Original Research Article

THE EFFICACY OF AN ORAL DIAZEPAM BASED PROTOCOL IN IMPROVING CARE AND REDUCING DURATION OF HOSPITALIZATION IN ALCOHOL WITHDRAWAL

Abstract :

Background

Complications from alcohol abuse are the fourth leading preventable cause of death in the United States. Hospital length of stay (LOS) for patients experiencing alcohol withdrawal syndrome (AWS) has become of particular concern and effective treatment protocols are needed.

Objective

At Danbury Hospital, a 371-bed community hospital in Danbury, Connecticut, the average LOS for AWS was historically nine days. We therefore designed a protocol for the treatment of AWS to provide effective treatment and thereby reduce LOS.

Methods

Our study was a single center, retrospective observational study of patients who were admitted to Danbury Hospital with a diagnosis of AWS. All patients 18 years and older admitted to Danbury Hospital between June 2015 and December 2016, with a primary diagnosis of AWS were included. A loading dose regimen was used whereby 20mg of oral Diazepam was given hourly for a total of eight doses within the first 24 hours until clinical improvement or mild sedation was achieved. The comparison group consisted of patients treated with a symptom-triggered regimen using Lorazepam.

We compared the primary outcome of LOS and secondary outcomes including need for transfer to a critical care unit, restraint use for aggressive behavior related to withdrawal, the need for a safety companion, and the need for Psychiatry consultation between the two groups.

Results

In the Diazepam group versus the comparison group, LOS was reduced to about four days, and fewer Psychiatry consultations were needed.

Conclusion

We conclude that a loading dose regimen of Diazepam may be used to safely reduce LOS in AWS patients.

KEYWORDS: Alcohol Withdrawal Delirium, Diazepam, Lorazepam, Length of Stay

INTRODUCTION

The prevalence of alcohol abuse in the United States is alarmingly high at 18% and the total estimated economic burden is greater than 200 billion per year, 11% of which is attributed to health care costs (1). According to the Global Burden of Disease study in 2016, alcohol use was the seventh leading risk factor globally for both deaths and disability adjusted life years (2). Withdrawal symptoms for patients who regularly abuse alcohol, may lead to complications that lead to prolonged hospitalizations.

Although many medications are used to treat patients with alcohol withdrawal, the cornerstone remains the use of benzodiazepines mainly due to their effect on GABA receptors in the limbic system and their cross tolerance with alcohol (3). Limited data exists on the superiority of using one benzodiazepine over the other, as well as optimal dosing strategies for these medications (3).

Traditionally benzodiazepines are administered using loading dose or symptom-triggered regimens for the treatment of AWS. With the loading dose technique, a long acting benzodiazepine is administered at specific intervals, until the patient shows clinical improvement and/or mild sedation. In the symptom-triggered

regimen, a short acting benzodiazepine is given on an as needed basis, depending on the severity of symptoms. A standardized score such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) or the Severity Assessment Scale (SAS) is used to assess the severity of withdrawal symptoms (3,4,5,6).

The two most commonly used benzodiazepines in the treatment of AWS are Diazepam and Lorazepam. Diazepam binds to GABA receptors causing inhibition of the limbic system. It is absorbed rapidly and its active metabolite, desmethyldiazepam, has a half-life of approximately 48 hours. Lorazepam has similar effects but with a shorter half-life of approximately 12-18 hours. Diazepam has a higher affinity for the GABA receptor, a longer duration of action and is less likely to produce respiratory depression compared to Lorazepam. This is advantageous in the treatment of AWS as the active metabolites of Diazepam are still present in the body even at 72 hours, the peak time for alcohol withdrawal symptoms, and drug levels gradually decrease in a self-tapering manner (7). A loading dose regimen with Diazepam therefore allows a high level of metabolites, which have cross activity with alcohol receptors. Furthermore, Diazepam discourages the drug seeking behavior seen in patients who are being given the drug on an as needed basis.

The purpose of this study was to compare the efficacy of a loading dose regimen using Diazepam with Lorazepam in the reduction of LOS for AWS hospitalizations.

METHODS

Background

Prior to June 2015, Danbury Hospital treated all patients experiencing AWS using a symptom-triggered regimen with Lorazepam and our LOS for AWS was historically

nine days. In an effort to reduce this, an inpatient loading dose regimen protocol using Diazepam was developed and instituted in June 2015 for the management of AWS, based on the pharmacokinetics of Diazepam and Lorazepam. The revised protocol called for 20mg of oral Diazepam every hour for a total of eight doses within the first 24 hours, holding doses for sedation. Patients were selected to receive Diazepam versus Lorazepam based on their ability to tolerate oral intake and the presence of severe liver dysfunction. Those with liver dysfunction and inability to tolerate oral intake, for example due to nausea or vomiting were treated with Lorazepam. All other patients received oral Diazepam.

