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Evaluation of Adjunctive Ketamine to Benzodiazepines for Management of Alcohol Withdrawal Syndrome

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Abstract

Background: Adjunctive medications to manage alcohol withdrawal syndrome (AWS) in patients not adequately responding to escalating doses of benzodiazepines (BZDs) are limited. The use of the *N*-methyl-D-aspartate antagonist ketamine, may serve as an effective adjunct agent; however, no published data currently exist for this practice. **Objective:** To determine the safety and efficacy of adjunct ketamine for management of AWS. **Methods:** The study was a retrospective review of adult patients from April 2011 to March 2014 who were administered ketamine specifically for management of AWS. Outcomes included changes in BZD requirements and ketamine-related adverse reactions. **Results:** Of 235 patients screened, 23 patients met study eligibility. Ketamine was initiated primarily with toxicology consultation for significant BZD requirements or delirium tremens. The mean time to initiation of ketamine from first treatment of AWS, and total duration of therapy were 33.6 and 55.8 hours, respectively. Mean initial infusion dose and median total infusion rate during therapy were 0.21 and 0.20 mg/kg/h, respectively. There was no change in sedation or alcohol withdrawal scores in patients within 6 hours of ketamine initiation. The median change in BZD requirements at 12 and 24 hours post–ketamine initiation were −40.0 and −13.3 mg, respectively. The mean time to AWS resolution was 5.6 days. There was one documented adverse reaction of oversedation, requiring dose reduction. **Conclusions:** Ketamine appears to reduce BZD requirements and is well tolerated at low doses. Prospective dose range evaluations in the management of AWS would be helpful in determining its place as an adjunctive agent.

Keywords

alcohol withdrawal delirium, alcohol withdrawal seizures, benzodiazepines, ketamine, toxicology

Introduction

Chronic alcoholism results in downregulation of the inhibitory neurotransmitter, γ-amino-butyric acid (GABA) receptor, and an upregulation of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA).[1] A subsequent dependence on alcohol is needed to maintain equilibrium and to prevent the hyperexcitatory clinical manifestations of alcohol withdrawal syndrome (AWS).[2] Benzodiazepines (BZDs) are GABA agonists and considered first-line agents for the management of AWS.[3] However, a subset of patients with severe AWS do not respond adequately to BZDs, despite escalating doses.[4]

The use of adjunctive agents to BZDs, such as dexmedetomidine, phenobarbital, and propofol in AWS management has been studied, with variable results.[5-17] These agents target different mechanisms, including adrenergic symptoms and alternative GABA receptors. NMDA antagonists, such as ketamine, have not been evaluated in the available literature and may serve as a beneficial adjunct to BZD therapy. Ketamine is classified as an anesthetic with a beneficial safety profile and has been shown to be an effective analgesic in nonneuropathic pain.[18] Additionally, ketamine was shown to produce beneficial responses in recovering ethanol-dependent patients.[19-22] The objective of this study was to evaluate the safety and efficacy of ketamine as an adjunctive agent to BZD therapy in patients with AWS.

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Methods

Patient Population and Setting

A retrospective cohort of adult patients was identified using pharmacy charges for ketamine infusions from April 2011 to March 2014 at one tertiary care center in the University of Pittsburgh Medical Center (UPMC) health system. The hospital is an academic medical center with 792 hospital beds and 150 intensive care unit (ICU) beds and is designated as a level 1 trauma center. This study was approved as an expedited study by the University of Pittsburgh Investigational Review Board.

From this population of patients with pharmacy charges for ketamine infusions (n = 235), a manual chart review using an electronic health record (Cerner Powerchart, Kansas City, MO) was conducted to identify patients in whom ketamine was added as adjunctive agent to the standard of care for active AWS management. Patients were excluded if they were less than 18 years of age or were initiated ketamine for reasons other than AWS management (ie, pain control).

