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Authors

Schomer, Kendra J
Duby, Jeremiah J
Firestone, Rachelle L
et al.

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Effect of Flumazenil on Hypoactive Delirium in the ICU: A Double-Blind, Placebo-Controlled Pilot Study

Kendra J. Schomer, PharmD[1]; Jeremiah J. Duby, PharmD, FCCM[1]; Rachelle L. Firestone, PharmD[1]; Erin L. Louie, PharmD[1]; Christian M. Sebat, DO[2]; Dawn M. Love, RN, BSN[3]; Christine S. Cocanour, MD, FCCM[4]; Timothy E. Albertson, MD, MPH, PhD[2,5]

Objectives: To determine whether the use of flumazenil reverses hypoactive delirium and increases delirium-free days in critically ill patients who were exposed to benzodiazepine therapy during the ICU admission.

Design: This was a single-center, double-blinded, randomized placebo-controlled pilot study.

Setting: Adult ICUs at a large academic medical center in the United States.

Patients: Adult, critically ill patients with benzodiazepine exposure and hypoactive delirium based on the Confusion Assessment Method-ICU and Richmond Agitation Sedation Scale assessments were considered for enrollment.

Interventions: Patients received a test dose of flumazenil starting at 0.1 mg intravenously and titrated up every 5 minutes by 0.1 mg increments up to a maximum total dose of 2 mg. Patients who demonstrated a Richmond Agitation Sedation Scale score increase of greater than 1 point were considered responders and randomized to flumazenil (0.05–0.3 mg/hr) or placebo infusion for up to 72 hours. Confusion Assessment Method-ICU scores were assessed twice daily for resolution of delirium.

Measurements and Main Results: The trial was stopped early based on the observed size effect and power analysis. Twenty-two of the 25 patients responded to the flumazenil test dose (88%). The median number of delirium-free days alive without coma within 14 days of enrollment was similar between the two infusion groups (12.7 vs 9.2; $p = 0.19$). There was no difference in the probability of delirium resolution within the first 14 days with 90% versus 70% in the flumazenil and placebo groups, respectively ($p = 0.2$). There was no statistical difference (odds ratio, 0.17; 95% CI, 0.022–1.23; $p = 0.079$) in delirium- and coma-free days at the end of the study drug infusion. There was no difference between groups in ICU length of stay (7.8 ± 4.8 vs 7 ± 8; $p = 0.74$). No serious adverse events occurred.

Conclusions: This study found that flumazenil test dose and infusion present a potential option for hypoactive delirium associated with benzodiazepine exposure; however, the possible benefit is unknown. Larger studies are warranted to further evaluate these findings.

Key Words: benzodiazepine; benzodiazepine antagonist; critical care; delirium; flumazenil; hypoactive delirium

Delirium occurs in a substantial number of patients admitted to the ICU and has been identified as an independent predictor of 6-month mortality, prolonged ICU and hospital length of stay (LOS), and prolonged mechanical ventilation (1–3). For every additional day spent delirious in the ICU, there is a 10% increased risk of death (3), and delirium duration has been found to be the strongest predictor of death, ventilation time, and ICU stay (4, 5). Diagnosing and managing delirium remains challenging despite the heightened awareness in more recent years. Hypoactive delirium is the most common motor subtype and is associated with greater risk of mortality; however, it is difficult to recognize and there are limited evidence-based treatment options available (6–8).

[1]Department of Pharmacy, University of California Davis Medical Center, Scramento, CA.

[2]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, School of Medicine, University of California Davis Medical Center, Sacramento, CA.

[3]Department of Patient Care Services, Medical Intensive Care Unit, University of California Davis Medical Center, Sacramento, CA.

[4]Division of Trauma and Emergency Surgery, Department of Surgery, School of Medicine, University of California Davis Medical Center, Sacramento, CA.

[5]Department of Veterans Affairs, VA Northern California Health Care System, Mather, CA.