Study Design

This study was a single center, retrospective observational study of patients who were admitted to Danbury Hospital with a diagnosis of AWS. Two groups of patients were compared; those treated with a symptom-triggered regimen using Lorazepam versus those treated with loading dose regimens using Diazepam. We looked at the impact of these two treatment approaches on LOS, use of restraints due to agitation and/or aggressive behavior, the need for a safety companion, transfers to a critical care unit and the need for Psychiatry consultation. This study was approved by the Institutional Review Board of the Biomedical Research Alliance of New York (BRANY IRB).

Patient Population

All patients 18 years and older admitted to Danbury Hospital between June 2015 and December 2016, with a primary diagnosis of AWS.

Data Collection

Medical charts were manually reviewed for all eligible patients. Relevant information was collected, including demographics, transfer to a critical care unit, restraint use for aggressive behavior related to withdrawal, the need for a safety companion, Psychiatry consultation for management of alcohol withdrawal, as well as the presence of comorbidities including history of liver disease, congestive heart failure, alcohol withdrawal seizures and active substance abuse.

Statistical Analysis

Summary statistics were provided for demographic and clinical history variables used to compare the patients in the Lorazepam (symptom-triggered regimen) group and the patients treated with Diazepam (loading dose regimen) before proceeding with further analysis. For age, Student's t-test was used to compare the means. For history of congestive heart failure, Fisher's exact test was used to compare the proportions. For all the other categorical variables, Pearson's chi-squared test was utilized to compare the proportions between the two groups.

Similarly, we also compared the outcome variables between the Diazepam and Lorazepam groups. For LOS, we employed Wilcoxon rank-sum test to compare the distributions between the two groups. For the variable transfer to a critical care unit, we considered no transfer, step down unit and intensive care unit as ordered levels of care, so that the contingency table between the variable "transfer to a critical care unit" and drug treatment was a singly ordered table. We transformed the ordered levels into numeric values, and used Wilcoxon rank-sum test to compare the distributions of care between the treatment groups. For the other outcomes, the Pearson's chi-squared test was used.

We noticed that the Lorazepam and Diazepam groups were unbalanced in terms of history of liver disease. This led us to check the associations between history of liver disease and each of the outcomes to see if adjustments were needed when comparing the outcomes between the treatment groups. The tests used were the same as described above. We log-transformed the LOS, and used ANOVA to test the difference of means between the two treatment groups while controlling for history of liver disease. The interaction effect was tested.

The significance level was set at .05 and all the original p-values were reported before adjusting for multiple hypotheses control. The statistical analyses were performed using R programming language.

RESULTS

A total of 307 patients were included in this study; 64% were treated with Lorazepam (symptom-triggered regimen) and the rest with Diazepam (loading dose regimen).

With regard to baseline variables, there was a statistically significantly higher proportion of patients in the Lorazepam group with a history of liver disease than those in the Diazepam group ($p = 0.046$). For all other baseline characteristics, no significant differences in means or proportions were found between the two groups (Table 1).

For the comparisons of outcomes between the patients treated with Lorazepam and the patients treated with Diazepam, LOS for patients treated with Lorazepam was significantly longer than that for patients treated with Diazepam ($p <0.001$). There was also a statistically significantly higher proportion of psychiatry consultations in the Lorazepam treatment group ($p <.001$). For all other outcome variables, no

statistically significant differences in proportions or distributions were found (Table 2).

Given the observation that the two groups were unbalanced in terms of history of liver disease, the associations between history of liver disease and the outcomes were assessed to determine if it needed to be considered in multivariate analysis (Table 3). The distribution of LOS was significantly longer in patients with liver disease history than those with no history of liver disease. Thus, multivariate analysis for LOS was performed considering both treatment type and history of liver disease using ANOVA. Log-transformation was done on LOS. The interaction effect was checked, but was not significant ($p = 0.579$), so it was disregarded in the ANOVA analysis. There was still a significant difference in mean LOS between patients treated with Lorazepam and patients treated with Diazepam ($p< 0.001$), and history of liver disease became not significant given that treatment type was in the model. Thus, the conclusion would be the same as described above in the marginal association analysis shown in Table 2.

DISCUSSION

The results of this study indicate that LOS was statistically significantly shorter and fewer Psychiatry consultations were needed in the patients treated with Diazepam compared with those treated with Lorazepam. The difference in LOS between our two groups suggests that treatment of AWS with the loading dose regimen may be more effective, and may lead to a shorter duration of withdrawal symptoms and shorter LOS.

