Journal of Clinical Neuroscience 31 (2016) 88–91

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

# Comparison of enteral ethanol and benzodiazepines for alcohol withdrawal in neurocritical care patients

Gregory Gipson [a,*], Kim Tran [a], Cuong Hoang [a], Miriam Treggiari [b]

[a] Department of Pharmacy, UW Medicine, 1959 NE Pacific Street, Seattle, WA 98195, USA
[b] Department of Anesthesiology & Perioperative Medicine, Oregon Health & Science University, Portland, OR 97239, USA

ARTICLE INFO

*Article history:*
Received 24 November 2015
Accepted 14 February 2016

*Keywords:*
Alcohol
Benzodiazepine
Ethanol
Neurocritical care
Neurosurgery
Withdrawal

ABSTRACT

We designed a study to evaluate the use of benzodiazepines and ethanol in patients being assessed for alcohol withdrawal and compare outcomes between the two agents. This is a retrospective chart review of patients admitted to neurocritical care or neurosurgical services who were at risk for ethanol withdrawal between June 2011 and September 2015. Patients were divided into two groups based on the first medication administered for alcohol withdrawal management, either benzodiazepine (n = 50) or enteral ethanol (n = 50). The primary endpoint was the maximum change in Clinical Institute Withdrawal Assessment of Alcohol scale (CIWA) score within the first 24 hours. Secondary endpoints included maximum and minimum CIWA score in 5 days, length of stay, and change in Glasgow Coma Scale. Study groups differed by mortality risk, level of coma at admission, and other clinical characteristics, with the ethanol group appearing less severely ill. There was no significant difference between the two groups in the maximum change in CIWA score at 24 hours (−0.97, 95%CI: −3.21 to 1.27, p = 0.39). Hospital and intensive care unit length of stay was 6.5 days and 1 day shorter for the ethanol group (p = 0.03 and p = 0.02, respectively). In summary, enteral ethanol was preferentially used in patients who are more likely to be capable of tolerating oral intake. We found that the change from baseline in CIWA score or other physiologic variables was not substantially different between the two agents. The overall utility of benzodiazepines and enteral ethanol remains unclear for this population and further study is needed to determine superiority.



## 1. Introduction

The close relationship between alcohol use and traumatic injury is readily apparent with an estimated 40–50% of trauma patients testing positive for ethanol upon hospital admission [1]. Alcohol withdrawal syndrome (AWS) may develop in as many as 31% of trauma patients and 15% of post surgical patients [2]. Both populations are frequently admitted to neurocritical care services for continued further disease and AWS management. Patients who develop AWS have markedly worse outcomes, with postoperative mortality increased three-fold [3,4]. Patients withdrawing from alcohol present with autonomic hyperactivity which may evolve into seizures, hallucinations and delirium tremens [5]. Safely controlling withdrawal symptoms, preventing progression, and minimizing long term neurologic sequelae often require judicious use of pharmacologic therapy [6].

Benzodiazepines are effective anticonvulsants that are considered first-line therapy for AWS [7–12]. These medications have favorable safety and efficacy profiles when compared to other treatment options [10]. Yet the sedating and respiratory depressant effects of benzodiazepines are well documented [13]. Excessive sedation of neurocritical care patients may compromise the utility of serial neurologic examinations and impair appropriate management of neurologic conditions. This has led to some neurocritical care providers to prefer the use of ethanol for AWS management.

Case reports supporting the use of intravenous ethanol are numerous, with prospective trials suggesting similar therapeutic effects on AWS with both benzodiazepines and ethanol [1,14–17]. Hospitals have begun using enteral ethanol products, such as beer, wine and liquor, due to recent unavailability of commercially prepared intravenous ethanol. Prospective assessment of enteral ethanol and benzodiazepines for AWS have shown comparable outcomes in patients experiencing acute coronary syndrome [18]. Concerns for evaluating the risk of hyponatremia with enteral ethanol products and need to compare safety and efficacy with benzodiazepines remain unresolved issues for neurocritical care patients. This study was performed to compare the ability of enteral ethanol and benzodiazepines to control AWS symptoms,

* Corresponding author. Tel.: +1 206 598 6060; fax: +1 206 598 6075.
*E-mail address:* gipson@uw.edu (G. Gipson).

http://dx.doi.org/10.1016/j.jocn.2016.02.028
0967-5868/

**Table 1**
Comparison of demographic and baseline clinical characteristics between benzodiazepine and ethanol groups for the treatment of alcohol withdrawal syndrome

| Patient characteristics | Benzodiazepine | Ethanol | p value |
|---|---|---|---|
| Age, mean (SD) | 51.5 (12.1) | 50.2 (13.2) | 0.38 |
| Males, n (%) | 36 (72) | 43 (86) | 0.14 |
| SAPS II score, mean (SD) | 20.9 (10.3) | 16.6 (8.1) | 0.02* |
| GCS, median (IQR) | 12 (10, 15) | 15 (14, 15) | 0.01* |
| CIWA score, median (IQR) | 11 (9, 16) | 9.5 (6.5, 15) | 0.16 |
| Temperature, mean (SD) | 37.1 (0.7) | 37.1 (0.5) | 0.57 |
| Heart rate, mean (SD) | 99.1 (2.8) | 86.9 (17.6) | 0.002* |
| Systolic blood pressure (mmHg), mean (SD) | 136.9 (26.5) | 136.5 (19.7) | 0.94 |
| Plasma sodium (mEq/L), mean (SD) | 138.0 (3.7) | 138.1 (3.6) | 0.87 |
| Admission blood alcohol level, median (IQR) | 114 (0, 281) | 232.5 (120, 310) | 0.03* |
| Treatment group crossover, n (%) | 4 (8) | 14 (28) | 0.02* |
| Admission diagnosis, n (%) | | | 0.1 |
| Subdural hematoma | 21 (42) | 19 (38) | NA |
| Vertebral fracture | 10 (20) | 5 (10) | NA |
| Subarachnoid hemorrhage | 8 (16) | 9 (18) | NA |
| Other | 11 (22) | 17 (34) | NA |

