

Ethanol Infusion for Alcohol Withdrawal Prophylaxis Does Not Cause Intoxication

Robert Dillard BS, Tanis Welch, PharmD RPh, Senan Abdul-Hamed MD,
Jennifer Kesity, MSN, RN, FNP-BC, Sharmila Dissanaiké MD, FACS

ABSTRACT

Objective: Alcohol Withdrawal Syndrome (AWS) remains a common problem, especially in trauma and surgical patients. An intravenous ethanol infusion protocol was developed at this institution and previously validated for AWS prophylaxis. One concern with intravenous ethanol has been potential for intoxication and/or side effects. This study was performed on patients receiving AWS prophylaxis with an intravenous ethanol protocol to evaluate for intoxication and the occurrence of any adverse effects.

Methods: We did a retrospective review of all patients in our hospital who received AWS prophylaxis by ethanol infusion between 2008 and 2013. Information collected specific to ethanol infusion included rate of administration, serum ethanol levels, serum sodium level, use of benzodiazepines and anti-emetics, and development of AWS. Intoxication was defined using the Texas limit for blood alcohol content in a driver of .08% (80mg/dL). The study period began at admission and lasted 7 days.

Results: Ninety-seven patient charts were reviewed. Average serum ethanol level on admission was 137 mg/dL. Serum ethanol levels increased in 12% of patients after administration of ethanol infusion, and levels generally decreased over time. Asymptomatic hyponatremia (serum sodium <135) occurred in 60% of patients. Benzodiazepines were administered to 52 patients (54%); of these, only 15 received increases in infusion rates indicating appropriate protocol use. In addition, 32 of the 52 had the ethanol infusion discontinued prior. Ethanol infusion for alcohol withdrawal prophylaxis in the hospitalized patient rarely induces alcohol intoxication. However, a majority of patients experience asymptomatic hyponatremia. The high rate of concomitant benzodiazepine use suggests possible low efficacy of the infusion, although low adherence to the protocol could be a contributing factor.

Key words: Clinical trial, alcohol withdrawal delirium, ethanol infusion

Corresponding author: Sharmila Dissanaiké, MD
Contact Information: Sharmila.dissanaiké@ttuhsc.edu
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INTRODUCTION

Excessive alcohol consumption is the third leading preventable cause of death in the United States, with 2.3 million years of potential life lost in 2001.¹ The lifetime prevalence of DSM-IV alcohol abuse in the general population is 17.8%. These data contrast with the prevalence of alcoholism and withdrawal in trauma and surgical patients. Chronic alcoholism occurs in 50-60% of trauma patients, and alcohol misuse is as high as 43% in some surgical patients.² The prevalence of Alcohol Withdrawal Syndrome (AWS) is correspondingly increased in these populations, with reported rates in surgical and trauma patients of 16% and 31%, respectively.^{3,4} Additionally, predicting the occurrence of alcohol withdrawal syndrome (AWS) is difficult, as the severity of alcohol abuse does not correlate with severity of AWS.⁵ The initial symptoms of AWS reflect autonomic hyperactivity. However, if left untreated, AWS can progress to disorientation and seizures with possible respiratory and cardiovascular collapse.⁶

Multiple modes of prophylaxis for AWS exist. Benzodiazepines remain the mainstay, and several studies have shown acceptable efficacy and safety profiles.⁷⁻⁹ However, due to concerns that benzodiazepines may cause excessive sedation or promote delirium in patients who are often receiving simultaneous high dose opioids for analgesia and who may have concomitant head injury, clinicians have been reluctant to use aggressive benzodiazepine based AWS protocols in these patients. Surgical specialties have historically used oral alcohol instead for this purpose, with a typical prescription being “two beers with meals,” for example. This approach runs counter to the notion that an acute illness or injury is a good opportunity for intervention in alcohol dependence, and oral alcohol may have side effects. However, the most significant drawback is the erratic dosing and distribution with this approach, which results in a high rate of failure.¹⁰

Our group and others have developed and implemented an intravenous ethanol infusion protocol that attempts to counteract some of the negative aspects of oral alcohol administration and have

shown that ethanol infusion is a feasible option for AWS prophylaxis.¹¹ A comparison study of ethanol, flunitrazepam-clonidine, clomethiazole-haloperidol, and flunitrazepam-haloperidol used for AWS prophylaxis in ICU patients found the failure rate of ethanol prophylaxis in preventing AWS was 4% (2 of 50 patients). This was not significantly different from the other methods used in this study.⁷ Further, a standardized protocol of ethanol prophylaxis significantly reduced the rate of withdrawal symptoms from 20% to 7% and decreased the duration of treatment in surgical patients.¹⁰ However, one recurrent concern raised by many healthcare providers has been potential for intoxication from the infusion, with corresponding adverse effects. The primary aim of this study was to determine the blood ethanol levels of patients receiving an established intravenous ethanol protocol for AWS prophylaxis and to assess the frequency of intoxication. Secondary aims were to evaluate safety and efficacy of the protocol in a primarily trauma-surgical population.

