reviewed of patients admitted with a diagnosis of AWS, 64 records met inclusion criteria (see Figure 1). Patients were first excluded if they did not require mechanical ventilation (n = 1533). Additional patients were excluded if they were intubated for an indication other than symptoms of AWS (n = 18), had incomplete medical records (n = 13), or did not meet DSM-IV criteria for AWS on chart review (n = 9). In all, 46 (72%) patients received a propofol-containing regimen (with or without benzodiazepine infusion), and 18 (28%) received benzodiazepine infusion monotherapy. Baseline characteristics are presented in Table 1. The cohort was 97% male, with a mean age of 45 years (±8.5). The median CIWA score of our cohort was 11 (4-19) at initial presentation and 21 (13-30) just before the initiation of continuous infusion sedation. Patients in the propofol-containing group received 56 mg (interquartile range [IQR] = 17-127 mg) of total lorazepam-equivalent benzodiazepine prior to intubation, compared with 15 mg (IQR = 5-66 mg) in the benzodiazepine monotherapy group (P = .03). All patients received benzodiazepine bolus doses, and no patient was started on continuous study drug infusion therapy prior to intubation.

Patients in the propofol-containing group (n = 46) received propofol infusion for a median time of 36 hours (IQR = 17-76). Approximately half (45%) of the patients in the propofol-containing group received benzodiazepine infusion prior to initiation of propofol for a median duration of 10 hours (IQR = 2-49). Patients in the benzodiazepine group (n = 18) received benzodiazepine infusion for a median duration of 48 hours (IQR = 32-93). Of the 38 patients receiving both agents, the infusions overlapped in 67% of patients, with a median overlap duration of 33 hours (IQR = 11-69). Of 46 patients who received propofol infusion, 29 (63%) received benzodiazepine bolus doses while receiving propofol (median = 10 mg [IQR = 4-34] lorazepam-equivalent benzodiazepine dosage), compared with 9 of 18 (50%) patients who received benzodiazepine monotherapy (median = 36 mg [IQR = 15-100] lorazepam-equivalent benzodiazepine dosage, P = .06).

Patients receiving propofol-containing regimens experienced 8 days (IQR = 5-13) of AWS symptoms compared with patients in the benzodiazepine monotherapy group, who experienced 7 days (IQR = 5-10) of AWS symptoms (P = .34; Table 2). Hospital and ICU lengths of stay were similar between groups (9 vs 10 days and 4 vs 4 days, respectively; P > .05 for both comparisons). No significant difference was noted between groups in days of required mechanical ventilation (P = .98). Documented study drug adverse events were more common in the benzodiazepine monotherapy group (28% vs 11%, P = .13). Of the 5 adverse drug events noted in the benzodiazepine group, 4 patients experienced hypotension requiring therapeutic intervention and 1 experienced bradycardia. In the propofol-containing group, 5 adverse drug events were reported, including hypotension (n = 2), pancreatitis (n = 1), bradycardia (n = 1), and acute kidney injury (n = 1). No cases of propofol infusion syndrome were reported. No difference was found in rates of reintubation or in-hospital mortality.

In a post hoc subgroup analysis, we compared patients who received propofol infusion monotherapy, patients who received both propofol and benzodiazepine infusions, and

Table 1. Patient Baseline Characteristics.[a]

Characteristic	Overall	Propofol-Containing Infusion[b]	BDZ Infusion	*P* Value
Number of patients	64	46	18	—
Age (years), mean (±SD)	45 (±8.5)	44 (±9.1)	48 (±5.6)	.07
Male gender, n (%)	62 (97)	45 (98)	17 (94)	.48
Race or ethnicity, n (%)				.03[c]
Hispanic	33 (52)	28 (61)	5 (28)	
Caucasian	30 (47)	17 (37)	13 (72)	
Black	1 (2)	1 (2)	0 (0)	
Height (inches), mean (±SD)	69 (±3.1)	68 (±2.9)	69 (±3.5)	.62
Weight (kg), mean (±SD)	82 (±17.7)	81 (±17.6)	83 (±18.5)	.61
DSM-IV symptoms, n[d]	2 (2-3)	2 (2-3)	2 (2-2)	.19
≥3 DSM-IV symptoms, n (%)	18 (28)	16 (35)	2 (11)	.07
CIWA score[d]				
Baseline (first recorded)	11 (4-19)	11 (4-19)	10 (2-30)	.62
Prior to initiation of sedation	21 (13-30)	24 (18-33)	20 (9-29)	.19
Total lorazepam equivalent BDZ dosage given prior to intubation (mg)[d]	46 (13-117)	56 (17-127)	15 (5-66)	.03[c]

Abbreviations: BDZ, benzodiazepine; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; CIWA, Clinical Institute Withdrawal Assessment of Alcohol; IQR, interquartile range.
[a]Student's *t* test or the Wilcoxon rank sum test was used to analyze continuous data, as appropriate. The χ^2 test or Fisher's exact test was used to analyze nominal data, as appropriate.
[b]With or without BDZ infusion.
[c]Statistical significance ($P < .05$).
[d]Median (IQR).