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Patients admitted to the ICU are exposed to several precipitating risk factors for delirium, namely benzodiazepine therapy (9, 10). Despite guideline recommendations to avoid benzodiazepines for routine ICU sedation, benzodiazepines are still used in patients where hemodynamic, pharmacodynamic, and severe patient-ventilator asynchrony concerns preclude the use of other sedatives (11–15). Bioaccumulation of benzodiazepines may result from prolonged exposure, high-dose therapy, and/or impaired clearance due to organ dysfunction.

Identification of persistent hypoactive delirium and reversal with flumazenil, a competitive antagonist for the benzodiazepine binding site, represents a novel therapy. Current studies of flumazenil continuous infusion lack guidance on dosing strategy and clinical outcomes such as delirium resolution for patients who remain in a persistent hypoactive state. This study was performed to determine the effect of flumazenil on diagnosing benzodiazepine-associated hypoactive delirium and its potential effect on delirium-free days. The hypothesis was that reversal of residual benzodiazepine activity with flumazenil would result in shorter duration of delirium.

MATERIALS AND METHODS

Patients

This study was approved by the institutional review board and was registered with ClinicalTrials.gov (NCT02899156). Informed consent was obtained from the patient's legally authorized representative and the patient when no longer delirious. Eligible patients were critically ill adults who previously received benzodiazepines while in the ICU and had hypoactive delirium associated with benzodiazepine exposure. Patients were observed for signs or symptoms of withdrawal for a minimum of 12 hours after receiving a benzodiazepine to mitigate the risk of exacerbating withdrawal with flumazenil. There was no maximum interval between benzodiazepine exposure and enrollment due to the variable bioaccumulation (e.g. morbid obesity) and unpredictable clearance of benzodiazepines (e.g. end-organ dysfunction). Each patient was individually evaluated by both the study investigators and the primary team to assess the probability that benzodiazepines were contributing to the patient's hypoactive delirium.

Hypoactive delirium was identified using the Confusion Assessment Method–ICU (CAM-ICU) and Richmond Agitation Sedation Scale (RASS) (16–18). Patients were identified as having hypoactive delirium if RASS score was –3 to 0 and the patient was CAM-ICU positive. Patients were excluded if they had contraindications to flumazenil use, an alternative explanation for altered mental status, acute brain injury, and/or history of seizures (**Appendices 1** and **2**, Supplemental Digital Content 1, http://links.lww.com/CCX/A142).

Design and Randomization

This was a prospective, randomized, double-blind, placebo-controlled pilot trial conducted at a large, tertiary, academic medical center from March 2016 to July 2018. The Investigational Drug Service Pharmacy sequentially assigned eligible patients based on an enrollment log randomly generated using www.randomizer.org. For an enrollment of up to 80 patients, 44 blocks of two were generated to account for screen failures and/or extra enrollment. Due to personnel availability, enrollment occurred between the hours of 07:00 and 15:30 7 days a week. At baseline, we recorded demographic data, medical history, and medication history of the patients. Evaluation of the patients' RASS was performed per hospital policy every 2 hours, and CAM-ICU was performed every 12 hours by trained ICU nurses. An additional RASS and CAM-ICU was performed every morning by a study team member for the duration of the study infusion.

Data Collection and Analysis

Baseline characteristics included age, sex, ICU service, Sequential Organ Failure Assessment (SOFA) score, Charlson Comorbidity Index, days in hospital prior to enrollment, time since last benzodiazepine administration, benzodiazepine indication, lorazepam equivalents (lorazepam 1 mg = midazolam 2 mg = diazepam 5 mg), home benzodiazepine use, and RASS prior to test dose. The original sample size calculation indicated that 40 patients in each group were required to detect a 30% difference (SD ± 2 d) in delirium-free days, assuming p value less than 0.05 and 80% power. Descriptive statistics and the Wilcoxon rank-sum test were performed. The Kaplan–Meier method was used to characterize the probability of being delirium and coma free.