METHODS

Setting: This study was conducted at a Level 1 Trauma Center and American Burn Association (ABA) verified regional burn center located within an academic teaching hospital. This facility has four adult ICUs, including: Trauma/Surgical, Burn, Cardiovascular, and Medical ICUs for a total of 82 adult ICU beds and 420 adult ward beds.

Clinical Practice: Benzodiazepines, oral ethanol, and intravenous ethanol are all available and used for AWS prophylaxis at this institution, at the discretion of the treating physician team. Any patient with a known history of daily ethanol use exceeding 1 drink per day, regular episodes of binge drinking greater than two days per week, a previous history of alcohol withdrawal, or current drinking with history of treatment for alcohol related disease process is eligible for alcohol withdrawal prophylaxis. Additionally, all trauma patients are routinely screened for alcohol dependence using a standard tool as part of Level 1 Trauma Center criteria mandated by the American College of Surgeons. As a result, screening for alcohol dependence is standard practice for surgical admissions in particu-

lar. Local practice patterns have resulted in surgical specialties primarily using the ethanol infusion while medical specialties use benzodiazepine prophylaxis only. We use a 10% ethanol solution mixed in dextrose 5% in water administered at an hourly rate of 0.4ml/kg/hour using ideal body weight with rate adjustments outlined in the protocol as depicted in **Figure 1**. Briefly, for signs and symptoms of withdrawal the rate is increased; if none arise then the infusion rate is decreased and tapered off over a 96-hour period. When the protocol was first developed at our institution in 2003, a commercial solution was available for use; however, the manufacturer discontinued it in 2006 due to the lack of a profit margin. Subsequently, the ethanol infusion has been constituted by the inpa-

tient pharmacy, resulting in increased costs.

Data Collection: This was a retrospective cohort review of all patients receiving ethanol infusion from April 2008 through March 2013. Since the study was conducted primarily for quality assurance and patient safety purposes, an exemption from formal IRB review was granted. Data collected included baseline characteristics and demographics: age, sex, weight, admission diagnosis, Glasgow Coma Score, co-morbid diagnosis and clinical outcome. The rate of ethanol administration was documented daily at midnight during the 7 day study period from admission. Serum ethanol levels were recorded at 2, 12, and 24 hours

Figure 1 Alcohol Withdrawal Prophylaxis Protocol

Indication: Any patient with known history of daily ethanol use exceeding 1 - 2 drinks per day, regular episodes of binge drinking greater than two days per week, previous history of alcohol withdrawal or current drinking with history of treatment for alcohol related disease process.

1. Initiate 10% alcohol drip at 0.4 ml/kg/hr using **ideal body weight**.
2. Measure a blood alcohol level at 6 hours, 24 hours, and 72 hours after the infusion is started. If blood alcohol level is greater than 80 mg/dl (0.08%), hold infusion for 2 hours and decrease rate by 50%.
3. Monitor patient for signs and symptoms of alcohol withdrawal. Signs and symptoms of alcohol withdrawal include: sweating, pulse greater than 100 bpm, increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile or auditory hallucinations or illusions, psychomotor agitation, anxiety, Grand mal seizures.

*Ensure symptoms are not due to general medical condition or by another mental disorder.
4. If the patient has no signs or symptoms of alcohol withdrawal after 24 hours from start, decrease the rate by 20% after 48 hours from start, decrease rate further by 50% after 72 hours from start, decrease rate further by 50% after 84 hours from start, and then discontinue infusion.
5. If patient develops signs and symptoms of alcohol withdrawal, increase rate by 50%. If symptoms of alcohol withdrawal continue for 6 hours after the infusion is increased, notify the resident on call.