Table 2. Primary and Secondary Outcomes for Patients on Propofol-Containing Infusion and BDZ-Infusion Monotherapy.[a]

Outcome	Propofol-Containing Infusion[b]	BDZ Infusion	*P* Value
Number of patients	46	18	—
Time to resolution of AWS, days[c]	8 (5-13)	7 (5-10)	.34
Duration of time on continuous infusion, hours[c]	36 (17-76)	48 (32-93)	.32
BDZ boluses while on continuous sedation, mg[c]	10 (4-34)	36 (15-100)	.06
Hospital LOS, days[c]	9 (7-16)	10 (7-16)	.92
ICU LOS, days[c]	4 (3-8)	4 (3-9)	.62
Mechanical ventilation, days[c]	4 (2-7)	3 (3-6)	.98
Reintubation, n (%)	2 (4)	1 (6)	1
In-hospital mortality, n (%)	2 (4)	0 (0)	1
Study drug adverse events, n (%)	5 (11)	5 (28)	.13

Abbreviations: BDZ, benzodiazepine; AWS, alcohol withdrawal syndrome; ICU, intensive care unit; LOS, length of stay; IQR, interquartile range.
[a]Student's *t* test or Wilcoxon rank sum test was used to analyze continuous data, as appropriate. χ^2 or Fisher's exact test was used to analyze nominal data, as appropriate.
[b]With or without BDZ infusion.
[c]Median (IQR).

patients who received benzodiazepine infusion monotherapy. No difference was detected in time to resolution of AWS symptoms or length of stay (Table 3).

Discussion

In our study, we found that propofol-containing regimens may be safe and reasonable in the management of refractory AWS. Outcomes between treatment groups were similar when comparing time to resolution of AWS, length of stay, days requiring mechanical ventilation, rates of reintubation, and in-hospital mortality.

Our study is the first to compare propofol-containing versus benzodiazepine infusions in AWS. Published case reports and case series have shown improved AWS symptoms in patients receiving propofol for AWS.[9-13] The first successful

Table 3. Subgroup Analysis of Propofol-Infusion Monotherapy Versus Propofol Plus BDZ Infusion Versus BDZ-Infusion Monotherapy.[a]

Outcome	Propofol Infusion	Propofol Plus BDZ Infusion	BDZ Infusion	*P* Value
Number of patients	8	38	18	—
Time to resolution of AWS, days[b]	8 (6-11)	9 (5-14)	7 (5-10)	.63
Duration of time on continuous infusion, hours[b]	28 (6-36)	49 (18-92)	48 (32-93)	.08
BDZ boluses while on continuous sedation, mg[b]	15 (3-76)	10 (5-27)	36 (15-100)	.16
Hospital LOS, days[b]	9 (7-15)	10 (7-16)	10 (7-16)	.99
ICU LOS, days[b]	3 (2-5)	4 (3-9)	4 (3-9)	.66
Mechanical ventilation, days[b]	3 (2-3)	4 (3-8)	3 (3-6)	.09
Study drug adverse events, n (%)	1 (12)	4 (11)	5 (28)	.24

Abbreviations: BDZ, benzodiazepine; AWS, alcohol withdrawal syndrome; ICU, intensive care unit; LOS, length of stay; IQR, interquartile range.
[a]ANOVA was used to evaluate 3-sample continuous data.
[b]Median (IQR).

use of propofol was reported by Coomes and Smith[10] in delirium tremens refractory to large doses of benzodiazepines, when the patient's agitation and tachycardia improved after propofol infusion. In a case series of 4 patients by McCowan and Marik,[11] patients continued to experience AWS symptoms despite increasing rates of lorazepam infusion; however, patients' agitation improved after initiating propofol infusion. Subramaniam et al[9] reported improved withdrawal symptoms and stable hemodynamics in 3 patients with polysubstance abuse after receiving propofol infusion. Mahajan et al[12] reported improved AWS symptoms after starting propofol infusion in a patient with inadequate symptom control with benzodiazepine infusion. The patient was maintained on propofol and lorazepam infusions with intermittent doses of diazepam and midazolam; the patient's AWS symptoms subsequently improved. In summary, all authors concluded that propofol should be considered an option for the treatment of refractory AWS and delirium tremens. Unfortunately, there remains no standard definition of *benzodiazepine refractory*. There is a large degree of variation in patients' responses to benzodiazepines, and we did not feel a specific dose cutoff would adequately separate those who were refractory versus those who were not; therefore *benzodiazepine refractory* was not an inclusion criteria for our study. Of note, all patients included in our study received benzodiazepine bolus doses prior to intubation and were required to be intubated for AWS symptoms, based on documentation in the medical record. Therefore, we considered our patients' AWS symptoms to persist despite bolus doses of benzodiazepines.

