Flumazenil Use in Benzodiazepine-Induced Delirium Reversal

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ABSTRACT

Delirium is a frequent and serious complication in critically ill patients, associated with increased mortality, prolonged hospitalization, and long-term cognitive impairment. The hypoactive subtype is particularly underrecognized, missed in up to 75% of cases, and carries worse outcomes. Benzodiazepines (BZDs), though often used for sedation in the intensive care unit (ICU), can contribute to or exacerbate delirium due to their pharmacokinetics, especially in patients with renal or hepatic dysfunction. Flumazenil, a competitive benzodiazepine receptor antagonist, has been primarily utilized for acute overdose but may have an emerging role in reversing BZD-related delirium. We present a case in which flumazenil administration led to rapid neurological recovery in a critically ill patient with persistent hypoactive delirium following BZD exposure. This report highlights the importance of considering BZD-induced delirium in ICU patients and highlights flumazenil as a potential therapeutic strategy warranting further investigation.

KEYWORDS: Flumazenil; Benzodiazepines; Delirium; Intensive care unit; Benzodiazepine receptor antagonist

INTRODUCTION

Delirium is common among patients admitted to the intensive care unit (ICU) and has been recognized as an independent factor associated with increased six-month mortality, extended ICU and hospital stays, and prolonged mechanical ventilation. The prevalence of delirium in adult ICU patients is approximately 64.6%, and the pooled prevalence of different subtypes of delirium is: hyperactive (4%), hypoactive (17%), and mixed (10%).[1,2] Notably, the prevalence of hypoactive delirium is substantially higher in patients with greater severity of illness (29%) and in mechanically ventilated populations (35%).[1] One study suggested a 10% increased risk of death for every additional day spent delirious in the ICU.[3] Although validated tools like the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) have facilitated delirium monitoring in the ICU,[4] delirium remains underrecognized, with rates of unrecognized delirium ranging from 55% to 70% in hospitalized patients; the hypoactive subtype is particularly prone to being missed and is linked to worse outcomes.[5] Hypoactive delirium is more common among older persons, often goes unrecognized, and is associated with higher rates of complications and mortality.[6] Early diagnosis and treatment of hypoactive delirium can reduce patient mortality.[7]

Benzodiazepines (BZDs) are often used in the ICU to manage anxiety, agitation, and to provide sedation, particularly in mechanically ventilated patients. BZDs work by enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA(A) receptor in the central nervous system, which in turn leads to a decrease in neuronal excitability, producing sedative and anxiolytic effects.[8] BZDs are lipophilic drugs that get stored in adipose tissues, resulting in prolonged effects in individuals with higher body fat. Among the benzodiazepines commonly used in clinical practice, midazolam and diazepam are the most highly lipophilic. Midazolam is water-soluble in its acidic formulation but undergoes intramolecular reconfiguration at physiologic pH (7.4), becoming highly lipid-soluble in vivo.[9,10] BZDs are primarily cleared from the body through hepatic metabolism and renal excretion. Moreover, acute kidney injury has been shown to reduce the hepatic metabolism of midazolam in critically ill patients, which is metabolized by CYP 3A enzymes.[11]

We present a case that revolves around the treatment and reversal of benzodiazepine-induced hypoactive delirium with flumazenil, which is a competitive antagonist for the benzodiazepine-binding site.

CASE DESCRIPTION

A 35-year-old man (Body mass index 26 kg/m^2) with a past medical history of HIV-AIDS with poor adherence to antiretroviral therapy and recurrent opportunistic infections in the past, including esophageal candidiasis and pneumocystis pneumonia, presented after an out-of-hospital cardiac arrest, likely due to an aspiration event. The exact downtime was unknown. He was intubated in the field emergently by emergency medical services (EMS) and started on a fentanyl drip for analgesia; no other sedating infusions were initiated at this time. He was stabilized in the emergency department and admitted to the Intensive Care Unit (ICU).

Initial laboratory evaluation [**Table 1**] demonstrated rhabdomyolysis and lactic acidosis. An echocardiogram revealed an ejection fraction of 60%. Imaging included a chest X-ray and CT chest with contrast which revealed a left, lower lung collapse; pulmonary embolism was excluded.

