Notes from the Field

Seizures, Hyperthermia, and Myocardial Injury in Three Young Adults Who Consumed Bromazolam Disguised as Alprazolam — Chicago, Illinois, February 2023

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Bromazolam is a "designer" triazolobenzodiazepine synthesized in 1976 but never approved for therapeutic use (*1*). Since its first detection in Sweden in 2016, a significant increase has persisted in both the toxicologic identification of bromazolam in combination with fentanyl and its identification in counterfeit benzodiazepine preparations (*2*). The number of law enforcement seizures in the United States that involved bromazolam increased from no more than three per year during 2016–2018 to 2,142 in 2022, and 2,913 in 2023.* In Illinois, bromazolam-involved† deaths increased from 10 in 2021 to 51 in 2022.§ Although human studies with clinical data are limited, animal models suggest bromazolam acts predominantly as a sedative, similar to other benzodiazepines, and to date, no signal for hyperthermia, myocardial injury, or seizures attributable to bromazolam intoxication exists (*3*). Although mostly detected alongside fentanyl or other opioids (88%–100% of tested samples),¶ consumption of bromazolam can be life-threatening even in the absence of other drugs. This report discusses a cluster of three young adult patients who were treated at local emergency departments for hyperthermia, seizures, and myocardial injury after consuming bromazolam disguised as alprazolam. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.**

Case Series

On February 1, 2023, in a southern suburb of Chicago, three previously healthy young adults, two men aged 25 years (patients A and B) and a woman aged 20 years (patient C), ingested pressed tablets of bromazolam that they reported they believed to be alprazolam, a drug prescribed for anxiety and panic disorders, but which is misused recreationally because its effects include disinhibition and euphoria. They were found unresponsive by patient A's mother approximately 8 hours later. All three received naloxone from emergency medical services without response and were unresponsive on arrival at local emergency departments.†† Patient A was hypertensive (blood pressure measurement = 152/100 mm Hg), tachycardic (heart rate 124/minute), and hyperthermic (temperature = 101.7°F [38.7°C]); pupils were dilated but reactive, and he experienced multiple generalized seizures. He was intubated to maintain airway control. Patient B was hyperthermic (temperature = 100.4°F [38.0°C]) and was intubated because of unresponsiveness and multiple generalized seizures. Patient C was obtunded with focal seizures and was intubated. All three had myocardial injury as demonstrated by elevated troponin levels. Urine drug screen for all three patients was positive for benzodiazepines. None of the patients received flumazenil, a benzodiazepine overdose antidote that can precipitate benzodiazepine withdrawal and cause seizures or tachyarrhythmias (*4*). All were admitted to an intensive care unit, and the Illinois Poison Center was contacted for assistance in evaluation and management (Table).

Patient A required intubation until hospital day 5 because of depressed mental status. After extubation, he had moderate aphasia and dysphagia, and was discharged on hospital day 11 with persistent neurologic deficits. Patient B was extubated on hospital day 1 and discharged on day 4 with mild hearing difficulty, but otherwise neurologically intact. Patient C progressed to status epilepticus despite administration of multiple antiepileptic medications (lorazepam, propofol, levetiracetam, and valproic acid), and persistent coma. She was transferred to a second hospital on day 11 and was subsequently lost to follow-up. Testing of serum (the preferred body fluid) or plasma samples from all three patients by the Drug Enforcement Administration's Toxicology Testing Program (DEA TOX)§§ confirmed the presence of bromazolam (range = 31.1–207 ng/mL), without the presence of fentanyl or any other opioid.

* The National Forensic Laboratory Information System (NFLIS) is an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of an estimated 1.5 million distinct annual federal, state, and local drug analysis cases. NFLIS-Drug includes drug chemistry results from completed analyses only. Query date was December 14, 2023; data for 2023 are still being reported. https://www.nflis.deadiversion.usdoj.gov/

† A case was categorized as bromazolam-involved if bromazolam was listed as a contributing cause of death on the death certificate in the Illinois Vital Records system.

§ https://dph.illinois.gov/data-statistics/vital-statistics.html

¶ Per surveillance from the Center for Forensic Science and Education, and the DEA TOX 2022 Annual Report. https://www.cfsre.org/images/content/reports/public_alerts/Public-Alert_Bromazolam_NPS-Discovery_061522.pdf

** 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

†† Patients A and B were transported to the same facility; patient C was transported to a separate facility.