Many studies have shown that Benzodiazepines are superior to other medications in the treatment of alcohol withdrawal. There is also data to support the

use of loading dose regimens over symptom-triggered regimens, with the advantages of reducing the risk of complications of alcohol withdrawal including delirium tremens and seizures, reducing the total dose of Benzodiazepines needed and reducing the duration of symptoms (3,4,6,8,9,10). To date, however, no studies have demonstrated a reduction in duration of hospitalization or the need for valuable, tertiary care level psychiatry consultations. Such a reduction is significant given the increased morbidity and mortality, and the consistently rising healthcare costs associated with alcohol withdrawal hospitalizations.

One of the limitations of our study was our small sample size. This may have limited power to show statistical significance in some of our outcome variables such as the need for restraints, need for a safety companion and transfers to critical care units. Our study showed a reduction in numbers that did not reach statistical significance for these variables. Further, as a retrospective study, our design is subject to confounding factors. Another limitation is in the lack of established cut off values for liver function tests to preclude the use of Diazepam. This may have led to patients with mild abnormalities in liver function being put on the Lorazepam symptom-triggered regimen depending on the admitting physicians comfort level. Further investigation with a prospective cohort or randomized control trial will be needed to assess the effect of a loading dose protocol on these outcome variables.

CONCLUSION

We conclude that a loading dose regimen of Diazepam may be used to safely reduce LOS in AWS patients.

Table 1. Demographic and clinical information between the patients treated with Lorazepam and the patients treated with Diazepam

Variable	Drug		P-value
	Lorazepam (n = 198)	Diazepam (n = 109)	
Age, mean (SD)	50.87 (14.384)	50.78 (11.910)	0.952
Gender, number of male (%)	139 (70.558%)	69 (63.303%)	0.120*
History of Psychiatric illness	106 (53.807%)	55 (50.459%)	0.658
History of CHF	6 (3.046%)	3 (2.752%)	1
History of liver disease	42 (21.320%)	14 (12.844%)	0.046 *
Evidence of active substance abuse	114 (57.868%)	63 (57.798%)	1
History of prior DTs/ Seizures	89 (45.178%)	56 (51.376%)	0.179*

Note: The p-values annotated with * were from one-sided tests.

Table 2. Comparisons of the outcomes between the patients treated with Lorazepam and the patients treated with Diazepam

Variable	Drug		P-value
	Lorazepam (n = 198)	Diazepam (n = 109)	
Length of stay, (Min, Q1, median, Q3, Max)	(1, 3, 5, 7, 31)	(1, 3, 4, 5, 21)	<0.001 *
Restraints (%)	22 (11.168%)	10 (9.174%)	0.363

Sitter (%)		23 (11.675%)	13 (11.927%)	1
Psychiatry consult (%)		77 (39.086%)	22 (20.183%)	<0.001 *
Transfer to	ICU	19	10	0.175*
	SDU	13	3	
	None	165	96	
Fall in house (%)		2 (1.015%)	0 (0%)	0.540

Note: The p-values annotated with * were from one-sided tests.

Table 3. Comparisons of the outcomes between the patients with history of liver disease and those with no history of liver disease

Variable		History of liver disease		P-value
		Yes (n = 56)	No (n = 250)	
Length of stay, (Min, Q1, median, Q3, Max)		(1, 3, 5, 7, 21)	(1, 3, 4, 6, 31)	0.031 *
Restraints (%)		7 (12.5%)	25 (10%)	0.756
Sitter (%)		8 (14.286%)	28 (11.2%)	0.338*
Psychiatry consult (%)		15 (26.786%)	84 (33.6%)	0.204*
Transfer to	ICU	7	22	0.127*
	SDU	4	12	
	None	45	216	
Fall in house (%)		0 (0%)	2 (0.8%)	1

Note: The p-values annotated with * were from one-sided tests.

SUMMARY OF KEY POINTS

- Hospital length of stay (LOS) for patients experiencing alcohol withdrawal syndrome (AWS) has become of particular concern and effective treatment protocols are needed.
- At Danbury Hospital, a community-based academic center in Connecticut, we designed a protocol for the treatment of AWS to provide effective treatment and thereby reduce our hospital length of stay which was historically nine days.
- A loading dose regimen of Diazepam was used until clinical improvement or mild sedation was achieved, compared with patients treated with a symptom-triggered regimen using Lorazepam.
- We found that in the Diazepam group versus the comparison group, LOS was reduced to about four days, and fewer Psychiatry consultations were needed
- We conclude that a loading dose regimen of Diazepam may be used to safely reduce LOS in AWS patients.

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