Intervention

Eligible, consented patients received a test dose of flumazenil starting at 0.1 mg intravenously and titrated up every 5 minutes by 0.1 mg increments up to a maximum total dose of 2 mg. Responders were defined as patients who demonstrated improved wakefulness (RASS increase of >1 point) or cognition. These patients were randomized to flumazenil infusion (flumazenil group, 2.5 mg/50 mL) or placebo infusion (placebo group, 0.9% NaCl). In addition to the principal investigator, the bedside nurse and critical care fellow caring for the patient were present during the test dose administration to determine validity of the change in RASS. The infusion was initiated at 0.1 mg/hr (2 mL/hr) and titrated to goal RASS 0 to +1, with a maximum infusion rate of 0.3 mg/hr (6 mL/hr). Dose titrations could occur every 60 minutes. The infusion was interrupted for up to 4 hours every morning during the study intervention (up to 72 hr). Study drug was restarted unless the patient experienced refractory agitation (RASS +2 to +4), required rescue benzodiazepine for signs of withdrawal, remained CAM-ICU negative after interruption, was discharged from ICU, or experienced an adverse event attributable to study drug (i.e. arrhythmia, seizure). In addition, the primary attending physician caring for patient was able to discontinue the study infusion if deemed medically necessary.

Outcomes

The primary efficacy outcome was delirium-free days. Delirium-free days were defined as the number of days in the first 14 days during which the patient was alive without delirium or coma from any cause. Duration of delirium for the study period was determined by subtracting the date/time of delirium conversion from date/time of initiation of study drug. This difference was subtracted from 14 days. Partial days of delirium were calculated to allow for greater precision in the primary outcome and to account for the variable initiation times of study drug. Patients who died within the 14-day study period were recorded as having 0 days free of delirium and

coma. Secondary outcomes included probability of delirium resolution, ICU LOS, maximum rate and duration of study infusion, rescue sedative use, and mechanical ventilator-free days. The primary safety outcome was the occurrence of severe refractory agitation, which was defined as RASS of +2 to +4 that did not resolve by decreasing the infusion rate of study drug. Patients were closely monitored for clinical seizure and arrhythmia with the intention of reporting these patient safety events to the Institutional Review Board. Electrocardiograms were performed 10 and 60 minutes after the test dose and documented in the electronic medical record.

RESULTS

Study Population

During the study period, a total of 126 patients were screened for inclusion, and 25 patients met inclusion criteria (**Fig. 1**). The most common reasons for exclusion were altered level of consciousness due to acute brain injury (n = 22; 17%) or altered level of consciousness attributable to an alternative pathology (e.g. remote brain injury, dementia) (n = 19; 15%). A planned interim analysis led to the trial being stopped early based on the observed size effect and power analysis.

Twenty-two of the 25 consented patients responded to the flumazenil test dose (88%) as defined by a greater than 1-point increase in the RASS. The three patients who were deemed nonresponders were not randomized to study infusion. Of the randomized patients, one patient randomized to the flumazenil group and one patient randomized to the placebo group never received the study infusion. The patient in the flumazenil group died from a massive hemorrhage within 1 hour of infusion initiation, and it was deemed nonattributable to study infusion. Twenty patients were included as the per-protocol population in the final analysis.

Baseline characteristics for the intention-to-treat population are shown in **Table 1**. The average age for the cohort was 58.8 ± 7.5 years old, and 56% were female. The indications for benzodiazepine therapy were alcohol withdrawal syndrome (AWS, 50%) and patient-ventilator asynchrony (50%). The duration of hospital LOS prior to enrollment was 8.5 ± 2.8 in the flumazenil group and 10.6 ± 7.5 days in the placebo group. The cumulative dose of benzodiazepines (lorazepam equivalents) and elapsed time between benzodiazepine exposure and enrollment was 117 mg and 43 hours respectively in the flumazenil group and 110.3 mg and 55 hours respectively in the placebo group.

The RASS in responders changed from an average of –2 (moderate sedation) to 0 (awake and alert) after the test dose. The average cumulative flumazenil test dose given to elicit a response was 0.3 ± 0.2 mg. The average maximum rate and duration of infusion was 5 mL/hr (0.25 mg/hr) and 54.8 hours in the flumazenil group compared with 5.2 mL/hr and 58.2 hours in the placebo group.

