Flumazenil in the Treatment of Benzodiazepine Toxicity: The Experience of a Large Urban Tertiary Care Hospital

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ABSTRACT **Background:** Flumazenil has been available since 1991 for the treatment of acute benzodiazepine overdose, yet many physicians remain reluctant to use it.

Objectives: To evaluate the frequency of flumazenil use for benzodiazepine overdose at a large, urban, tertiary care center. To assess its effectiveness and associated adverse events.

Methods: The study was conducted in an emergency department with approximately 220,000 annual visits. Medical records of patients who received a medical toxicology consultation and were treated with flumazenil between 1 January 2019, and 31 December 2023 were reviewed. Data collected included patient demographics, medical history, substances involved, presence of seizures, indications for flumazenil use, clinical response, and adverse effects.

Results: Of 263 patients evaluated for suspected benzodiazepine overdose and referred to medical toxicology, 79 received flumazenil and comprised the study cohort. Among them, 64 cases involved intentional overdose. Indications for flumazenil administration included severe overdose with impaired consciousness and ventilatory failure (37 patients) or without ventilatory failure (42 patients). Co-ingestion of tricyclic antidepressants was documented in 4 patients and other antidepressants or antipsychotics in 35. Clinical improvement, including enhanced consciousness and/or reduced need for mechanical ventilation, was observed in all 79 patients. No adverse effects, including seizures, were reported.

Conclusions: In this retrospective cohort, flumazenil was administered without serious adverse events and was associated with improved alertness and ventilation. While caution is required, particularly in mixed overdoses, flumazenil may have a role in managing benzodiazepine-induced respiratory depression when guided by toxicology consultation.

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KEY WORDS: benzodiazepine, flumazenil, emergency department, overdose

Flumazenil, a competitive antagonist at the benzodiazepine receptor, is indicated for the reversal of the sedative effects of benzodiazepine agents [1]. It acts at central benzodiazepine receptors to counteract or reverse the behavioral, neurologic, and electrophysiologic effects of benzodiazepine agonists, as well as non-benzodiazepine hypnotics such as zolpidem and zopiclone [2]. In the emergency department (ED), flumazenil can serve as a valuable tool for reversing benzodiazepine toxicity, particularly in patients presenting with respiratory depression or decreased level of consciousness, thereby facilitating clinical assessment and management [3].

Although its safe and effective use in the treatment of acute benzodiazepine overdose has been reported in both pediatric and adult populations since its introduction in 1991 [4], many physicians remain reluctant to use the drug [5].

Several concerns contribute to this hesitation. First, the clinical indications for flumazenil are relatively limited, given the wide safety margin of benzodiazepine, even in overdose. Second, there is no well-established correlation between flumazenil dose and seizure risk in susceptible individuals. Third, in patients with tolerance or dependence on benzodiazepine receptor agonists, flumazenil may precipitate acute withdrawal, including seizures [6]. Seizures have been reported with doses ranging from 0.2 to 10 mg [7]. Last, in cases of mixed overdose, particularly with proconvulsant agents such as tricyclic antidepressants (TCAs), the anticonvulsant properties of benzodiazepines may be beneficial and should not be antagonized [5].

The aim of this retrospective study was to assess the frequency of flumazenil use for benzodiazepine overdose management at a large, urban, tertiary care center and to evaluate its clinical effectiveness and adverse event profile.

PATIENTS AND METHODS

A retrospective study was conducted on all patients who presented with benzodiazepine overdose to the ED of our university-affiliated, tertiary care referral center over a 5-year period from 1 January 2019 to 31 December 2023. The hospital, located in central Israel, serves a population of approximately 2.2 million people, has 1500 inpatient beds, and receives approximately 220,000 annual ED visits, including 145,000 adults.

Patients were eligible for inclusion if they met both of the following criteria: evaluation by a medical toxicologist and administration of flumazenil as an antidote. To identify eligible cases, electronic medical records of all suspected poisoning patients referred for toxicology consultation during the study period were searched for the term *flumazenil* in both substance codes and free-text entries. Patients were excluded if flumazenil was not administered.

Data were extracted onto a spreadsheet (Microsoft Excel 2007, Microsoft® Corporation, Redmond, WA, USA) by a single investigator who was not blinded to the study objective. Collected variables included demographics, medical history, substances involved in the overdose, co-exposures, treatments received prior to arrival, occurrence of seizures (before or after flumazenil), and clinical response to interventions.