A standardized institutional AWS treatment protocol has been adopted at our institution utilizing the Withdrawal Assessment Scale (WAS). The WAS is a validated tool in medicine that was derived from the Clinical Institute Withdrawal Assessment (CIWA) tool and indicates severity of AWS on a scale from 0 to 96, stratifying points based on symptoms.[23] The WAS assesses 4 objective symptoms relating to AWS: temperature, heart rate, respiratory rate, and blood pressure. In brief, BZDs are administered based on symptoms when the WAS score is greater than 10, and housestaff are notified when the score is greater than 14. Lorazepam or chlordiazepoxide are preferred agents for BZD administration in the WAS protocol. Evaluation is completed every 4 hours unless the score is greater than 20, when evaluation is completed every 2 hours. The WAS is meant only to guide BZD dosing and administration. Ketamine use is not part of the WAS protocol, and this scale is not used in the ICU as sedation scores take preference. The decision to admit a patient to the ICU is physician directed and is based on the severity of symptoms and the quantity and frequency of BZD administration.

Data Collection

Data collection included change in BZD requirements at 12 and 24 hours post–ketamine infusion, pharmacological ketamine management (initial and median doses, and documented adverse effects), additional adjunctive agents used for management of AWS, and the clinical outcomes associated with management of these patients, including incidence of resistant alcohol withdrawal (RAW), time to resolution of AWS, incidence of nosocomial pneumonia, the length of ICU and hospital length of stay, incidence of endotracheal intubation, and associated documented symptoms from AWS (including arrhythmias, delirium tremens, hallucinations, and seizures). Pharmacological management information was only collected from the medical record for those medications that were documented as being used for management of AWS. RAW was defined as the literature definition of a BZD-equivalent requirement of 40 mg of diazepam administered in 1 hour for the management of AWS.[14] 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) for both enteral and intravenous routes.[24,25] Time to resolution of AWS was defined as documentation of resolved AWS symptoms in a patient's medical record by the provider. Symptoms of AWS and adverse drug events were collected systematically through evaluation of all notes in a patient's medical record and depended on provider documentation. Nosocomial pneumonia was defined as pneumonia that occurs at least 48 hours after admission, which was not present at the time of hospital admission.[26] Collection of data occurred until there was documentation of resolved AWS or patient discharge. Demographic information included the use of the Simplified Acute Physiology Score II (SAPS) to evaluate severity of illness at ICU admission.[27] The SAPS was evaluated within 24 hours of ICU admission for patients admitted to the ICU and at the time of RAW designation for patients who were not admitted to the ICU. Agitation assessment in patients who were mechanically ventilated were based on the Riker Sedation-Agitation Scale (SAS) as part of usual care.[28] Agitation scores were collected as closely before and after the time of ketamine initiation as possible, with a maximum time window of 6 hours. Data on the incidence of specialty consultation, documented symptoms associated with AWS, time to resolution of AWS, and patient disposition at discharge were also collected.

Statistical Analysis

Data in this study were analyzed using SPSS (SPSS Inc, Chicago, IL). Median and interquartile ranges were presented for skewed data, and mean and standard deviations were provided for nonskewed data. A paired Wilcoxon rank-sum test was used for continuous data, as appropriate. A P value less than 0.05 was considered to be statistically significant.

Results

Patients

Of 235 patients screened, 23 patients (9.8%) met study eligibility criteria. Baseline demographics are detailed in Table 1. In summary, patients were primarily middle aged, male, and Caucasian. Approximately 20% of patients had

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Table 1. Baseline Characteristics.

	Ketamine (n = 23)
Age, median, years (IQR)	50.0 (47.0, 54.0)
Male, n (%)	14 (60.9)
Caucasian, n (%)	20 (87.0)
Past medical history, n (%)	
AWS	4 (17.4)
Seizure	1 (4.3)
Delirium tremens	1 (4.3)
SAPS, median (IQR)	19.0 (13.0, 23.0)
Primary diagnosis, n (%)	
AWS	8 (34.8)
Toxicology (other)	4 (17.4)
Trauma	4 (17.4)
Gastrointestinal	3 (13.0)
Altered mental status	2 (8.7)
Other	2 (8.7)
Initial admit to floor, n (%)	11 (47.8)
Admission blood ethanol concentration, median, mg/dL (IQR)	0 (0, 38.5)
RAW designation, n (%)	19 (82.6)
AWS complications, n (%)	
Arrhythmias	0
Delirium tremens	17 (73.9)
Hallucinosis	2 (8.7)
Seizure	1 (4.3)
ICU admission, n (%)	23 (100)
AWS-related ICU admission, n (%)	17 (73.9)
Invasive mechanical ventilation, n (%)	8 (34.8)
For management of AWS	6 (75.0)
Prior to ketamine initiation	6 (75.0)

