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Diazepam May Not Add to Symptom-Titrated Midazolam/Lorazepam for Alcohol Withdrawal Syndrome

Meredith Mozzone[1], Duncan Manthous[2], Rodrigo Vazquez Guillamet[3] and Constantine Manthous[4]*

1 Connecticut College, USA
2 East Lyme High School
3 Department of Medicine, University of New Mexico, USA
4 Lawrence & Memorial Hospital, USA

***Corresponding author:** CA Manthous

constantinemanthous@gmail.com

MD, Attending Physician, Lawrence & Memorial Hospital, 6 Hemingway Road, Niantic, CT 06357, USA.

Tel: 2039092089

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Abstract

Objective: To determine whether diazepam, administered with symptom-triggered regimes, improves outcomes of critically ill patient with alcohol withdrawal syndrome (AWS).

Design: Retrospective cohort syndrome.

Setting: Intensive care units of a community teaching hospital.

Patients: Admitted to ICU between January 2014 and December 2015 with a primary diagnosis of AWS.

Measurements & results: Demographics, physiologic variables, treatments and outcomes are compared for patients receiving versus not receiving scheduled diazepam plus symptom-triggered lorazepam or midazolam. 67 patients who received symptom-titrated benzodiazepine averaged 48.9 ± (SE) 1.4 years and APACHE II 2.7 ± 0.3; 20 were female. Over the course of admission, patients received an average of 130 ± 26 mg LE, i.e., 18.7 ± 2.0 mg LE/day over mean LOS 7.8 days. The use of 0, ≤ 20 mg and ≤ 40 mg diazepam were associated with significantly less lorazepam equivalents (65 vs. 159 mg, P=0.02; 60 vs. 185 mg, P=0.008; 64 vs. 210 mg, P=0.01). Those receiving 100 mg or more of diazepam received far more lorazepam equivalents (252 vs. 66 mg, P=0.01). There was no difference in hospital length of stay for patients receiving diazepam vs. no diazepam. Four of 21 patients receiving no diazepam were intubated, compared to 6 of 46 who received diazepam (NS), a relationship that persisted across strata of diazepam doses. Because intravenous diazepam is substantially more expensive in our hospital (midaz $0.15/mg, diaz $2.07/mg, loraz $0.27/mg), diazepam regimens raised costs substantially across strata of administered doses.

Conclusion: These data do not support that scheduled diazepam complements effectiveness of symptom-titrated benzodiazepine administration for AWS.

Keywords: Alcohol withdrawal syndrome; Delirium tremens; Critical illness; Benzodiazepine; Diazepam; Lorazepam; Midazolam

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Introduction

In the United States, alcohol withdrawal syndrome (AWS) presents in roughly 16-31% of patients in ICUs [1,2]. While there are few prospective randomized studies of critically patients with AWS, symptom-triggered benzodiazepines administration has become a standard of care [3-5]. Some studies have suggested that long-acting benzodiazepines have the greatest evidence base for effectiveness [5,6]. We hypothesized that scheduled or symptom-titrated long-acting benzodiazepine (diazepam) compared to symptom-triggered short-acting benzodiazepines would: a) reduce total benzodiazepine requirements, b) reduce length of stay, and c). reduce medication costs for critically ill AWS patients.

Methods

The Lawrence & Memorial Institutional Review Board deemed this non-interventional records review exempt per regulation HHS46.101. The hospital uses symptom-triggered benzodiazepine administration for care of ICU and wards patients with AWS. In the ICU, the MINDS (Minnesota detoxification) scale is used until patients approach readiness for transfer to wards at which point their medications are subsequently symptom-titrated using the CIWA (clinical institute withdrawal assessment) score. In the ICU, endotracheal intubation is deferred, at clinicians' discretion, for worsening gas exchange and/or airway incompetence.

The ICU at Lawrence & Memorial maintains a logbook of admitted patients and their primary diagnoses. Electronic records of patients admitted for AWS between January 2014 and December 2015 were examined. Demographic, physiologic, treatment and outcomes data were extracted and APACHEII scores were computed for the first 24 h of ICU admission. The total quantity of midazolam, lorazepam and diazepam were recorded and adjusted to "lorazepam equivalents" (LE) where 1 mg lorazepam=2 mg midazolam=5 mg diazepam. Other administered medications, including paraldehyde, valproate, clonidine, metoprolol and haloperidol, were also recorded. Clinical outcomes of interest included seizures, pneumonia during ICU stay the need for endotracheal intubation and length of hospital stay. Patients receiving no scheduled diazepam and lower *ad hoc* doses (i.e., <20 mg, <40 mg total) were compared to those receiving scheduled diazepam in higher doses by univariate analyses. Multiple logistic regression analyses were performed to adjust for acuity of illness and physiologically plausible effectors on outcomes (mainly total administered benzodiazepine and length of stay). A P less than 0.05 were considered statistically significant.