The study was approved by the institutional research ethics committee and conducted in accordance with the principles of the Declaration of Helsinki.

DEFINITIONS

Clinical evidence of poisoning was defined as a decreased level of consciousness in the context of a suggestive exposure history. Improvement in consciousness was defined as a documented increase in alertness following flumazenil administration. Improvement in ventilation was defined as an increased respiratory rate with improved capnography values or partial pressure of carbon dioxide (pCO_2) levels. Although the decision to administer flumazenil was not based on a predefined protocol, its use at our center follows internationally accepted toxicology practices. The primary indication was suspected benzodiazepine overdose with impaired consciousness, with or without ventilatory compromise. All flumazenil administrations occurred under the supervision of a medical toxicologist following bedside consultation. The standard initial dose for benzodiazepine reversal was 0.2 mg intravenous, given slowly over one minute [8]. If no clinical response was observed after one minute, an additional 0.3 mg was administered over 30 seconds. If a second bolus was required, it was followed by a continuous infusion to prevent re-sedation [8]. The infusion was prepared by diluting 0.5 mg flumazenil in 500 ml of either 0.9% sodium chloride or 5% dextrose, yielding a concentration of 1 µg/ml. The infusion was initiated at 0.1–0.2 mg/hour (100–200 µg/hour) and titrated according to clinical response [9]. Adjustments were made based on overdose severity and patient tolerance. Patients who experienced rapid re-sedation after initial dosing and failed to respond to both the second bolus and infusion were not given further flumazenil [10].

Given flumazenil's mechanism as a competitive GABA-A receptor antagonist, there is a risk of seizure precipitation due to abrupt reversal of benzodiazepine-mediated inhibition. To mitigate this risk, specific precautions were taken in patients with a history of seizures, co-ingestion of pro-convulsant or cardiotoxic agents, or chronic benzodiazepine use [11-13]. These safety measures included cardiac monitoring, exclusion of alternative causes of altered mental status or respiratory failure, assessment of contraindications prior to administration, avoidance of flumazenil following intubation, and use of the lowest effective dose. All cases were managed under direct toxicologist supervision.

STATISTICAL ANALYSIS

Categorical variables are reported as frequencies and percentages. Continuous variables are presented as mean ± standard deviation when normally distributed, and as median with interquartile range when non-normally distributed.

RESULTS

A total of 263 patients with suspected benzodiazepine overdose were evaluated by a bedside medical toxicologist in the ED during the study period. Of these, 79 patients received flumazenil and comprised the study cohort. Their demographic and clinical characteristics are summarized in Table 1.

Among the 184 patients who did not receive flumazenil, none exhibited severe altered mental status or hypoventilation that would have warranted its use. None required endotracheal intubation or intensive care unit admission.

Of the 79 patients treated with flumazenil, 64 were related to attempted suicide, 7 to accidental ingestion, and 8 to substance abuse. Seven patients had a known history of

chronic obstructive pulmonary disease. Antipsychotic and/or antidepressant use was documented in 35 patients. Four patients had co-ingestion of tricyclic antidepressants. All had normal electrocardiograms on presentation, with a mean corrected QT interval (QTc) of 421 ± 25.7 milliseconds.

Table 1. Demographic and clinical details of study patients

Characteristic	Number=79
Age in years, mean ± standard deviation (range)	65.3 ± 19.2 (16–94)
Male sex, n (%)	37 (46.8)
Repeated intravenous push therapy in mg, n=20	0.79 ± 0.21
History of chronic obstructive pulmonary disease, n (%)	7 (8.8)
Co-ingestion of tricyclic antidepressants, n (%)	4 (5.1)
Co-ingestion of antipsychotics-antidepressants, n (%)	35 (44.3)
Hospital site of first flumazenil administration, n (%)	
Emergency department	69 (87)
Ward	6 (8)
Intensive care unit	4 (5)
Dose of flumazenil: mean ± standard deviation	
Slow IV push therapy in mg: all patients, n=79	0.35 ± 0.27
Continuous intravenous therapy in mg/hour, n=14	0.33 ± 1.4
Indication for flumazenil therapy, n (%)	
Altered consciousness with ventilatory failure	37 (47)
Altered consciousness without ventilatory failure	42 (53)
Positive effect of flumazenil therapy, n (%)	
Improvement in ventilatory failure	29/37 (78.3)
Improvement in alertness	79/79 (100)
Flumazenil precautions, n (%)	
Pro-convulsant ingestion	14 (17.7)
History of seizure	5 (6.3)
Benzodiazepine-dependent	12 (15.2)

