

**Evaluation of Flumazenil Adverse Effects when Used in the Iatrogenic Benzodiazepine Delirious Patient: a retrospective study at one center**

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Background: Since the introduction of flumazenil in 1987, there has been controversy regarding the potential risk in its administration.

Research Question: What is the incidence of adverse drug events when using flumazenil for patients with suspected iatrogenic benzodiazepine delirium?

Methods: This is a retrospective cross-sectional study over a 3-year period in a single academic center. Patients were included who were ordered both flumazenil and benzodiazepines during their hospitalization, had a diagnosis of delirium, and toxicology service involvement. A single investigator abstracted all data. Adverse drug events were considered temporally associated with flumazenil use if they occurred within one hour of administration. The Common Terminology Criteria for Adverse Events (CTCAE) v4.0 was used to assess the adverse events.

Results: 286 of 501 patients met inclusion criteria: 189 males, 97 females. Benzodiazepines were administered for multiple conditions including benzodiazepine withdrawal, hepatic encephalopathy, and 43 with opiate overdose and/or withdrawal. Some had more than one diagnosis. Benzodiazepines were used chronically in 100 patients, 30 patients had a known seizure disorder or history of seizure, and 40 patients had a documented seizure during the hospitalization or just prior to arrival. Median total flumazenil dose was 1.5mg (IQR 0.5-3.5). Improved objective delirium parameters were identified in 242 patients after flumazenil, 49 patients had no change. In intubated patients, 82/98 were successfully extubated with flumazenil administration. Complications from flumazenil were noted in 10 patients. Of these, six were categorized Grade 2 or Grade 3 (moderate) on the CTCAE scale, including one self-limited seizure.

Discussion: This study was important to evaluate the use of flumazenil in patients who had suspected iatrogenic benzodiazepine delirium. This unique population all had toxicologist involvement in the flumazenil administration. Six patients (2.1%) required intervention within an hour of flumazenil administration. In comparison, a naloxone review showed agitation/combativeness as an adverse drug effect in 7.9-15% of patients.

Conclusion: Flumazenil can be safely administered in patients with suspected iatrogenic benzodiazepine delirium to evaluate for the cause of delirium and to assist in further treatment if needed. Flumazenil can also be used effectively in patients with iatrogenic benzodiazepine delirium to assist in extubation.