Abbreviations: IQR, interquartile range; AWS, alcohol withdrawal syndrome; SAPS, Simplified Acute Physiology Score II; RAW, resistant alcohol withdrawal; ICU, intensive care unit.

some history of previous AWS. There were few patients (n = 3) who had documented hepatic dysfunction (eg, cirrhosis). Patients had a low SAPS; approximately a third were admitted for AWS; and the majority of patients were admitted initially to the general medicine floor. Approximately 75% of our population experienced delirium tremens, and all patients required ICU admission, with 75% requiring ICU admission for management of AWS. However, no patient developed delirium tremens or any other AWS complication after ketamine was initiated. The majority of patients met RAW designation due to significant BZD requirements, which occurred in all patients prior to ketamine administration.

Treatment and Outcomes

Dosing parameters for ketamine are detailed in Table 2. Ketamine was predominantly initiated by our inpatient toxicology service for management of active delirium tremens.

Table 2. Ketamine Treatment and Outcomes.

	Ketamine (n = 23)
Toxicology initiated, n (%)	17 (73.9)
Reason for ketamine initiation, n (%)	
Delirium tremens	10 (43.5)
Significant BZD requirements	3 (13.0)
Other/Unknown	10 (43.5)
Mechanical ventilation throughout ketamine therapy, n (%)	2 (8.7)
Diazepam equivalent prior to ketamine, median, mg (IQR)	170.0 (100.0, 570.0)
Diazepam equivalent per hour prior to ketamine initiation, median, mg (IQR)	8.8 (6.0, 20.0)
Time from first treatment of AWS to ketamine initiation, mean, hours (SD)	33.6 (29.1)
Time from RAW designation to ketamine initiation, median, hours (IQR)	12.3 (1.5, 42.6)
Initial infusion dose, mean, mg/kg/h (SD)	0.21 (0.11)
Ketamine loading dose, n (%)	8 (38.1)
Infusion dose during therapy, median, mg/kg/h (IQR)	0.20 (0.12, 0.23)
Duration of ketamine therapy, mean, hours (SD)	55.8 (30.5)
Change in diazepam equivalent 12 hours pre-post ketamine initiation, median, mg (IQR)[a]	−40.0 (−106.7, +21.7)
Diazepam equivalent change per hour, 12 hours post–ketamine initiation, median, mg (IQR)	−3.3 (−8.9, +1.8)
Change in diazepam equivalent 24 hours pre-post ketamine initiation, median, mg (IQR)[b]	−13.3 (−86.7, +50.0)
Diazepam equivalent change per hour, 24 hours post–ketamine initiation, median, mg (IQR)	−0.6 (−3.6, +2.1)
Total diazepam equivalent for management of AWS, median, mg (IQR)	740.0 (390.0, 1270.0)
Total ketamine dosage, median, mg (IQR)	9.7 (4.5, 14.2)
Change in sedation scores with ketamine initiation, median (IQR)	
WAS (n = 8)	+1.0 (−4.5, +2.0)
SAS (n = 5)	+1.0 (0, +2.0)

Abbreviations: BZD, benzodiazepine; IQR, interquartile range; AWS, alcohol withdrawal syndrome; SD, standard deviation; RAW, resistant alcohol withdrawal; WAS, Withdrawal Assessment Scale; SAS, Riker Sedation-Agitation Scale.
[a] $P = 0.110$.
[b] $P = 0.330$.

Patients who were initiated on ketamine had already been administered a substantial amount of hourly and total dose

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Table 3. AWS Characteristics and Outcomes.

