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Short communication

Management of benzodiazepine-resistant alcohol withdrawal across a healthcare system: Benzodiazepine dose-escalation with or without propofol☆

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ABSTRACT

Background: Severe cases of alcohol withdrawal syndrome (AWS) may not resolve despite escalating doses of benzodiazepines (BZDs). Benzodiazepine-resistant alcohol withdrawal (RAW) is a subset of severe alcohol withdrawal defined by the requirement of ≥40 mg of diazepam administered within one hour. Use of adjunct agents, such as propofol, may be beneficial to minimize BZD adverse effects and improve symptom control. While limited evidence suggests propofol as an effective adjunct in AWS through improved sedation, evidence is currently lacking for the addition of only propofol to BZDs for management of RAW.

Methods: Retrospective review of adult patients from January, 2009 to March, 2012 with RAW. Patients were categorized into BZD dose-escalation only or BZD plus propofol. The primary endpoint was time to resolution of AWS. Secondary endpoints included safety outcomes associated with medication use.

Results: Of 1083 patients with severe AWS, 66 RAW patients ($n = 33$ BZD only, $n = 33$ BZD plus propofol) met inclusion. Median time to AWS resolution was 5.0 and 7.0 days for BZD only vs. BZD plus propofol ($p = 0.025$). Duration of mechanical ventilation, ICU and hospital length of stay were significantly higher with propofol ($p = 0.017$, <0.001 and <0.001, respectively). Ten patients required intervention for management of propofol-induced adverse reactions.

Conclusions: The addition of propofol for RAW treatment is associated with significant increases in clinical care. While randomized, prospective evaluations are necessary to determine the cause of this association, our data suggests use of adjunctive propofol therapy in RAW is associated with longer and more complicated hospital admissions.

1. Introduction

Alcohol withdrawal syndrome (AWS) occurs in patients due to cessation of alcohol, which is an agonist of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter (Bayard et al., 2004). Alcohol-induced alterations of GABA and upregulation of the excitatory neurotransmitter *N*-methyl-D-aspartase (NMDA) results in associated withdrawal symptoms (Sarff and Gold, 2010). Benzodiazepines (BZDs) often serve as first-line therapy as they target the GABA-A receptor, which mediates the primary GABA effects of ethanol in the body (Brathen et al., 2005; Mayo-Smith et al., 2004; Nakagawa and Iwasaki, 1995). Despite escalating doses of BZDs, a subset of patients do not adequately respond (Gold et al., 2007; Hack et al., 2006). Benzodiazepine-resistant alcohol withdrawal (RAW) is defined as the requirement of ≥40 mg of diazepam (or equivalent) administered within one hour (Hack et al., 2006).

The use of agents that target another binding site of the GABA receptor or other modes of action may be beneficial in RAW patients (Liang et al., 2009; Radel and Goldman, 2001; Wong et al., 2015).

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Propofol has GABA-agonist activity at an alternative GABA receptor binding site, antagonizes NMDA, and has a relatively short duration of action allowing for ease in titration (Liang et al., 2009). Studies evaluating propofol for management of AWS initiated propofol after patients received significant amounts of BZDs, with variable effectiveness ranging from no benefit to effective management of agitation (Coomes and Smith, 1997; Hughes et al., 2014; Lizotte et al., 2014; Lorentzen et al., 2014; Sohraby et al., 2014). Other adjunct agents were allowed in these studies, including antipsychotics and phenobarbital, which may confound the effects of propofol alone on studied outcomes.

The purpose of this study is to describe the clinical characteristics of dose escalation of BZDs alone (BZDO) compared to BZDs plus propofol (PRO) in a RAW population, as evidence currently is lacking for the addition of only propofol without other adjunctive agents to BZDs for management of RAW. The primary endpoint was the time to resolution of AWS, with secondary endpoints including safety outcomes associated with medication use.

2. Materials and methods

2.1. Patient population and setting

A retrospective cohort of adult patients were identified via *International Classification of Diseases, Ninth Revision* (ICD-9) codes with severe alcohol withdrawal (291.0, 291.2, 291.3, 291.81, 303.01, 303.91) from January, 2009 to March, 2012 in the University of Pittsburgh Medical Center health system.

From this population, a chart review using an electronic health record (Cerner Powerchart®, Kansas City, MO) was conducted to identify patients who met RAW criteria (requirement of ≥40 mg of diazepam [or equivalent] administered within 1 h). Patients were excluded if they received any documented agent other than BZDs or propofol, for management of AWS. For patients not receiving diazepam, a BZD equivalent was applied (alprazolam 1 mg = chlordiazepoxide 25 mg = clonazepam 0.5 mg = diazepam 10 mg = lorazepam 1.5 mg = midazolam 1 mg = oxazepam 30 mg; Dopheide and Pliszka, 2012; Guthrie and Augustin, 2008). At the time of RAW designation, patients must have received BZDs for management of AWS and not for other indications. The BZDO group required patients to have a dose escalation of BZDs from 12 h before RAW designation to 12 h after RAW to ensure that these patients required escalation of therapy. Dose escalation was defined as any increase in BZD requirements. The PRO group did not require dose escalation of BZDs.