*****Do not hold or discontinue alcohol infusion for diagnostic or operative procedures*****

The alcohol infusion is appropriate for patients admitted to a floor status level of care.

from admission for the first day, followed by levels every 24 hours until the end of the 7 day study period. Intoxication was defined using the Texas limit for blood alcohol content in a driver of 0.08% (80mg/dL). Benzodiazepine and anti-emetic use and indication during the study period were recorded. Serum sodium levels were reviewed. The lowest sodium level measured in each patient over the 7 day study period was recorded, and each chart was reviewed for documentation of symptomatic hyponatremia requiring treatment. Charts were reviewed for documentation of AWS and for increased ethanol infusion rates or use of anti-emetics and benzodiazepines. Patients were classified into three groups based on alcohol withdrawal symptoms: the first was apparent or documented alcohol withdrawal; the second was no sign of alcohol withdrawal; and the third was possible alcohol withdrawal based on documentation of increased ethanol infusion rates or anti-emetic and benzodiazepine use, but AWS was not listed as a diagnosis. Data collectors audited 10% of the charts picked at random to verify consistency in data abstraction. Statistical analysis was performed using Microsoft Excel.

RESULTS

Ninety-seven patient charts were reviewed. The cohort included 90 men and 7 women with an average age of 49 years. The average hospital length of stay was 7.03 days, and there were 4 deaths (4.12%).

Ethanol infusion was started in both intensive care and floor units. Ninety-three percent of patients were managed by either surgery, trauma, or burn teams, while 7.2% of patients were managed by medical care teams. Clinical outcomes indicated that 81.4% were discharged home, 13.4% of patients were discharged to another facility, and 1% of patients were transferred. No significant changes in the average Glasgow Coma Scale (GCS) score were noted over the 7 day study period (14/15 on admission versus 14/15 on discharge).

Intravenous ethanol was commonly initiated on day 1 of hospitalization; the peak infusion rate occurred on day 3 of the hospitalization. Average alcohol level on admission was 137 mg/dL with a range of 0 to 409 mg/dL. Positive ethanol levels were found in the serum of 49.5% of patients after initiation of the ethanol infusion, with serum ethanol levels mostly decreasing over time. Only 12% of patients experienced an increase in alcohol levels after administration of ethanol infusion. On average, these patients' ethanol levels were 17.2 mg/dL on admission and increased 46.8 mg/dL to 64 mg/dL before beginning to trend downward. Two patients (2%) were below the legal limit of 80 mg/dL and subsequently rose above this limit. The trend of ethanol levels over time is illustrated in **Figure 2** showing a clear decrease in measured ethanol levels over time from admission. Average ethanol levels decreased every day in these patients (**Table 1**).