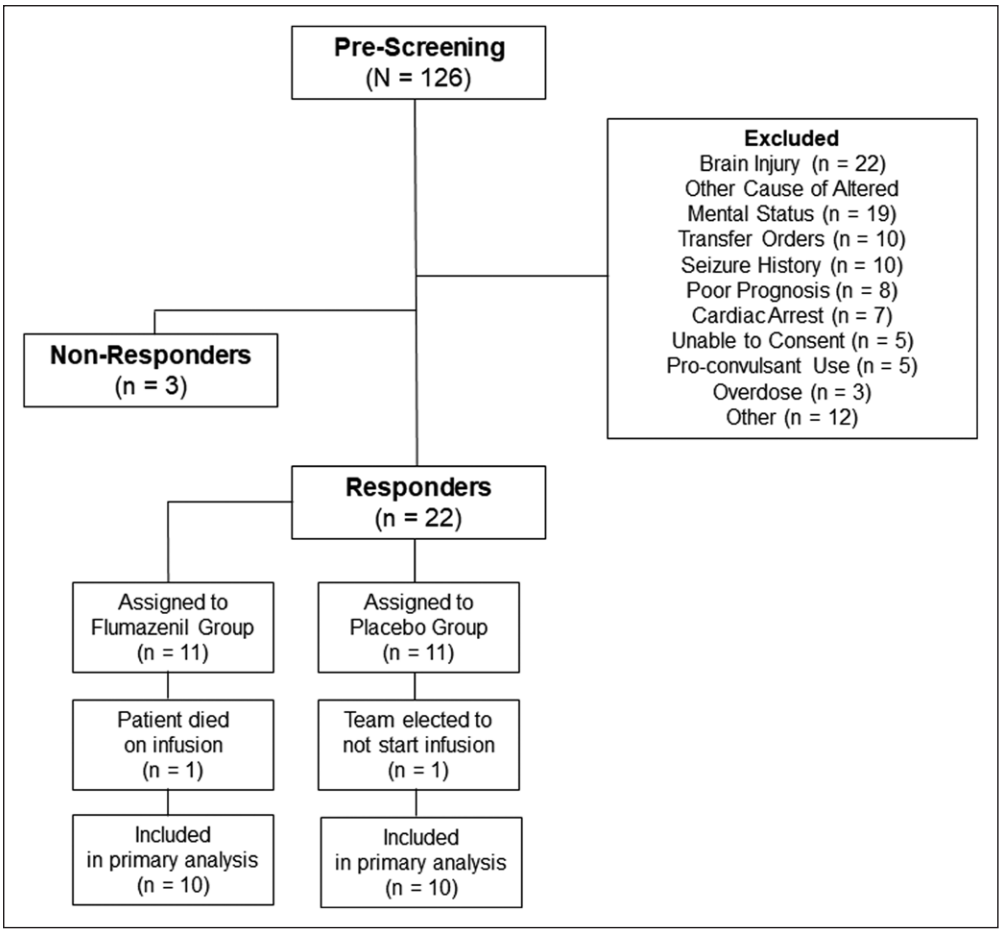

Figure 1. Flow diagram.

Outcomes

There was no significant difference in the primary efficacy outcome—median delirium-free days alive—between the flumazenil and placebo groups, 12.7 (interquartile range [IQR], 7.2–13.4) versus 9.2 (IQR, 0–10.2) (p = 0.13) (**Fig. 2**). There was no difference in the secondary outcome within the first 14 days (**Fig. 3**) (p = 0.2) with 90% and 70% probability of delirium resolution in the flumazenil and placebo groups, respectively. The probability of delirium resolution on day one of study drug infusion was 50% in the flumazenil group and 10% in the placebo group (odds ratio [OR], 0.11; 95% CI, 0.01–1.24; p = 0.074). There was no statistical difference (OR, 0.17; 95% CI, 0.022–1.23; p = 0.079) in delirium-and coma-free days at the end of the study drug infusion (Fig. 3). ICU LOS (7.8 ± 4.8 vs 7 ± 6 d; p = 0.74) and ventilator-free days (23.6 ± 4.4 vs 24.9 ± 5; p = 0.62) were similar between groups.