	Ketamine (n = 23)
Duration of mechanical ventilation, median, days (IQR)	2.5 (2.0, 4.0)
Nosocomial pneumonia, n (%)	4 (17.4)
Time to resolution of AWS, mean, days (SD)	5.6 (1.8)
Length of stay, mean, days (SD)	
ICU	6.3 (3.0)
Hospital	12.3 (6.6)
Discharge disposition, n (%)	
Home	12 (52.2)
Rehabilitation	7 (30.4)
Inpatient psychiatry	4 (17.4)

Abbreviations: AWS, alcohol withdrawal syndrome; IQR, interquartile range; SD, standard deviation; ICU, intensive care unit.

of BZDs. Ketamine was initiated approximately 34 hours after first treatment of AWS and approximately 12 hours of RAW designation. The use of a loading dose, and services initiating therapy other than toxicology, appeared to be more common in the later portion of our evaluation (late 2013-2014). The loading dose used was 0.3 mg/kg. Ketamine was continued for approximately 56 hours and resulted in a decrease in BZD requirements, which was not statistically significant at 12 or 24 hours post–ketamine initiation ($P = 0.110$ and 0.330, respectively). Additionally, there were no changes in sedation scores. Ketamine was the only adjunctive agent used in 5 patients, whereas additional adjunctive agents were required in 11 patients while on ketamine therapy; the remaining 7 patients required additional adjunctive agents but not while on ketamine therapy. Other adjunctive agents included dexmedetomidine (n = 7), phenobarbital (n = 6), haloperidol (n = 5), and propofol (n = 4). Before ketamine initiation, dexmedetomidine, phenobarbital, and propofol were administered to 3 patients each. Two patients were administered haloperidol prior to ketamine initiation. After ketamine initiation, a total of 5 patients required administration of phenobarbital, whereas dexmedetomidine and haloperidol were administered to 3 patients each. Two patients were administered propofol, and 1 patient was administered clonidine after ketamine initiation. Only 1 documented adverse event occurred from ketamine therapy, which was oversedation requiring dose adjustment.

AWS outcomes for the patient population are detailed in Table 3. Duration of mechanical ventilation was short, and patients were largely discharged to home. No patients in the study population died.

Discussion

In our retrospective cohort study of patients administered adjunctive ketamine for management of AWS, we found that ketamine may potentially reduce BZD requirements, but it did not appear to affect sedation scores. Ketamine was commonly initiated after a significant amount of BZDs were administered and after patients had already developed some manifestation of AWS, typically delirium tremens. Ketamine use, dose, and monitoring were at the discretion of the physician because this is not part of our institution's protocol. We noted that a set rate of ketamine was administered, with a dose reduction of approximately half of the infusion rate when the patient's symptoms began to resolve.

Despite the low SAPS in these patients, ICU admission was still required in all patients, although approximately half of our population was initially admitted to the general medicine floor. This may be reflective of the large amount of BZDs administered to these patients or the fact that severity of AWS is not adequately predicted from hospital admission.

The low doses of ketamine used in this patient population reflect recommended doses for the management of nonneuropathic pain.[18] Ketamine initiation was primarily via our inpatient toxicology consult team, who generally manage more complicated AWS patients. More recently in our study period, ketamine was initiated by our critical care medicine services, which may illustrate anecdotal evidence that ketamine is effective in select AWS patients. Evaluating objective evidence of its effect indicates that the initiation of ketamine reduced BZD requirements, although the largest difference was seen in the first 12-hour period after initiation rather than in the subsequent 24 hours. This surrogate assessment for the effectiveness of ketamine was chosen because other studies have used this as a common assessment end point.[11,12] Whether this is truly reflective of the benefit of ketamine or resolving AWS is difficult to determine, especially in a retrospective study. We had a limited ability to evaluate AWS or sedation scores, given our time window of 6 hours pre–ketamine initiation and post–ketamine initiation. This time window was chosen to be most reflective of actual changes caused by ketamine. An evaluation of the statistical significance of change was not completed because of small sample sizes. Additional adjunctive agents were used either before or after ketamine was initiated, which may have influenced outcomes, including the amount of BZDs administered, and AWS or sedation scores. A significant proportion of our ketamine population still required additional adjunctive agents for management of AWS, which may reflect the lack of effect of ketamine in these patients or that the dose of ketamine administered to our patients may not be adequate. Ketamine dose range studies as an adjunctive agent in alcohol withdrawal, along with comparative effectiveness research on alternative adjunctive agents, would be beneficial to determine its place in therapy.