Figure 2 Alcohol level over time

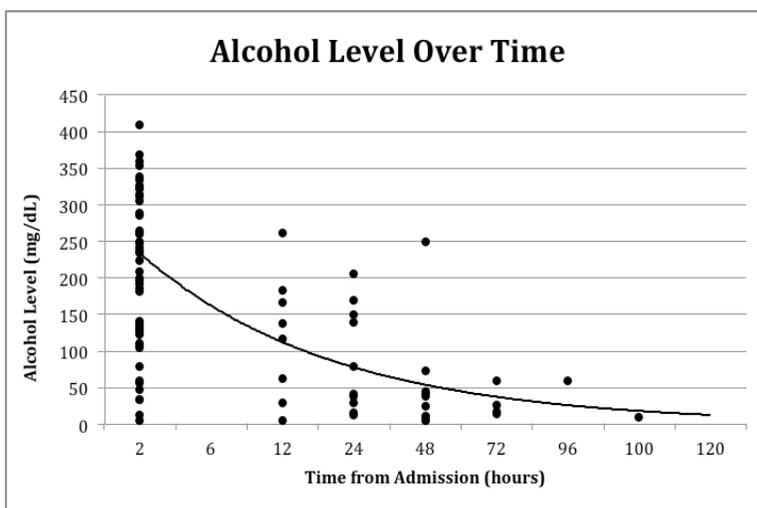


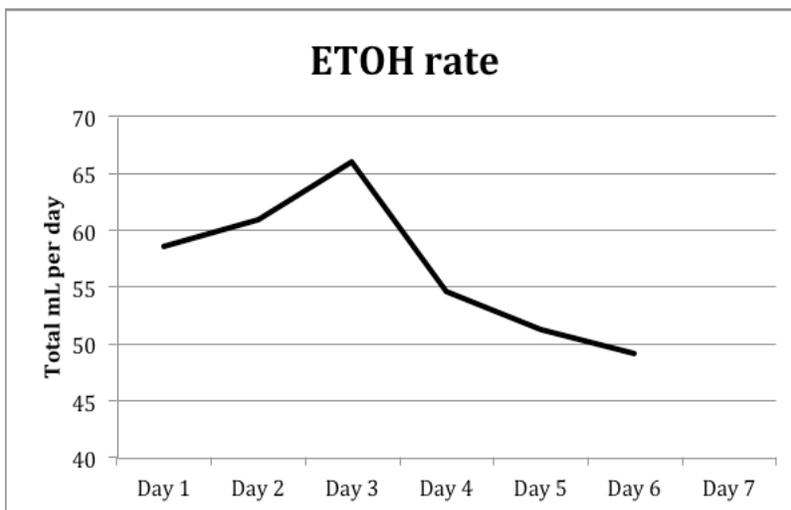
Table 1. Average serum ethanol levels over time

| Hour 0-2 | Hour 6-12 | Hour 13-24 | Hour 25-48 | Hour 49-72 | Hour 73-96 | Hour 97-120 | Hours 121+ |
|-------------|------------|------------|------------|------------|------------|-------------|------------|
| 137.1 mg/dL | 41.8 mg/dL | 19.6 mg/dL | 8.4 mg/dL | 4.3 mg/dL | 2.2 mg/dL | 0.7 mg/dL | 0 mg/dL |

Infusion rate for the ethanol infusion was also evaluated. The peak ethanol infusion rate occurred on day 3 of admission. Total volume of ethanol infused per 24 hour period over the 7 day study period is shown in **Figure 3**. Peak average infusion total for the study period was 66 ml (6.6g) on day 3. For reference, one standard drink in the United States contains 14g of ethanol according to the Centers for Disease Control.¹² Therefore, the maximum total infusion for one day on average is less than half of a standard alcoholic beverage.

period. Of these, 21 had hyponatremia on admission. The range of lowest serum sodium levels was 119-143 mEq/L, with an average of 133 mEq/L. There were no documented cases of symptomatic hyponatremia requiring treatment.

An antiemetic was given in 38% of patients at any time during the 7-day study period. Benzodiazepines were administered to 54% of the patients during the study period, but the indication for use was not documented in the majority of cases. Of the 52 patients who received benzodiazepines, only 15 re-

Figure 3 Average ethanol infusion per day

Twenty six percent of patients had documented AWS, 8% had possible AWS, and 66% had no AWS. Thirteen patients (13.4%) received oral ethanol in addition to ethanol infusions. Of these, 9 had no AWS, and 2 had possible AWS.

Hyponatremia (serum sodium level <135) occurred in 58 (60%) patients during the 7 day study

ceived increases in ethanol infusion rates indicating appropriate protocol use. In addition, 32 of the 52 had the ethanol infusion discontinued early, before the scheduled protocol wean.

DISCUSSION

Ethanol infusion was used primarily by sur-

gical services in our hospital as opposed to medical services. The ethanol infusion seems to cause hyponatremia. However, no cases of symptomatic hyponatremia were documented in this cohort. Additionally, the infusion rarely causes intoxication; however, there was a significant rate of concomitant benzodiazepine administration, indicating a potential lower efficacy rate than previously reported by this group.

It is difficult to diagnose AWS in critically ill patients, especially in those who also have pain and delirium, which are commonly encountered in the intensive care unit.¹³ After a patient has been identified as having AWS or is at high risk of developing symptoms, it is prudent to implement preventative strategies to avoid more severe symptoms.¹⁴ The pharmacotherapeutic regimen should be designed to achieve three goals. The first goal is to ensure the patient is comfortable, awake, calm, and cooperative. This may not always be practical in the event of AWS, in which the patient may require large doses of sedative drugs in order to maintain control of AWS symptoms. The second goal is to prevent complications, such as severe autonomic symptoms, hallucinations, and seizures. The third goal is to reduce long term central nervous system complications that may occur due to repeated withdrawal episodes. To achieve these goals, the recommended first line therapy for both prevention and management of AWS are benzodiazepines due to their ability to increase transmission of GABA. However, the use of benzodiazepines may lead to excessive sedation and respiratory depression. Consequently, less sedating alternative therapies would potentially be very useful.¹³

