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

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Objectives

The primary objectives was to determine the effect of flumazenil on delirium-free days for critically ill patients with benzodiazepine-associated hypoactive delirium. 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

The primary safety objective 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.

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 hypothesis was that flumazenil continuous infusion may decrease duration of delirium by reversing benzodiazepine-associated hypoactive delirium.

Study Design

This was a single-center randomized, double-blind, placebo-controlled study. Critically ill adult patients with suspected BZD-associated hypoactive delirium may be eligible.

Upon completion of screening and determining eligibility, patients received a test dose of flumazenil. If response was noted (defined as a change in RASS of +1 to +2), patients were randomized to receive standard of care and placebo infusion or standard of care and flumazenil infusion.

Methods

The PI or a co-investigator screened for subjects for inclusion via a daily drug utilization report of benzodiazepine use in the Intensive Care Units. Upon pre-qualification via EMR screening, the investigator performed an in-person assessment to confirm inclusion criteria have been met and patients do not meet exclusion criteria.

Screening included:

- review of the subjects current and prior to admission medication list (via medication reconciliation performed by PI/pharmacy medication reconciliation team, or urine drug toxicity screen)
- review of past medical history (history of seizure, TBI, etc.) to identify exclusion criteria
- review of available urine drug toxicity screen to identify ingestion of pro-convulsant or home benzodiazepine medication. If there was no available urine drug toxicity screen and the patient was greater than 72 hrs from admission there was no requirement for ordering one unless there was a high suspicion for recreational drug use prior to admission
- review of available pregnancy test in females aged 18 -55 y.o. If pregnancy testing was not already performed, the PI discussed ordering a pregnancy test with the primary ICU attending prior to enrollment. If the pregnancy test was positive, the subject was not enrolled.

- all patients who were screened will be tabulated in order to document reasons for exclusion. PHI was not retained for this process.
- confirmed documentation of **RASS -3 to 0 and CAM-ICU positive**
- the study was then discussed with the primary attending physician caring for the patient and permission was obtained to approach patient and/or LAR to obtain consent. At that time the patient's home medication list was confirmed with the LAR to identify any history of taking pro-convulsants.

Test dose administration and monitoring (ICU-only):

- after consent was obtained enrollment into the trial occured, subjects received a test dose of flumazenil 0.1-0.5 mg as IV push over 15 seconds administered by the bedside nurse. May repeat every 5-10 minutes up to a MAX of 2 mg total (assess for up to 60 minutes after last dose) (onset of 0.6 mg dose in healthy volunteers was 5 minutes).
- for all patients meeting inclusion criteria and for whom consent had been obtained the PI entered each subjects test dose response (positive/negative) on a study log
- subjects' response was assessed by the PI, bedside nurse and a member of the primary care team who remained at bedside for 30 minutes after the last test was administered
- a copy of the EKG was performed 10 minutes and 60 minutes after the first dose and was scanned into the subject's profile
- if response (defined as a change in RASS of +1 to +2) was noted, then randomization to standard of care and flumazenil or standard of care and placebo occurred
- responders had a sign posted on his/her door to indicate that the patient was part of a study
- patients that did not respond to test dose were not randomized
- to ensure proper safety monitoring, the PI, a member of the primary care, and the bedside nurse (administering) were present to monitor for any complications for 30 minutes after the last test dose.

Infusion titration post-randomization (ICU-only):

1. Responders to flumazenil:
   - standard of care + flumazenil 2.5 mg/50 mLs 0.9% NaCl, or 5% dextrose (0.05 mg/mL) IV continuous infusion
     - Dosing range: 0.025 mg/hr – 0.3 mg/hr (0.5 -6 ml/hr)
     - Start at @ 2 mLs per hour (0.1 mg/hr., 2.4 mg/24 hours)
     - Titration by 1 mL (0.05 mg) or as clinically indicated per study investigator every 60 minutes for target RASS (0 to +1)
       **Patient care order placed for nurse to monitor RASS every 1 hour (standard of care is every 2 hrs.).
     - Maximum Rate: 6 mLs/hr. (0.3 mg/hr.)
     - If RASS +2 to +3, decrease dose by 0.05mg (1 mL) or as clinically indicated per study investigator every 60 minutes or HOLD if at the lowest rate of 0.025 mg/hr (0.5ml/hr) and re-assess in 1 hour.
     - If RASS +4, HOLD regardless of rate and re-assess in 1 hour.

   - standard of care + placebo (50 mLs 0.9% NaCl, 5% dextrose) IV continuous infusion

- Dosing range: 0.025 mg/hr – 0.3 mg/hr (0.5 -6 ml/hr)
- Start at @ 2 mLs per hour
- Titration by 1 mL (0.05 mg) or as clinically indicated per study investigator every 60 minutes for target RASS (0 to +1)
- Maximum Rate: 6mLs/hr. (0.3 mg/hr.)
- If RASS +2 to +3, decrease dose by 0.05mg (1 mL) or as clinically indicated per study investigator every 60 minutes or HOLD if at the lowest rate of 0.025 mg/hr (0.5ml/hr) and re-assess in 1 hour.
- If RASS +4, HOLD regardless of rate and re-assess in 1 hour.

2. PI or co-investigator assessed patient response daily during the intervention phase (no longer than 72 hours).
   - Daily interruption of infusion starting @ 0900 for 4 hours or until RASS of -1 to -2 .
     A. Assess & document CAM-ICU and RASS BEFORE continuous infusion is interrupted
     B. At the end of the interruption, assess patient's RASS and CAM-ICU.
     C. If patient regresses back to RASS -1 to -3 and CAM-ICU positive, then study infusion was restarted at the previous rate and re-assessed daily.
     D. If daily interruption results in no change in RASS or CAM-ICU scores then study infusion was restarted @ the previous rate
   - Daily interruption occurred daily unless one of the following criteria were met resulting in discontinuation of study drug in the interim:
     A. Primary attending caring for patient deemed discontinuation appropriate
        a. Primary care team must *prospectively* notify the PI if the primary care team wishes to interrupt or discontinue the study infusion to provide clinical care to the patient.
     B. RASS +2 to +4 while on infusion and agitation not controlled with standard treatments (i.e. anti-psychotics)
     C. Rescue benzodiazepine needed due to signs of withdrawal according to the SHOT Scale
     D. Remains CAM-ICU negative after interruption
     E. ICU discharge (determined by physical transfer to lower level of care)
     F. Adverse event attributable to study drug (i.e. supraventricular arrhythmia, seizure)
3. If episodic sedation was needed for a procedure (i.e. bronchoscopy)
   - Study drug could be held (i.e. 30-60 minutes prior) and once the procedure was completed the study infusion could be restarted at previous rate.

As delineated above, the primary investigator and co-investigators were active participants in the study from pre-screening, enrollment, data collection, and data analysis. Relevant staff, including nursing personnel and medical staff, were utilized for coordination purposes.

Statistical 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.