Fourteen patients had been prescribed anticonvulsant medications. Six received carbamazepine, five levetiracetam, two valproic acid, two phenytoin, and two lamotrigine (one patient was on combination therapy). None of these patients experienced seizures during hospitalization.

Sixteen patients had received intranasal naloxone hydrochloride (4 mg) by emergency medical services prior to hospital arrival, with no effect on level of consciousness.

Ventilatory failure was documented in 37 patients (47%), while 42 (53%) presented with impaired consciousness without ventilatory compromise. No patient had metabolic or hematologic abnormalities severe enough to account for the depressed mental status (data not shown).

The first flumazenil dose was administered in the ED in 69 patients (87%). Twenty patients required an additional dose, and 14 of these were subsequently treated with a continuous infusion due to re-sedation. The infusions, maintained for several hours, were well tolerated and associated with further clinical improvement.

No patients required intubation following flumazenil administration. All 79 patients (100%) demonstrated clinical improvement in alertness. Among the 37 patients with ventilatory compromise, 29 (78%) experienced improved ventilation following treatment,

No adverse events, including seizures, cardiac dysrhythmias, or withdrawal symptoms such as emotional lability, were observed following flumazenil administration.

DISCUSSION

This study documents the safe and effective use of flumazenil in a large cohort of patients presenting over a 5-year period to a busy tertiary care medical center with both single- and multi-drug benzodiazepine overdoses. Poisoning is a major global public health issue and remains one of the leading causes of injury-related death in EDs [14]. Benzodiazepines are among the most commonly prescribed or illicitly used substances [13], and their misuse has been increasing in recent years [10]. Although severe respiratory depression and hemodynamic instability are uncommon in benzodiazepine overdose, supportive care alone may be insufficient in some cases, and flumazenil administration may be indicated.

Studies evaluating effort-dependent respiratory parameters, such as vital capacity, have supported flumazenil use in cases of benzodiazepine-induced respiratory depression [15]. The proposed mechanism is the restoration of conscious control of breathing. In our study, none of the patients with ventilatory compromise experienced adverse events following flumazenil administration. Nevertheless, given the ongoing debate regarding its use in severe coma or respiratory depression [15], flumazenil was administered only after a thorough bedside evaluation by a medical toxicologist. This approach ensured that polypharmacy and alternative etiologies were excluded, and that benzodiazepines were the likely cause of impaired consciousness or ventilatory failure.

In our cohort, flumazenil was safely administered to patients with respiratory depression and elevated pCO_2, particularly in the absence of suspected stimulant exposure, chronic benzodiazepine use, seizure history, or electrocardiogram abnormalities such as QRS or QTc prolongation [16].

Previous literature suggests an increase in antidepressant prescriptions preceding suicidal presentations to the ED [17]. Although our study did not specifically evaluate this issue, the characteristics of our cohort are in line with these observations.

A meta-analysis by Penninga and colleagues [5] reported that common side effects of flumazenil included agitation and gastrointestinal symptoms, while serious adverse events included supraventricular arrhythmias and seizures. Although this study demonstrated a higher risk of adverse events in the flumazenil group (risk ratio for serious adverse reactions 3.81, 95% confidence interval 1.28–11.39, $P = 0.02$), no patient died during the blinded trial phases. In contrast, our investigation did not identify any serious adverse effects. This situation may be attributed to the cautious, tailored use of flumazenil under toxicology supervision in a controlled clinical environment.