Ethanol is a small polar molecule that has both lipophilic and hydrophilic characteristics. The amphipathic abilities of ethanol help explain its pharmacokinetics within the body. Ethanol's lipophilic characteristics result in passive diffusion across the cell membranes. The combination of the hydrophilic and polar properties of the ethanol molecule makes it completely water-soluble with a similar volume of distribution to total body water.¹³ These characteristics of the ethanol molecule indicate that its pharmacology is complex and why it is described as the "perfect drug".¹⁵

Therefore, intravenous ethanol should, in theory, be an effective alternative means of preventing and treating AWS, while causing less sedation, which would allow trauma patients to better participate in respiratory maneuvers to limit atelectasis and decrease secretions and in other aspects of patient care.¹⁴ However, critics argue that intravenous ethanol has a short duration of action, a narrow margin of safety, and possible precipitation of acute hepatic failure. In addition, the use of ethanol in AWS contradicts the prevention efforts of alcohol abuse.^{10,14} Many of these conclusions are made on the assumption that to detoxify a patient the dose required for intravenous ethanol is initially equal to the patient's average daily consumption. However, the amount of intravenous ethanol to prevent withdrawal may be much less. In fact, when administered at very small doses, it has been successful in aiding in detoxification, as well as preventing acute manifestations of AWS.¹⁶ Furthermore, using intravenous ethanol does not provide the main addictive reinforcements such as intoxication and socialization, which are characteristics of oral alcohol use, and therefore does not represent a barrier to efforts to start rehabilitation from alcohol dependency.¹⁰

Ethanol has been shown to be as effective as other methods of AWS prophylaxis. Spies et al conducted a prospective randomized control trial and found that prophylaxis with ethanol, benzodiazepines, chlormethiazole, and haloperidol all had similar efficacy in preventing AWS. Further, the ICU stay did not differ among the groups.⁷ In a systematic review of randomized control trials, Unger et al concluded that either benzodiazepines or ethanol can be used for AWS prophylaxis in ICU patients based upon similar efficacy.⁹ Additionally, our group has shown that a standardized protocol for ethanol prophylaxis is significantly more effective in avoiding AWS than non-standard ethanol administration.¹⁰

Unfortunately, in the current study we did note a significant failure rate with ethanol infusions, with 8% developing AWS and an additional 26% having signs or symptoms of possible AWS. Of equal concern was the high proportion of patients who were administered benzodiazepines while receiving the etha-

nol infusion; in the absence of clearly documented indications for the benzodiazepine administration, we have to assume that a significant proportion of these patients may have received the drug to treat AWS. It is likely that this occurred due to the assumption on the part of the provider that any signs or symptoms represent failure of the protocol and the need to switch to alternate medication. However, even benzodiazepine protocols are commonly administered on an "as needed/ PRN" basis rather than a regimen of scheduled medications in AWS prophylaxis protocols.¹⁷ To consider the development of any signs or symptoms of withdrawal as a failure of the protocol is a higher bar than expected in standard practice. The significant limitation of this study was that there was no systematic validated method of measuring and documenting AWS in use during this study, thus preventing us from accurately assessing efficacy of the protocol. This is unfortunately a widespread problem in many busy trauma centers, although increased awareness of the importance of AWS and the high rate of recidivism in injured patients with alcohol dependency have led to nationwide efforts to improve the monitoring and treatment of alcohol related complications in these patients.¹⁸ A protocol based on the CIWA-Ar scale has since been included in the electronic order set for AWS prophylaxis at our institution. However, during the time period for this study there was inconsistent use of formalized protocols for monitoring of AWS.

LIMITATIONS

Limitations of this study include the small sample size and the retrospective nature of the research. The inability to determine the indications for benzodiazepine administration in this cohort is also a significant confounding factor in judging the overall efficacy of the protocol, beyond the documented 8% failure rate. Inconsistent use and documentation of formalized instruments to monitor AWS also led to deficits in the documentation available for review.

CONCLUSIONS

Ethanol infusion for alcohol withdrawal prophylaxis in the hospitalized patient does not induce

alcohol intoxication. However, a significant rate of deviations from the protocol and concomitant use of benzodiazepines was noted, raising doubts about the efficacy of the protocol. Additionally, asymptomatic hyponatremia was observed in a majority of patients. More research is needed into comparing efficacy of ethanol infusion with other modes of AWS prophylaxis.

Author Affiliation: Robert Dillard, Senan Abdul-Hamed, Jennifer Kesey, and Sharmila Dissanaikie work in the Department of Surgery at Texas Tech University Health Sciences Center in Lubbock, TX. Tanis Welch is a pharmacist at University Medical Center in Lubbock, TX.

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