* p value < 0.05 was considered statistically significant, SD = standard deviation, IQR = interquartile range, N = total number, CIWA = Clinical Institute of Withdrawal Assessment of Alcohol Scale, GCS = Glasgow Coma Score, SAPS II = Simplified Acute Physiology Score II, NA = not applicable.

compare the sedating effects of each agent, and assess clinical outcomes in the neurocritical care population.

## 2. Methods

This retrospective study was conducted in a 450 bed academic, regional trauma, and county safety net hospital. Patients were included if they were admitted to the neurosurgical or neurocritical care services between June 3, 2011 and September 1, 2015, received either benzodiazepines written on an alcohol withdrawal order set or received beer/50% ethanol, and had suspected or confirmed AWS on chart review. Patients were excluded if it was unclear whether ethanol or benzodiazepines were administered as initial therapy or were less than 18 years of age. Pharmacy billing data and utilization of alcohol withdrawal order sets were used to identify participants. Manual chart review was performed in reverse chronological order until 50 patients were included in the benzodiazepine and ethanol treatment groups.

Individuals were assigned to either the benzodiazepine or ethanol group based on the first medication administered upon presentation to the hospital. This first dose marked time zero in the study. Baseline demographics, laboratory values, blood alcohol, and vital signs were defined as the last value recorded before the first medication for managing AWS, was administered. Data was then collected for the following 5 days. Crossover was defined as administration of drug therapy from the opposing treatment group within 5 days of entering the study. Lorazepam equivalents were calculated using the following assumption, lorazepam 1 mg = diazepam 5 mg = chlordiazepoxide 10 mg. Simplified Acute Physiology Score II (SAPS II) was calculated using baseline data to estimate the risk of hospital mortality [19]. The primary outcome was defined as maximum increase in Clinical Institute of Withdrawal Assessment of Alcohol Scale (CIWA) from baseline within 24 hours of entering the study. Secondary outcomes were hospital and intensive care unit (ICU) length of stay, maximum and minimum CIWA values in the first 5 days, maximum heart rate (HR) increase from baseline in 24 hours, maximum increase in systolic blood pressure (SBP) from baseline in 24 hours, maximum decrease in Glasgow Coma Scale score (GCS) from baseline in 24 hours, and administration of antihypertensive medication not required prior to admission.

Patient demographic data were analyzed with descriptive statistics. Student t-tests, Wilcoxon Rank-Sum, and chi-squared tests compared differences between groups. *Post-hoc* linear regression analysis assessed correlation between the independent variables adjusted for baseline characteristics. Natural log transformation was applied to the length of stay variables to account for skewed distribution. A two-tailed significance level of $p < 0.05$ was used in this analysis. Data were analyzed with STATA 11 (StataCorp, Texas, USA).

This study was approved by the UW Medicine Institutional Review Board. Informed consent was not obtained due to the retrospective nature of this study.

## 3. Results

A total of 192 patient charts were reviewed for inclusion and one subject was excluded for inability to determine if ethanol or benzodiazepines were administered first. Demographic and clinical characteristics of the benzodiazepine and enteral ethanol groups were comparable in terms of age, sex, baseline CIWA score, and admission diagnosis (Table 1). Benzodiazepine patients displayed higher mortality risk scores (SAPS II score), lower GCS scores, higher blood alcohol levels, and showed a lower proportion of crossover than the ethanol group.

We failed to find a difference in the unadjusted or adjusted maximum CIWA score increase from baseline over the first 24 hours of the study when comparing benzodiazepine to enteral ethanol treated groups (Table 2). When comparing the highest CIWA score reached by each patient during the 5 day study period our data showed benzodiazepine patients reached 25% higher CIWA scores than ethanol patients ($p = 0.002$). When adjusted for baseline characteristics, the increase was not significant. Hospital and ICU length of stay were 6.5 days and 1 day shorter for ethanol treated patients, $p = 0.03$ and $p = 0.02$ respectively. Adjusted hospital length of stay showed no difference between groups when accounting for SAPS II, GCS and blood alcohol level. Groups differed significantly in the cumulative amount of ethanol and benzodiazepines they received ($p < 0.001$ for both) (Table 3). The number of participants receiving adjunctive therapies for alcohol withdrawal and treatment for hyponatremia were not different between groups.

## 4. Discussion

Neurocritical care patients at risk of ethanol withdrawal are in need of safe, effective and minimally sedating therapeutic options. We were unable to find a significant difference between patients treated with benzodiazepines or enteral ethanol with respect to our primary endpoint, the maximum CIWA score increase from