A standardized institutional AWS treatment protocol, the Withdrawal Assessment Scale (WAS), was utilized to guide BZD dosing and administration. The WAS indicates severity of AWS by stratifying points and determining subsequent BZD administration based on symptoms (Wetterling et al., 1997). This score was not used in the ICU, as sedation scores take preference. Lorazepam or chlordiazepoxide were preferred agents for BZD administration in the WAS protocol. This study was approved as an expedited study by the University of Pittsburgh Investigational Review Board.

2.2. Data collection

Data collection included baseline demographics and clinical outcomes associated with management, including time to resolution of AWS, incidence of nosocomial pneumonia, length of ICU and hospital length of stay, and associated documented symptoms from AWS, including delirium tremens, hallucinations and seizures. Demographic information included use of the Simplified Acute Physiology Score (SAPS II) to evaluate severity of illness (Le Gall et al., 1993). The SAPS was evaluated within 24 h of ICU admission or at time of RAW designation for patients who were never admitted to the ICU. Time to resolution of AWS was defined as documentation of resolved AWS symptoms in a patient's medical record. Symptoms of AWS and adverse drug events were collected through evaluation of a patient's medical record and depended on documentation by the provider. Hypotension was defined as a systolic blood pressure less than 90 mmHg. Bradycardia was defined as a heart rate less than 60 bpm and was only collected for the propofol group. Nosocomial pneumonia was defined as pneumonia that occurred at least 48 h after admission, and not present at time of hospital admission. (American Thoracic Society, 2005) Collection of data occurred for 7 days after RAW designation to best evaluate the typical time to resolution of AWS (Bayard et al., 2004). Agitation assessment in mechanically ventilated patients was based on an ICU sedation score (Supplementary Table 1[1]), reported as an equivalent Riker Sedation-Agitation Scale (SAS) score (Riker et al., 1999). This score was derived from a comparison of the Motor Activity Assessment Scale, the Ramsay score and the SAS, to standardize scores amongst our health system (Devlin et al., 1999; Ramsay et al., 1974). The incidence of specialty consultation, and patient disposition at discharge were also collected. A post hoc analysis was performed on outcomes associated with the BZDO group who were mechanically ventilated, compared to the PRO group.

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2.3. Statistical analysis

Data in this study were analyzed using SPSS (SPSS Inc., Chicago, IL, USA). The primary and secondary outcomes were determined a priori. A Mann–Whitney *U* test was used for continuous data and a chi-square or Fisher's exact test were used for categorical data, as appropriate. A *p*-value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patients

Of 1083 records reviewed of patients with ICD-9 codes for severe alcohol withdrawal, a total of 66 (6.1%) patients met eligibility. Patients were excluded due to lack of BZD-qualifying dosing for RAW ($n = 834$), receiving their RAW-designating dose for other indications, ($n = 65$), use of additional adjunctive agents for management of AWS ($n = 106$), or lack of BZD dose-escalation in the BZDO group ($n = 12$). Baseline demographics are provided in Table 1. There were differences at baseline between the groups in terms of gender.

3.2. Treatment and outcomes

AWS characteristics and outcomes are detailed in Table 2. The PRO group had a significantly higher incidence of hallucinations and mechanical ventilation, a higher duration of mechanical ventilation, a longer ICU and hospital length of stay, and a longer time to resolution of AWS. Patients experiencing mortality were not due to AWS, but due to comorbidities that these patients had prior to admission (e.g., end-stage liver disease). No patients experienced any AWS complications after propofol was initiated.

In the BZDO group, the median BZD requirements 12 h pre- and post-RAW designation were 53.2 (IQR 20.0, 114.2) and 225.0 mg (IQR 101.7, 477.5), respectively. In the PRO group, median time to propofol initiation from RAW designation was 9.0 h (IQR 2.0, 31.0). Median diazepam equivalents from RAW designation to propofol initiation was 160.0 mg (IQR 93.0, 366.7). Median total diazepam equivalents 12 h post-RAW designation was 126.7 mg (IQR 80.0, 404.5). The median dose of propofol was 30.1 mcg/kg/min (IQR 23.0, 37.6) and propofol was continued for a median of 58.5 h (IQR 40.0, 102.5). Within the PRO group, propofol initiation resulted in a median 60 mg decrease in diazepam equivalents (IQR −143.1, 0, $p = 0.298$) 12 h pre- (median 126.7 mg) and post-propofol (median 13.3 mg) initiation.

The post hoc analysis comparing the BZDO group requiring mechanical ventilation ($n = 14$) to the PRO group ($n = 33$) indicated a significantly increased incidence of AWS complications ($p = 0.008$), delirium tremens ($p = 0.042$), hallucinosis ($p = 0.042$), and pneumonia in the PRO group. The duration of mechanical ventilation ($p = 0.017$), ICU ($p = 0.003$) and hospital length of stay ($p = 0.001$) were also significantly increased. These findings were similar to the full sample analysis of outcome data.

There was no difference between groups in the incidence of hypotension (30.3 vs. 39.4%, $p = 0.438$). A total of 6 patients experienced bradycardia while on propofol. Interventions for hypotension were required for 10 patients in the propofol group, compared to zero in the BZD group ($p < 0.001$).

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2015.07.005.