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Multicenter evaluation of pharmacologic management and outcomes associated with severe resistant alcohol withdrawal☆

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ABSTRACT

Introduction: A subset of patients with alcohol withdrawal syndrome does not respond to benzodiazepine treatment despite escalating doses. Resistant alcohol withdrawal (RAW) is associated with higher incidences of mechanical ventilation and nosocomial pneumonia and longer intensive care unit (ICU) stay. The objective of this study is to characterize pharmacologic management of RAW and outcomes.

Methods: Adult patients were identified retrospectively via *International Classification of Diseases, Ninth Revision* codes for severe alcohol withdrawal from 2009 to 2012 at 3 hospitals. Data collected included pharmacologic management and clinical outcomes.

Results: A total of 184 patients met inclusion criteria. Sixteen medications and 74 combinations of medications were used for management. Propofol was the most common adjunct agent, with dexmedetomidine and antipsychotics also used. One hundred seventy-five patients (96.2%) were admitted to the ICU, with 149 patients (81.9%) requiring ventilator support. Median time to resolution of alcohol withdrawal syndrome from RAW designation was 6.0 days. Median ICU and hospital length of stay were 9.0 and 12.7 days, respectively.

Conclusion: Diverse patterns exist in the management of patients meeting RAW criteria, indicating lack of refined approach to treatment. High doses of sedatives used for these patients may result in a high level of care, illustrating a need for evidence-based clinical guidelines to optimize outcomes.

1. Introduction

Alcohol is the most commonly abused mood-altering substance, with its abuse affecting 8.5% of the total adult US population [1]. In 2009, alcohol abuse was associated with approximately $195 billion in costs to the economy with health care expenditures for the medical consequences alone accounting for approximately $26 billion [2]. Medical consequences such as alcohol withdrawal syndrome (AWS) may manifest as mild symptoms such as agitation and tremors but may also be severe enough to cause seizures, delirium, and death [3]. Mortality rates resulting from AWS have been estimated as high as 15%, even with treatment. However, recent data estimates associated mortality at approximately 5% due to a better understanding and recognition of the syndrome and a better understanding of treatment strategies [4].

Alcohol enhances the inhibitory neurotransmitter γ-amino-butyric acid (GABA) [3]. Chronic alcoholism leads to a down-regulation of the GABA receptor, up-regulation of the excitatory receptor *N*-methyl-D-aspartase, and a subsequent dependence on alcohol to maintain equilibrium. Abrupt cessation of alcohol results in the hyperexcitatory clinical manifestations seen in withdrawal. Benzodiazepines (BZDs) are considered first-line agents for the management of AWS, as they are GABA agonists [5,6]. However, a subset of severe AWS patients does not respond adequately, despite escalating doses of BZDs [7]. *Resistant alcohol withdrawal* (*RAW*) is defined as the requirement of greater than 40 mg of diazepam or equivalent in 1 hour for management of AWS [7,8]. Resistant alcohol withdrawal is associated with a higher incidence of mechanical ventilation, a higher incidence of nosocomial pneumonia, and a longer intensive care unit (ICU) stay.

Strategies studied to manage severe AWS include increasingly higher doses of BZDs, dexmedetomidine, phenobarbital, and propofol [9-20]. However, the preferred management of RAW remains unclear, as only phenobarbital has been evaluated [8]. In this case report, phenobarbital added to escalating doses of BZD was found to improve symptom control with no respiratory depression. In addition, evaluation of clinical outcome data may help further delineate appropriate management of RAW. The objective of this study is to characterize the pharmacologic management of RAW patients and describe related outcomes.

2. Methods

2.1. Patient population and setting

A retrospective cohort of adult patients were identified via *International Classification of Diseases, Ninth Revision* codes for severe alcohol

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withdrawal (291.0, 291.2, 291.3, 291.81, 303.01, and 303.81) from January 1, 2009 to March 1, 2012 at 1 tertiary care (hospital 1) and 2 community medical centers (hospitals 2 and 3) in the University of Pittsburgh Medical Center health system. Hospital 1 is an academic medical center with 792 hospital beds and 150 ICU beds, and is designated as a level 1 trauma center. Hospital 2 is a 412-bed hospital with 47 ICU beds. Hospital 3 is an academic medical center with 520 hospital beds with 68 ICU beds.

Patients were identified, and data were obtained from the Medical Archival Retrieval System database, an electronic repository used for the health system that contains clinical and financial data used in prior studies [21,22]. From this severe alcohol withdrawal population, a manual chart review using an electronic health record (Powerchart; Cerner, Kansas City, MO) was conducted to identify patients meeting RAW criteria, consistent with the literature of a BZD equivalent of 40 mg of diazepam in 1 hour for management of AWS. For patients not receiving diazepam, a BZD dose 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) [23,24]. At the time of RAW designation, patients must have received BZDs for management of AWS and not for other indications such as procedural use.