In the ICU, the patient was managed for aspiration pneumonia with IV antibiotics. Subsequently, he underwent a bronchoscopy with broncho-alveolar lavage (BAL) which revealed thick secretions without any obstructive mass. BAL was negative for bacteria, AFB, fungi, PCP, and malignant cells. His ICU course was also complicated by acute kidney injury requiring dialysis. Four days after admission to the ICU, due to ongoing persistent respiratory acidosis and electrolyte abnormalities, he developed non-sustained ventricular tachycardia, promptly followed by the onset of another cardiac arrest, consistent with pulseless electrical activity. CPR was initiated with the return of spontaneous circulation (ROSC) after 40 minutes. Post-arrest echo did not show any abnormalities or change in ejection fraction.

Following this, he was started on a midazolam drip, in addition to the fentanyl drip due to ventilator desynchrony. Gradually, his hemodynamic status improved, and his sedatives were weaned and stopped within 72 hours.

However, despite the termination of sedatives the patient remained unresponsive with absent neurological and brainstem reflexes. Routine labs did not reveal significant electrolyte derangements, hepatic injury, or hypoglycemia that would explain the persistent unresponsiveness [**Table 1**], and CT scan of the brain and MRI Brain revealed no intracranial abnormalities. He was empirically treated with ceftriaxone, vancomycin, and acyclovir for possible meningitis, which were eventually stopped when lumbar puncture ruled out any infectious etiology. Continuous EEG monitoring revealed diffuse cerebral slowing suggestive of encephalopathy but no epileptiform activity.

After four days without sedation, there was still no gross neurological improvement, but weak cough and gag reflexes were noted, findings inconsistent with brain death and prompting further investigation into reversible causes of unresponsiveness. A trial of naloxone yielded no improvement. Subsequently, the patient

Table 1. Routine labs and other investigations during hospital stay

Labs	Day of admission	Before Flumazenil Administration	After Flumazenil Administration
Complete Blood count			
White blood cell count (x103/uL)	5.7	11.2 with neutrophilic predominance	10.3
Hemoglobin (g/dL)	16.3	8.7	8.6
Hematocrit (%)	47.4	27	27
Platelets (x103/uL)	242	236	230
Comprehensive Metabolic Panel			
Sodium (mEq/L)	138	135	137
Potassium (mEq/L)	5.6	4.1	4
Chloride (mEq/L)	101	92	94
Bicarbonate (mEq/L)	24	23	23
Anion gap	13	20	20
Calcium (mg/dl)	8.3	9.3	9.4
Blood urea nitrogen (mg/dl)	18	67	61
Creatinine (mg/dl)	1.09	8.7	8.05
Glucose (mg/dl)	100	108	114
Alkaline Phosphatase (U/L)	50	138	116
ALT (SGPT) (U/L)	60	27	24
AST (SGOT) (U/L)	103	33	28
Total bilirubin (mg/dl)	0.7	0.4	0.5
Magnesium (mg/dl)	2	2.9	2.7
Phosphate (mg/dl)	8.9	8.5	5.8
Lactate (mmol/L)	4.9	0.7	-
Creatine Kinase (U/L)	7,823	—	—
Troponin (ng/ml)	0.11	—	—
Lactate Dehydrogenase (U/L)	379	—	—
Ammonia (ug/dl)	—	59.7	—
Arterial blood gas (pH/pCO2/pO2/bicarbonate)	7.18/59.5/ 60.7/22	7.3/45/ 117/98	—
Thyroid Panel			
TSH (uU/ml)/Free T4 (ng/dl)	6.03/1.07	—	—
Toxicology Screen			
Blood Ethanol and Urine drug screen	Negative	—	—
HIV panel			
CD4+ Helper cell # (/uL)	89	161	—
CD4+ Helper cell (%)	9.9	10.7	—
CD4/CD8 Ratio	0.16	—	—
HIV 1 RNA Quantitative copies/ml	160	—	—
Hepatitis B and C Panel	Negative	—	—

was started on a trial of Flumazenil 0.5 mg bolus, followed by 0.2 mg hourly infusion, which resulted in significant improvement in sensorium. Within minutes of initiating the flumazenil bolus, the patient began opening his eyes spontaneously and demonstrating purposeful movements. By 12 hours, he was following simple commands, and by 24 hours, he was fully alert and oriented. After 24 hours, he was successfully extubated and eventually returned to his baseline mentation, leading to both the diagnosis and treatment of BZD-induced hypoactive delirium.