A significant proportion of our patients developed delirium tremens, which was most likely to occur during the beginning of their hospitalization, reflective of the expected

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time to onset from last consumption of alcohol of 48 hours.[2] Interestingly, no AWS complications (delirium tremens, hallucinations, and seizures) occurred after ketamine was initiated, which may illustrate the potential benefit of targeting the neurotransmitters involved in AWS. Given the large quantity of BZD administered in these patients, a significant proportion met RAW designation, indicating a high incidence of severe AWS in our population. Additionally, there was no mortality experienced in our cohort, although this was likely reflective of our small sample size or better understanding of the recognition and treatment of AWS.

The safety evaluation of ketamine in our population was limited for a few reasons. First, we were dependent on documentation of adverse drug effects. Although ketamine has a good safety profile, side effects, including nausea, vomiting and emergence reactions have been reported.[29] Emergence reactions, including hallucinations and delirium, are estimated to occur in approximately 10% of patients and are more common in young patients, ketamine-naïve patients, or when the drug is not administered intramuscularly. Studies have attempted to determine how to mitigate this risk and have found that administration of concurrent BZDs may be effective at reducing incidence.[30,31] Given our AWS population receives a significant amount of BZDs prior to and during ketamine initiation, this potential risk may be reduced or mitigated. Although ketamine stimulates respiratory drive, oversedation with ketamine, especially in addition to BZDs, can potentially result in respiratory compromise. In our population, many patients did not require mechanical ventilation at any time during their hospital stay. Additionally, ketamine is associated with increased blood pressure and tachycardia, which are mediated through an unknown mechanism.[32] These cardiovascular effects may be similar to that of patients presenting with AWS, and it would be difficult to differentiate the instigating cause. The WAS score uses hemodynamic parameters, which may explain the potential rise in scores after ketamine initiation, but we are unable to determine if this was the case or if a patient's AWS was worsening after ketamine initiation.

In general, our institution uses the WAS for monitoring AWS patients because it is driven by the nursing staff and is specific for AWS manifestations. The SAS would have been used when patients were mechanically ventilated as part of usual care, which only occurred in a total of 8 patients. Otherwise, patients should have been managed with the WAS, per institution protocol. Potential limitations for SAS would be the subjective evaluation of AWS with the SAS and lack of specificity for AWS-related manifestations, including hallucinations, seizure, and tremors. However, the use of SAS sedation scores studied in the ICU may have an advantage in this population. The CIWA and the WAS have not been verified in the ICU population because they were originally studied in outpatient or general medicine floor management of AWS. Additionally, some of the parameters that the CIWA or WAS evaluates would not be obtainable in a mechanically ventilated patient, including parameters based on patient report, such as disturbances and headaches.

Several limitations exist with this study. This study was a single-center, retrospective cohort study evaluating patients treated with ketamine for AWS, which limits potential associations resulting from ketamine administration. The study was also limited to a small sample size. Additionally, outcome data were dependent on documentation in the medical record, which led to likely underreporting of outcome data, including past history of AWS, adverse drug effects, and sedation scores. Finally, there is no formalized protocol for the use of adjunctive agents for the management of AWS, which contributed to the variable management of these patients. Ketamine was rarely the only adjunctive agent used, and these other adjunctive agents may have contributed to the reduction in BZDs for some patients.

Conclusion

In summary, this retrospective cohort study evaluated the safety and efficacy of ketamine for the management of AWS. The use of ketamine as an adjunctive agent trended toward a decreased amount of short-term BZDs administered but did not change sedation scores after initiation. Patients in this population commonly required ICU admission for AWS management but rarely required mechanical ventilation. This study illustrates that ketamine appears to be safe, but there remains a need for prospective dose range evaluations or comparative effectiveness research regarding the use of ketamine as an adjunctive to BZDs for the management of AWS.

Declaration of Conflicting Interests

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