A standardized institutional AWS treatment protocol has been adopted at these 3 institutions using the Withdrawal Assessment Scale (WAS). However, no standardized protocol for the management of severe AWS or severe AWS with RAW exists. The WAS indicates severity of AWS on a scale from 0 to 96, stratifying points based on severity of symptoms [25]. In brief, BZDs are administered based on symptoms when the WAS score is greater than 10, and house staff are notified when the score is greater than 14. Evaluation is completed every 4 hours, unless the score is greater than 20, when evaluation is completed every 2 hours. This study was approved as an exempt study by the University of Pittsburgh Investigational Review Board.

2.2. Data collection

Data collection included pharmacologic management (initial, median, and maximum maintenance doses and documented discontinuation due to adverse effects of medications) and the clinical outcomes associated with management of these patients, including time to resolution of AWS, incidence of nosocomial pneumonia, the length of ICU and hospital length of stay, and associated documented symptoms from AWS, including delirium tremens, hallucinations, and seizures. *Nosocomial pneumonia* was defined as pneumonia that occurs at least 48 hours after admission, which was not present at time of hospital admission [26]. Collection of data occurred for 7 days, after a patient had been identified with RAW. This time frame was chosen to best evaluate the typical time to resolution of AWS in patients [3]. Demographic information included the use of the Simplified Acute Physiology Score (SAPS) II to evaluate severity of illness at ICU admission [27]. Agitation assessment in patients who were mechanically ventilated was based on the Ramsay Score, Riker Sedation-Agitation Scale, or the Motor Activity Assessment Scale, depending on institution [28-30]. Agitation scores were collected as closely before time of RAW designation as possible, with a maximum time window of 6 hours. The incidence of specialty consultation, documented symptoms associated with AWS, time to resolution of AWS, and patient disposition at discharge were also collected.

2.3. Statistical analysis

Data in this study were analyzed using SPSS (SPSS Inc., Chicago, IL, USA). A student's t-test or Mann-Whitney U test were used for continuous data and a chi-square test 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 *International Classification of Diseases, Ninth Revision* codes for severe alcohol withdrawal, a total of 184 (17.0%) patients met eligibility criteria for RAW and active management of AWS. Baseline demographics are provided in Table 1. Most patients were middle-aged, White males with low severity of illness scores.

3.2. Treatment and outcomes

A total of 16 unique medications (Table 2) and 74 unique medication combinations were used for patients for management of AWS, with the greatest number of medications used for 1 patient totaling 7 unique medications. Propofol was the most frequently used adjunct agent to BZD therapy, with dexmedetomidine and antipsychotics common additions as well.

Dosing parameters of commonly used agents are detailed in Table 3. At time of RAW designation, a total of 2, 28, 15, and 32 patients had already been initiated on dexmedetomidine, continuous lorazepam, and continuous midazolam and propofol, respectively. Four patients who were administered adjunct phenobarbital for AWS management received multiple doses. However, all doses were administered over a 24-hour period, with the greatest number of doses totaling 4 for 1 patient. Sedative doses were on the mid-high end of the range for suggested doses used in the ICU [31].

Alcohol withdrawal syndrome–related outcomes and characteristics are provided in Table 4. Nearly half of patients experienced at least 1 AWS complication. Despite a low median SAPS, a vast majority of patients were admitted to the ICU, with the documented reason being AWS in approximately half of patients. Mechanical ventilation was common in this predominately ICU population with airway protection provided as the most common indication. Time to resolution of symptoms was 6.0 days from the designation of RAW. Evaluation of outcomes between BZD-only and BZD plus non-BZD therapies is detailed in Table 5.

4. Discussion

Pharmacologic management for RAW patients is quite variable based on evaluation of 3 hospitals in the University of Pittsburgh Medical Center health system. Little guidance is currently available for pharmacologic management of RAW [7]. The most common treatment for RAW included further increases in BZD dosing or adding another BZD, with a total of 45 patients requiring only a BZD for management. The fact that 16 unique medications and 74 combinations of medications were used suggests that medication selection needs to be refined. These findings confirm that the lack of evidence-based guidelines for the treatment of RAW has resulted in a varied selection of sedatives for management, with therapy guided by health care provider preference. This is a call for more studies to guide therapy and develop clinical guidelines.

Our study evaluated all possible combinations of adjunctive agents for the management of AWS, which is lacking in other trials that focus on a specific non-BZD treatment of severe AWS. Evaluation of the commonly used adjunct agents to intermittent BZDs illustrates that continuous infusion BZDs are the first agents initiated as well as the agents that are used longest. Midazolam may be the agent of choice given ease of availability at our health system, as ready-to-use bags are accessible in the ICU setting through automated dispensing as well as lack of potential propylene glycol toxicity, which may occur from continuous infusion lorazepam. The dosing characteristics of dexmedetomidine were reflective of our health system policy of a maximum dose of 0.7 mg/kg per hour. Dexmedetomidine's duration of therapy was shorter than other adjunct agents, despite evidence supporting safety in infusion up to 7 days for sedation in the ICU [32]. Of interest, the phenobarbital was almost exclusively used (90.0%) with recommendation by a