The control group included 28% of our study population, and the propofol-containing group comprised 72%. This was an unexpected finding considering the lack of published, peer-reviewed data supporting the use of propofol for refractory AWS. There is no formalized protocol for the treatment of AWS in the emergency department or ICUs of our institution; rather, treatments administered are prescriber driven. The increased use of propofol-containing regimens in this patient population may have been a result of prescribers preferring propofol in patients with persistent symptoms despite large intermittent doses of benzodiazepines. In addition, a second agent may have been required in controlling persistent AWS symptoms after reaching high dosages of benzodiazepine infusion. Patients in the propofol-containing group received a median of almost 4 times the amount of lorazepam-equivalent benzodiazepine dosage prior to being intubated (56 vs 15 mg; $P = .03$), raising the question of whether the patients receiving propofol may have experienced more severe symptoms; however, CIWA scores were similar at the time of presentation and prior to initiation of study drug infusion between groups.

Benzodiazepines bind at the GABA receptor in the central nervous system. When these receptors become saturated, additional drug can no longer bind.[9,16] In addition, benzodiazepines are highly lipophilic and may sequester in tissue after high-dose therapy, resulting in residual sedation and potentially extending time requiring mechanical ventilation, rehabilitation, and lengths of stay.[17] In contrast, we did not detect a difference in days requiring mechanical ventilation nor lengths of stay in our study. Residual sedation could also hinder the health care providers' assessment of neurological status to determine whether AWS symptoms have improved; this would further delay patient downgrade from ICU as well as discharge.

There are several limitations to this study. The study was single center and conducted at one tertiary care medical center. The patient population at this institution is mostly uninsured and without a primary care access, which may limit the generalizability of our findings. In addition, only patients with ICD-9 codes for AWS were included in this study; therefore, some patients may have been excluded during the screening process. Patients' comorbidities were not taken into account in this study; the authors felt that the exclusion of patients intubated for reasons other than AWS reduced confounders that may have influenced duration of time requiring mechanical ventilation, length of stay, and mortality. In addition, we did not assess concomitant medication used for AWS. We detected fewer patients in the benzodiazepine monotherapy arm than expected, possibly because patients did not respond adequately to intermittent benzodiazepine therapy prior to intubation. It should be noted that although there is no clear, universally accepted definition for *benzodiazepine refractory*, AWS symptoms persisted despite benzodiazepine bolus doses in this population. Because of the retrospective nature of the study and the small sample size, the reader should exercise caution when interpreting these findings. Although we collected CIWA scores at admission, prescribers' perceived severity of illness may have influenced the prescription of one agent over another. There is no protocol in the emergency department of our institution for objective assessment and treatment of refractory AWS based on the severity of the presentation, rendering evaluations of withdrawal severity at baseline difficult to ascertain. At this time, there is no standardized scale adopted in a clinical setting that allows providers to objectively quantify severity of AWS in mechanically ventilated patients. Study adverse drug events were recorded by electronic record documentation, creating the potential for errors in either documentation or interpretation, even though adverse events were predefined by researchers.

Conclusions

Propofol provides an alternative treatment for patients with AWS inadequately managed by benzodiazepine bolus doses and requiring mechanical ventilation. Propofol-treated patients experienced similar days of AWS symptoms despite receiving almost 4 times the amount of lorazepam-equivalent benzodiazepine bolus doses prior to mechanical ventilation. Propofol should be considered a therapeutic alternative in patients experiencing AWS requiring mechanical ventilation.

Authors' Note

Prior presentations are as follows. January 22, 2013: poster presentation at Society of Critical Care Medicine Critical Care Congress, San Juan, PR. April 17, 2012: poster presentation at 8th Annual Louis C. Littlefield Celebrating Pharmacy Research Excellence Day, Austin, TX. April 13, 2012: platform presentation at Alcáldé XXVI Southwest Leadership Conference, Dallas, TX.

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Declaration of Conflicting Interests

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