Based on our experience and previous literature, including that of Winkler et al. [18], we recommend that flumazenil be used only in consultation with a medical toxicologist, especially in patients without isolated benzodiazepine intoxication or with unclear etiology for altered mental status and respiratory depression unresponsive to naloxone. Bedside toxicology consultation assists in determining the need for airway protection and intubation, while avoiding unnecessary interventions. Flumazenil should be administered at the lowest effective dose. In our protocol, flumazenil was not administered after intubation. When a second bolus was required, a continuous infusion (0.3–0.5 mg/hour) was initiated to prevent re-sedation [9]. If the patient rapidly re-sedated and failed to respond to an infusion at 0.5–0.7 mg/hour, further flumazenil administration was not pursued [14].

Use of flumazenil in the ED may help avoid unnecessary head computed tomography scans, lumbar punctures, and intubations, and may assist in distinguishing benzodiazepine overdose from other causes of central nervous system or respiratory depression [19].

This study has several limitations. First, its retrospective design introduces the possibility of incomplete or inconsistent documentation, as it relies on physician charting. Second, data extraction was conducted by a single, non-blinded reviewer, which may introduce bias. Third, this was a single-center study, which may limit generalizability to other settings. Last, we did not assess whether patients were chronically prescribed benzodiazepines prior to ED presentation, which may influence flumazenil safety and effectiveness. Nonetheless, no adverse reactions were observed, likely due to careful administration in monitored settings with toxicology oversight.

In addition, only patients who underwent a bedside evaluation by a medical toxicologist were included in this study. Patients with suspected contraindications to flumazenil, such as mixed overdoses or TCA co-ingestion, may not have been referred for toxicology consultation or considered for treatment, and thus were not captured in our cohort. Although toxicology consultation is available 24/7 at our institution, some benzodiazepine overdose cases may have been managed without involvement of a toxicologist, potentially affecting both case identification and the generalizability of our findings. Furthermore, only four patients in the cohort had documented TCA co-ingestion. While no adverse events were observed in these cases, this sample size is too small to support conclusions about the safety of flumazenil in this subgroup. Finally, toxicological screening was not performed in all patients and reported drug exposures were based primarily on patient history.

Despite these limitations, our toxicology service is involved in many serious benzodiazepine overdose cases and for all cases in which flumazenil is administered at our institution, supporting the relevance and validity of the findings.

CONCLUSIONS

This study evaluated the safety of flumazenil in patients with suspected benzodiazepine overdose who were managed under the supervision of a medical toxicologist. Flumazenil was administered without serious adverse events in a monitored emergency setting. However, the number of patients with TCA co-ingestion was too small to draw definitive conclusions regarding its safety in such cases.

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Capsule

H5N1 influenza virus stability and transmission risk in raw milk and cheese

Nooruzzaman and co-authors evaluated H5N1 virus persistence in raw-milk cheeses (n=3 per condition) made with milk acidified to pH 6.6, 5.8, and 5.0 before cheese making and validated our findings in raw-milk cheeses (n=4) inadvertently produced with naturally contaminated raw milk. The pH values tested (6.6, 5.8, and 5.0) reflected the pH range encountered in raw-milk cheeses at the marketplace. The authors observed pH-dependent virus survival, with infectious virus persisting through the cheese-making process and up to 120 days of aging in cheeses made with raw milk at pH levels of 6.6 and 5.8, whereas at pH 5.0, the virus did not survive the cheese-making process. Notably, while ferrets (Mustela furo) fed H5N1 virus-contaminated raw milk (n=4) became infected, those fed raw-milk cheese (n=4) or cheese suspension (n=4) did not. These results demonstrate that the H5N1 virus can remain infectious for extended periods in raw-milk cheeses under specific conditions, underscoring the potential public health risks associated with consuming raw-milk cheese produced from contaminated milk and highlighting the need for additional mitigation measures in cheese production to prevent human exposure to the virus.

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Capsule

Neutrophils retain memories of hypoxia

Acute respiratory distress syndrome (ARDS) is a life-threatening condition associated with inflammation, lung damage, and low blood oxygen levels. **Sanchez-Garcia** et al. found that for several months after patients recovered from ARDS, their neutrophils were abnormal, showing reduced antimicrobial effector functions, changes in metabolism, and loss of a histone modification that is critical for regulating gene expression. These changes resembled those observed in healthy individuals who had experienced lowered blood oxygen induced by altitude. In mice exposed to hypoxia, neutrophil precursors within the bone marrow exhibited an irreversible shortening of histone proteins, a process known as histone clipping, that resulted in the defective histone modifications observed in mature neutrophils.

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