§§ The Drug Enforcement Agency has contracted with the University of California San Francisco to analyze biologic samples from patients who overdose on suspected novel psychoactive substances as part of the DEA TOX program. https://www.deadiversion.usdoj.gov/dea_tox/annual_reports/2022_Annual_Report.pdf

TABLE. Characteristics, circumstances, and co-occurring substances among bromazolam overdose patients — Chicago, Illinois, February 2023

Characteristic	Patient A	Patient B	Patient C
Age, yrs; sex	25; Male	25; Male	20; Female
Blood pressure, mm Hg	152/100	Unknown	132/109
Bromazolam level, ng/mL (plasma or serum) by LCMS	207 (plasma)	70.5 (plasma)	31.1 (serum)
Heart rate per min	124	Unknown	118
In-hospital neurologic recovery (HD)	Yes (HD 5)	Yes (HD 1)	No
Myocardial injury (peak troponin, ng/L)	Yes (154)	Yes (239)	Yes (430)
Neurologic deficits at discharge	Moderate aphasia	Hearing loss	Unknown
Other LCMS findings using plasma (level, ng/mL)	8-aminoclonazolam (0.2)*	Aripiprazole (NQ), methamphetamine (0.5),† midazolam (NQ)	None
Rhabdomyolysis (finding)	Yes (CK 4067/Cr 1.41)	No	No
Seizures	Multiple	Multiple	Refractory status epilepticus
Temperature	101.7°F (38.7°C)	100.4°F (38.0°C)	98.8°F (37.1°C)
Urine drug screen result	BZD	AMP, BZD, THC	BZD

Abbreviations: AMP = amphetamine; BZD = benzodiazepine; CK = creatinine kinase; Cr = creatinine; HD = hospital day; LCMS = liquid chromatography–mass spectrometry; NQ = not quantified; THC = delta-9 tetrahydrocannabinol.

* 8-aminoclonazolam is the primary metabolite of the designer BZD clonazolam, which is the 1,4-triazolo derivative of clonazepam. 0.2 ng/mL is under the lower limit of quantification (0.4 ng/mL) but above the lower limit of detection (0.1 ng/mL).

† Above the lower limit of detection (0.4 ng/mL) but below the lower limit of quantification (6.0 ng/mL).

Preliminary Conclusions and Actions

Bromazolam has been misrepresented[¶¶] as a benzodiazepine approved by the Food and Drug Administration. The constellation of signs and symptoms in this case series is unexpected for a benzodiazepine overdose, which might 1) be a product of anoxic brain injury attributable to prolonged obtundation, 2) represent additional features of bromazolam in overdose or withdrawal, or 3) be due to an additional intoxicant not detected on liquid chromatography–mass spectrometry. Since 2021, 114 cases analyzed via DEA TOX had specimens that were positive for bromazolam, with mean blood levels reported as 44.8 ng/mL. Bromazolam has also been detected in drivers arrested for driving under the influence, in whom it produced a largely sedative toxidrome (*5*).

It is essential that physicians, medical examiners, toxicology laboratories, public health officials, and emergency responders be aware of the increased presence of bromazolam both in polydrug ingestions and in substance use disorder patients who report the use of benzodiazepines. Clinically, this knowledge can inform prognosis (two out of three patients in this cluster had confirmed recovery to near independence) and could indicate the need for aggressive seizure control. From a public health perspective, the constellation of findings reported should prompt close involvement with public health officials and regional poison centers, given the more severe findings in these reported cases compared with those expected from routine benzodiazepine overdoses. Clinicians, responders, and health officials should also consider bromazolam in cases of patients requiring treatment for seizures, myocardial injury, or hyperthermia after illicit drug use, as occurred in these case reports. Bromazolam intoxication should also be suspected in patients with a sedative toxidrome who do not respond adequately to naloxone reversal. In cases of suspected bromazolam exposure, clinicians should call their poison center for additional guidance. Testing for bromazolam is not routinely available but can be arranged through a variety of send-out reference laboratories.[***]

¶¶ Bromazolam, sold as alprazolam, submitted anonymously as sample ID 16949 analyzed by DrugsData, an independent laboratory testing. https://drugsdata.org/view.php?id = 16949

*** Send-out reference laboratories offer a wide variety of specialized testing that is typically not available at primary hospital laboratories. Examples include NMS Labs and Quest Diagnostics, among others, in addition to the DEA TOX program.

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