TABLE 1. Baseline Characteristics

Characteristics	Flumazenil Group ($n = 11$)[a]	Placebo Group ($n = 11$)[a]
Age (yr), mean ± SD	58 ± 7	59.4 ± 7.6
Female, *n* (%)	4 (36)	3 (27)
ICU service, *n* (%)		
Medical	7 (64)	11 (100)
Cardiology	3 (27)	0 (0)
Surgical	1 (9)	0 (0)
SOFA at time of enrollment, mean ± SD	6.5 ± 3.4	6.1 ± 2.1
Charlson Comorbidity Index, mean ± SD	5 ± 3	5 ± 3
Days in hospital prior to enrollment, mean ± SD	8.5 ± 2.8	10.6 ± 7.5
Time since last benzodiazepine (hr), mean ± SD	43 ± 23	55 ± 37.1
benzodiazepine indication, *n* (%)		
Ventilator asynchrony	6 (55)	5 (45)
Alcohol withdrawal syndrome	5 (45)	6 (55)
Lorazepam equivalents (mg), median (the interquartile range)	117 (85.8–476)	110.3 (57–221)
Renal insufficiency, *n* (%)	5 (45)	4 (36)
Home benzodiazepine Use, *n* (%)	2 (18)	1 (9)
Pre-test dose Richmond Agitation Sedation Scale[b], mean ± SD	−2 ± 1.2	−2 ± 1.1

Data in table are presented as the mean ± SD or as a number with the percentage in parenthesis or as the median with in square brackets
[a]Intention-to-treat population. One patient was excluded from outcomes analyses from each group. See Figure 1.
[b]Richmond Agitation Sedation Scale: −2 = lightly sedated.

Safety

There was no difference in the primary safety outcome of episodes of severe refractory agitation, 0 versus 0. One patient in the flumazenil group was given olanzapine as a rescue medication for agitation; however, no patients were withdrawn from the study due to refractory agitation. There were no clinical seizures or arrhythmias observed.

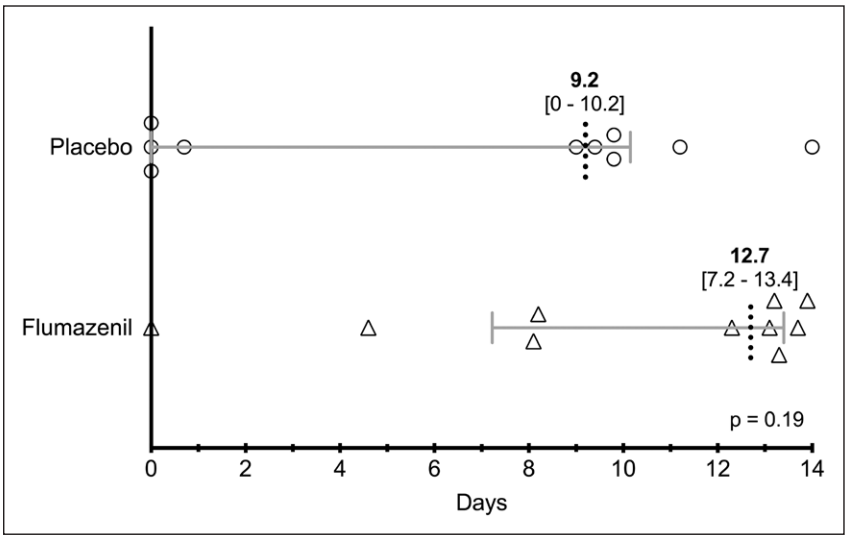

Figure 2. Median days alive without delirium or coma during the first 14 d after enrollment. Median days (*dotted lines*) with interquartile ranges are presented. The *circles* represent an individual patient randomized to the placebo group, and the *triangles* represent a patient randomized to the flumazenil group.

