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A POISON CENTER'S TEN-YEAR EXPERIENCE WITH FLUMAZENIL ADMINISTRATION TO ACUTELY POISONED ADULTS

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□ **Abstract—Background: The frequency of seizures among acutely poisoned adults who are administered flumazenil has not been well established. Study Objective: The objectives of the study were: to determine the frequency of seizures among acutely poisoned adults administered flumazenil; to identify factors associated with seizures; and to determine the mental status of subjects before and after administration of flumazenil. Methods: This study was a historical case series of acutely poisoned adults reported to a poison control system from 1999 to 2008. Included cases were those involving administration of flumazenil to subjects who were ≥ 18 years of age. Both genders were included. Variables collected included: presence of seizure or death, exposure to a pro-convulsant drug, and mental status before and after flumazenil administration. Results: Over the 10-year period studied, 904 cases were identified that met inclusion criteria. Thirteen subjects (1.4%) developed seizures after flumazenil was administered. One death occurred. There were 293 subjects exposed to a pro-convulsant drug, and 8 of these had seizures after flumazenil administration. Development of seizures after flumazenil administration was significantly associated with exposure to a pro-convulsant drug (odds ratio 3.41; 95% confidence interval 1.13–10.72). Mental status before and after flumazenil administration was available for 546 subjects (60.3%). Of these, 291 (53.3%) became awake after administration of flumazenil. Conclusions: Flumazenil administration to acutely poisoned adults resulted in a low frequency of seizures and death. Development of seizures was associated with exposure to a pro-convulsant drug. More than half of the subjects for whom mental status was recorded became awake after receiving flumazenil.** © **2012 Elsevier Inc.**

□ **Keywords—flumazenil; seizures; benzodiazepine; poisoning; antidote**

INTRODUCTION

Benzodiazepine overdose can cause central nervous system and respiratory depression (1–4). Flumazenil is a competitive benzodiazepine receptor antagonist that is effective in reversing the sedative effects of benzodiazepines (5). Seizures are a potential adverse event of flumazenil administration and are considered a clinical manifestation of reversal of the benzodiazepine's anticonvulsant effect (5,6). In 2009, the American Association of Poison Control Centers reported 1793 uses of flumazenil among adults 20 years of age and older during a 1-year period (7).

Flumazenil use as a diagnostic agent to identify benzodiazepine overdose among acutely poisoned patients presenting with an unknown overdose is controversial. Whereas some authors have advocated safe use of

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flumazenil in the unknown overdose patient, others have cautioned use in this patient population due to the risk of precipitating seizures by unmasking the potential pro-convulsant ingested drugs (8–15). Patients traditionally considered at risk for developing seizures after flumazenil use are those who have co-ingested a pro-convulsant drug (e.g., a tricyclic antidepressant), those with a history of seizure, and those who chronically use benzodiazepines (6,14). These patients may be difficult to identify in the acute setting, and thus, flumazenil administration may occur in the presence of these contraindications (14,16).

The frequency of seizures in a large population of acutely poisoned adults administered flumazenil is not well established. We sought to determine the frequency of seizures among a large population of subjects administered flumazenil and to determine factors associated with the development of seizures. A secondary goal was to determine the mental status of subjects before and after the administration of flumazenil.

MATERIALS AND METHODS

This was a historical case series that was approved by our institutional review board. The California Poison Control System (CPCS) serves California and a population of approximately 36,760,000. Annual call volume to the CPCS is > 320,000. Calls to the CPCS are voluntary. CPCS data for each case were collected by trained poison center telephone specialists (Specialist in Poison Information) and entered into a statewide electronic database. For each case, drugs of exposure were recorded, and standardized codes were entered for common signs, symptoms, and treatments. Additionally, a time-stamped, free text section allowed the poison center specialist to document the ongoing developments of each case. No specific CPCS guideline exists for the administration of flumazenil.

We performed a search of the CPCS electronic database (Visual Dotlab, Madera, CA) from 1999 through 2008 for all cases involving the use of flumazenil among subjects ≥ 18 years old. Standardized substance coding and free text descriptions of each case were searched for the term "flumazenil." Both genders were included. Cases were excluded if adverse outcomes were unknown or if, upon review of the case, flumazenil had not been administered (miscoded cases). Cases that matched the search criteria were de-identified with regard to patient name and were reviewed.

An electronic data collection spreadsheet was created using Microsoft® Excel (Microsoft Corporation, Redmond, WA) before data abstraction. Data variables collected for each case included: age, gender, presence of seizure, death, drugs to which the patient was exposed by history in the CPCS note, history of seizure disorder, history of chronic benzodiazepine use, and mental status before and after administration of flumazenil. Mental status was defined as: unresponsive, drowsy, or alert. Mental status was determined by the data abstractors based on standardized data fields and free text notes contained in each case.

Seizures for each case were considered present if notation of such was made as a standardized outcome or if noted in the free text notes. Seizures were documented convulsions that occurred any time after the administration of flumazenil. Using the free-text notes for each case, we attempted to determine the temporal relationship between flumazenil administration and the occurrence of seizures. If this relationship was unclear, we used the time-stamps of the serial free text notes written for each case. If seizures developed during the time between the CPCS follow-up notes, the time difference was recorded as the time during which seizures may have occurred.

For each case, two toxicologists (A.A.K. and C.A.T.) reviewed the drugs of exposure recorded and determined if those drugs were pro-convulsant based on a literature search for each drug or a classification under "xenobiotic-induced seizures" in a medical toxicology textbook (17).

Before data collection, four un-blinded data abstractors were trained by one of the investigators (A.A.K.) and collected data on 20 cases. The investigators and data abstractors collectively reviewed errors or misunderstandings regarding data abstraction. Subsequently, each data abstractor reviewed 25% of the cases included in this study. Both standardized data fields and free text descriptions were used for abstracting data. In the case of discrepancies, the free text content was used. The free text documentation allowed for a progressive review of the narrative description of each case and may have contained additional details not captured by standardized data fields.

We hypothesized that no flumazenil-associated seizures would be present. Primary descriptive statistics were recorded. We performed unadjusted odds ratios with 95% confidence intervals for comparing subjects who developed seizures and who were exposed to pro-convulsant drugs.

RESULTS

There were 988 subjects identified, 84 of whom were excluded due to miscoding (no flumazenil administered) or unknown adverse outcome, yielding a total of 904 subjects included in this study. Mean age was 43.3 years (range 18–92 years), and 583 (64.4%) were female. Overall, 13 subjects (1.4%) developed seizures. Of those with seizures, 11 were female, with an average age of 41.1 years. Nine of the 13 subjects developed seizures immediately after the administration of flumazenil. Among the remaining