DISCUSSION

This case report highlights the potential role of flumazenil in the management of benzodiazepine-induced delirium, particularly in a patient with the hypoactive subtype. Despite guideline recommendations to minimize benzodiazepine administration for sedation, they continue to be used in specific patient populations where alternative sedatives are contraindicated due to hemodynamic or pharmacologic considerations.[12] The prolonged half-life and bioaccumulation of benzodiazepines can result in persistent neurocognitive impairment, further complicating delirium management.[13] In this patient, acute kidney injury likely played a role in impaired drug clearance, leading to prolonged effects of the drug. In patients with acute renal failure, midazolam clearance is reduced (1.9 vs 2.8 mL/min/kg) and half-life is prolonged (7.6 vs 13 hours). Furthermore, the 1-hydroxy-midazolam glucuronide metabolite, which has substantial pharmacological activity, accumulates to approximately 10 times the parent drug level in renal failure and can cause prolonged sedation that is immediately reversible with flumazenil.[14,15]

It is important to note that the patient was receiving ongoing hemodialysis during the period when flumazenil was administered. No other sedating medications were initiated or discontinued during this time, supporting the hypothesis that the clinical improvement was attributable to flumazenil administration rather than other concurrent interventions.

Our case report supports the hypothesis that targeted reversal of benzodiazepines with flumazenil may provide clinical benefits in reducing delirium duration and further unnecessary work-up and intervention. Flumazenil is a competitive benzodiazepine receptor antagonist and has been primarily utilized in the acute reversal of benzodiazepine overdose. The observed improvement following flumazenil administration suggested that residual benzodiazepine played a significant role in the persistence of delirium. This aligns with prior studies indicating that benzodiazepines contribute to prolonged ICU stays, cognitive dysfunction, and increased mortality.[3]

A pilot, prospective, double-blinded, randomized placebo-controlled study investigated the use of flumazenil as a potential treatment for hypoactive delirium linked to benzodiazepine exposure.[2] Given flumazenil's relatively short half-life of approximately 60 minutes, a continuous infusion strategy was implemented to counteract the prolonged sedative effects of benzodiazepines. The study revealed that patients receiving flumazenil were 83% less likely to experience delirium by the end of the 72-hour infusion, with this beneficial effect persisting for an additional 24 hours after discontinuation. However, it is important to note that these results did not reach statistical significance, likely due to the study being underpowered with a small sample size. Additionally, ventilator-free days and ICU length of stay were similar between the flumazenil and placebo groups.[2] Despite these limitations, the study provides preliminary evidence supporting the potential benefit of flumazenil in this setting and highlights the need for larger, adequately powered trials.

Another study by Moore et al[16] observed a 79% positive response rate (calm and awake) using sequential flumazenil intravenous bolus dosing for reversal of benzodiazepine-associated delirium as a complication of treatment for patients with alcohol withdrawal. This retrospective review demonstrated that flumazenil administration was a low-risk yet highly effective intervention, significantly altering the course and management of delirium caused by over-sedation. This approach also minimized the need for further resource-intensive evaluations and unnecessary diagnostic workups for altered mental status.

Despite these promising findings, the use of flumazenil for this indication warrants cautious consideration. One of the primary concerns surrounding its administration is the risk of precipitating withdrawal symptoms or seizures, particularly in patients with chronic benzodiazepine use. The FDA label specifically cautions that flumazenil should be used with care in the ICU setting due to the risk of precipitating withdrawal seizures in patients physically dependent on benzodiazepines, and notes that seizures induced by flumazenil may be refractory to standard doses of first-line anticonvulsants.[17] In our case, no significant adverse events were observed, suggesting that careful patient selection and dosing strategies can mitigate these risks. Future research should focus on establishing optimal dosing protocols and identifying patient populations that are most likely to benefit from flumazenil therapy.

Additionally, the long-term effects of flumazenil administration on cognitive recovery and functional outcomes remain unknown. While our findings suggest that flumazenil contributes to delirium resolution, further studies are needed to assess whether this translates into improved long-term neurological function, reduced ICU length of stay, or lower mortality rates.[18] Prospective, randomized controlled trials with larger sample sizes will be essential in confirming the efficacy and safety of flumazenil in this context.

CONCLUSION

In conclusion, our case report provides preliminary evidence supporting the use of flumazenil in a patient with persistent benzodiazepine-induced hypoactive delirium. While these findings are promising, further research is required to refine treatment protocols, assess long-term outcomes, and ensure patient safety with flumazenil use. Optimizing delirium management strategies in the ICU remains a critical priority, and targeted benzodiazepine reversal may represent a novel and effective approach in select patient populations.

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