DISCUSSION

This was a novel randomized, controlled pilot study evaluating the effect of flumazenil infusion on clinical outcomes in delirious patients. In this pilot study, there was a clinically important difference in duration of delirium although this difference did not achieve statistical significance. Furthermore, patients in the flumazenil group were 83% less likely to be delirious at the end of the 72-hour infusion. This effect was sustained an additional 24 hours after stopping flumazenil infusion (Fig. 3).

In this cohort, flumazenil test dose and infusion were administered without adverse effect. This is consistent with prior literature supporting the safety of flumazenil for reversal of benzodiazepine sedation and overdose (19–29). This study used rigorous inclusion and exclusion criteria and a novel test dose to mitigate risk of adverse effect and identify patients most likely to benefit from further dosing.

The flumazenil test dose proved to be a low risk and high impact intervention because it appeared to substantially change course and management of patients' delirium and over-sedation. The diagnostic utility of the test dose potentially minimized further resource utilization and work-up for altered mental status.

Continuous infusion was selected as the dosing strategy for this study based on the prolonged duration of sedation associated with exposure to

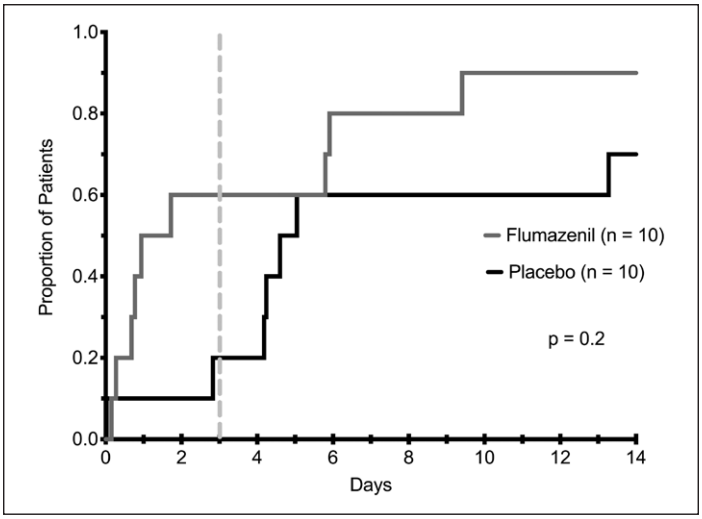

Figure 3. Probability of delirium resolution over time during the first 14 d after enrollment. End of the study infusion is represented by a *dotted line*.

benzodiazepines and the relatively short half-life of flumazenil (i.e. 60 min) (30). Recurrence of over-sedation commonly occurs with intravenously intermittent bolus dosing within both the general anesthesia population (i.e. 10–15%) (30) and critically ill ICU patient population (53%) (25). Successful reversal of resedation has been accomplished with the use of flumazenil continuous infusion in the critically ill (25). Last, the infusion strategy allowed bedside nurses to more precisely titrate to light sedation (RASS –1 to +1), facilitated blinding, and improved compliance to the protocol. A bolus strategy may be effective if the goal is limited to diagnosing benzodiazepine-associated hypoactive delirium or reversing benzodiazepines with short half-lives and could subsequently avoid further unnecessary diagnostic work-up for altered mental status. Moore et al (24) observed a 79% positive response rate (calm and awake) using sequential flumazenil intravenously bolus dosing for reversal of benzodiazepine-associated delirium as a complication of treatment for AWS patients. For future study, utilizing the cumulative test dose administered to elicit a response for subsequent intermittent dosing for delirium would be of interest.

The majority (88%) of patients who met the study inclusion responded positively to the test dose. The inclusion and exclusion criteria used in this study provide clinicians with the framework to use flumazenil as a diagnostic tool to work-up altered mental status and potentially reverse delirium in patients exposed to benzodiazepines within the ICU.

Delirium remains a challenging condition to identify and treat within the ICU. The transition from hyper- to hypoactive delirium within the same patient often escapes recognition, and treatment of this dynamic condition is complicated. Antipsychotics agents are commonly used for ICU delirium based on a small pilot study (31). However, a recent study found that this practice did not reduce the duration of delirium (8). Therefore, the best management strategy within the ICU continues to be reducing exposure to precipitating factors and use of nonpharmacologic interventions. Despite this awareness, 50–80% of mechanically ventilated ICU patients still experience delirium during their ICU course (16). The use of flumazenil to both diagnose and reverse delirium provides a novel tool for the management of hypoactive delirium associated with benzodiazepine exposure.