Results

67 participants (20 female) averaged 48.9 ± (SE) 1.4 years and APACHE II 2.7 ± 0.3 **(Table 1)**. Mean hospital length of stay was 7.8 d and patients received an average of 130 ± 26 mg LE (18.7 ± 2.0 mg LE/d). Ten patients required endotracheal intubation, 2 were diagnosed with pneumonia and 10 had seizures. All patients survived to hospital discharge.

The use of no diazepam, ≤ 20 mg and ≤ 40 mg were associated with significantly less LE (65 vs. 159 mg, P=0.02; 60 vs. 185 mg, P=0.008; 64 vs. 210 mg, P=0.01, respectively; **Table 2**). Those receiving 100 mg or more of diazepam received far more LE (252 vs. 66 mg LE, P=0.01). There was no difference in length of stay across strata of total administered diazepam. Rates of endotracheal intubation and seizures were also not greater in diazepam-treated patients. Older age was associated with longer length of stay. For example, patients older than the population average 50 years stayed 9 vs. 4 days length of stay of patients 50 years or less (P<0.0001).

Adjusting for APACHE II score and gender, age (P<0.0001) and use of diazepam (P=0.004) were independently associated with length of stay. Only diazepam administration tended to be associated with endotracheal intubation (P=0.06) and no variables predicted seizures.

Discussion

This study does not support that diazepam improves outcomes of patients with AWS. Patients whose regimens included (mainly scheduled, but some *ad hoc*) diazepam required more (not less) total benzodiazepine and incurred greater drug costs as a result. Older age was independently associated with longer length of stay. Observation in this cohort also confirm, in a second hospital, that high doses of benzodiazepine, with endotracheal intubation deferred for physiologic decompensation, can be administered safely in patients with AWS [7].

Despite the frequency of AWS in hospitalized patients, there is insufficient published data to demonstrate approaches that improve patient's outcomes [1-11]. One reason is that algorithms for drug therapy and measures of outcomes have differed substantially among studies. For example, symptom-triggered

Table 1 Characteristics of AWS patients.

	n=67
Age, years	48.9 ± 1.4
APACHE II score	2.7 ± 0.3
ICU length of stay, days	7.8
Sex	
Male	47
Female	20
Seizures	10
O_2 assisted	8
Pneumonia	2
#treated with diazepam	21
Additional meds	
Paraldehyde	1
Valproate	5
Clonidine	19
Metoprolol	3
Haloperidol	30

Table 2 Univariate comparisons across strata of diazepam total dose.

	Total LE (mg)	LE/day	Benzo $/day	LOS days	# intubated	seizures	# got haldol
0 (n=21) vs. any diaz (n=46)	65 159*	12 22**	3 44***	6.5 7.0	4 6	3 7	5 27*
≤ 20 mg (n=30) vs. >20 mg diaz (n=37)	60 185**	12 24**	6 52***	5.9 7.6	5 5	6 4	11 21
≤ 40 mg (n=37) vs. >40 mg diaz (n=30)	64 210**	13 26**	9 59***	5.8 8.1	5 5	7 3	16 16

*P=0.05-0.01; **P=0.01-0.001; ***P<0.01

therapy is a relatively new development (since the early 2000's; [3,4]) and much of the data on benzodiazepines were gathered before the era in which this strategy gained popularity. While an abundance of non-benzodiazepine-based approaches have been studied, there are no data to support better outcomes and benzodiazepines have remained the standard-of-care mainstay until such data arrive [9]. We reasoned that use of long-acting benzodiazepines would require less symptom-titrated treatment and improve outcomes because existing data – albeit weak [5,6] – suggest long-acting benzodiazepines may be (or at least trend toward) superior. Recent data [7] and reviews [2,8,9] highlight how little high-quality evidence exists to guide care of the sickest (any hospitalized) patients with AWS.

This study has several limitations. First, it is a small sample of patients increasing the likelihood of Type II error. While possible, this seems unlikely since the observed result was opposite of the hypothesized result (i.e. diazepam-treated patients got more, not less LE). Second, the retrospective design permits detection of associations, but cannot attribute causation. Third, these observations were gathered at a single hospital that depends highly on symptom-titrated algorithms for administration of benzodiazepines for AWS. Results are unlikely to be generalizable in other circumstances. Additionally, for the purposes of analysis, we distilled doses of benzodiazepines to lorazepam equivalents conversion for which are somewhat arbitrary (but we abided conventional conversion factors). Cost of medication is also likely to vary considerably from hospital-to-hospital (note the far greater cost of intravenous diazepam compared to lorazepam and midazolam), so we did not emphasize cost impacts in our analyses.

Conclusion

Patients receiving diazepam either superimposed on or as primary symptom-titrated benzodiazepine, received more, not less, total benzodiazepine during treatment for AWS requiring ICU stay. Age was the single best independent predictor of prolonged hospital stay and benzodiazepine costs were substantially greater in patients receiving diazepam. While this observation should be tested in a formal prospective, randomized trial, in the meantime clinicians might reconsider [5,6] the role of long-acting agents in the context of symptom-titrated management.

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