Several limitations of our study deserve to be acknowledged. The results are suggestive of potential benefit, but the applications are limited by the small sample size and single-center design. The study was stopped early due to a smaller than expected size effect, slow enrollment rate, and planned interim analysis which indicated the study required extension of the enrollment period beyond a reasonable duration. There were no serious adverse effects observed in the study; however, it was underpowered to detect rare adverse effects (e.g. seizure). Larger studies are warranted to further investigate potential benefits and risks.

This was a complex patient population. A common indication for sedation was to facilitate ventilator asynchrony and mitigate lung injury (50%). Selection of a benzodiazepine continuous infusion likely signaled patients and/or conditions that were refractory to guideline-based sedative therapy. Patients were enrolled after prolonged hospital LOS (8.5 vs 10.6 d) and substantial benzodiazepine exposure (117 vs 110.3 mg, lorazepam equivalents). The high severity of illness was further reflected in the SOFA score at the time of study enrollment (6.5 vs 6.1) and in the subsequent LOS in the ICU (7.8 vs 7 d). All these factors likely conspired to limit the translation of any difference in delirium-free days into a subsequent improvement in ICU LOS and ventilator-free days.

In this study, strict patient selection criteria and a conservative dosing strategy were applied to safely use flumazenil in patients with benzodiazepine-associated hypoactive delirium within the ICU. The flumazenil infusion rate (0.025–0.3 mg/hr) was well below those previously studied (0.5–1 mg/hr) (25); therefore, it is possible that the dose used in this study was subtherapeutic. In this study, strict patient selection criteria and a conservative dosing strategy were applied to safely use flumazenil in patients with benzodiazepine-associated hypoactive delirium within the ICU. The flumazenil infusion rate (0.025–0.3 mg/hr) was well below those previously studied (0.5–1 mg/hr) (25); therefore, it is possible that the dose used in this study was subtherapeutic, and future studies could explore a higher initial infusion rate based on the test dose that was required for response. The use of other deliriogenic medications (opioids) was not collected; rather, the test dose was performed to distinguish the relative contribution of benzodiazepines from other potential causes of delirium. Further, a large proportion (50%) of the population enrolled was treated with benzodiazepines for alcohol withdrawal. These factors not only limit the generalizability of the results but also allow identification of a specific subset of patients who could benefit from therapy with flumazenil.

There may be diagnostic benefits to the flumazenil test dose through the reduction of CNS imaging, electroencephalographic monitoring, or work up of metabolic encephalopathy. However, the study was not designed to measure these effects.

The continuous infusion dosing strategy allowed for a more gradual change in effect rather than drastic changes with bolus dosing. However, it is possible that bedside practitioners, and the study team could have been unblinded if the patient's mental status vastly improved after the infusion began. In addition, the flumazenil test dose could have had a variable duration of effect after

incremental increased doses were given. As a result, the placebo group could have had a residual flumazenil effect, impacting initial data points that were collected.

CONCLUSIONS

This study found that flumazenil test dose and infusion present a potential option for hypoactive delirium associated with benzodiazepine exposure; however, the possible benefit is unknown. Larger studies are warranted to further evaluate these findings.

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Drs. Schomer and Duby had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Dr. Schomer contributed to conception of the study, literature review, study design, study execution, data collection, data analysis, data interpretation, and writing of the study. Dr. Duby contributed to conception of the study, study design, study execution, data analysis, data interpretation, and writing of the study. Drs. Firestone and Louie, Ms. Love, and Dr. Cocanour contributed to study execution, data interpretation, and writing of the study. Drs. Sebat and Albertson contributed to study design, study execution, data interpretation, and writing of the study.

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For information regarding this article, E-mail: kjschomer@ucdavis.edu

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