

# Flubromazolam overdose: A review of a new designer benzodiazepine and the role of flumazenil

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## Abstract

Designer products, a term referring to analogs of known chemical compounds with no established medical use, represent an easily accessible alternative to prescription-only products. During the past decade, designer benzodiazepines have become widely available on the online forums. Although these agents offer individuals an inexpensive and accessible alternative to prescription-only products, they are not without risk. Because of the lack of federally enforced quality standards, these designer products come with an intrinsic risk of unpredictable and potentially toxic adverse effects. This article presents a 36-year-old male with prolonged bradycardia resulting from the use of flubromazolam, a designer benzodiazepine purchased from the Internet. A PubMed search was conducted for *flubromazolam*, *designer benzodiazepine*, and *flumazenil*. This article will summarize the available literature regarding flubromazolam and the role of flumazenil in managing these overdoses.

**Keywords:** designer benzodiazepines, flubromazolam, flumazenil, overdose

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## Background

Benzodiazepines are a popular class of anxiolytics often implicated in both intentional and unintentional overdoses.<sup>1</sup> The American Association of Poison Control Centers' National Poison Data System includes benzodiazepines within the sedative/hypnotic category. According to their most recent report,<sup>1</sup> this was the second most common category of substances involved in adult overdoses reported to US poison centers in 2016. Furthermore, they were implicated in the largest number of fatal overdoses

that year.<sup>1</sup> Compared with 2015, the rate of increase for sedative/hypnotic overdoses was greater than for all other substance categories.<sup>1</sup>

In addition to prescription benzodiazepines, a number of new designer benzodiazepines were introduced to the illicit drug market beginning in 2012.<sup>2</sup> These *designer products*, a term referring to analogs of known chemical compounds with no established medical use, represent an easily accessible alternative to prescription-only benzodiazepines.<sup>3</sup> Reported uses for the designer benzodiazepines include self-medicating for anxiety, reducing the symptoms of prescription benzodiazepine withdrawal, and seeking recreational intoxication.<sup>4,5</sup> Because of their broad scope of use, the designer substances have presented an enormous challenge to both clinical and forensic toxicologists as well as policy makers.<sup>5</sup>

Flubromazolam is just one example of a designer benzodiazepine marketed on Internet shops as a research chemical.<sup>2-4</sup> Although it is available for purchase, it is not a prescription product regulated by the US Food and Drug

Administration. Flubromazolam has yet to be classified as a controlled substance in the United States at the federal level. The only state to classify it as a Schedule I controlled substance is Virginia.<sup>4,6</sup> Unlike the United States, European countries have federally regulated flubromazolam since 2015. It was classified as a narcotic substance in Switzerland in 2015 and has been illegal to produce, supply, or consume in the United Kingdom since 2016.<sup>4</sup> Prescription benzodiazepines are generally regarded as having a more favorable safety profile than their barbiturate predecessors and undergo extensive premarket testing. Designer benzodiazepines, however, do not undergo the same safety and toxicity testing and therefore have indeterminate potency and the potential to cause unforeseen clinical manifestations (eg, uncharacteristic signs/symptoms, unintentional overdose).<sup>3</sup>

## Case Report

A 36-year-old male with a history of schizoaffective disorder, anxiety, posttraumatic stress disorder, opioid use disorder, and seizures presented to an inpatient psychiatric facility for worsening anxiety. His home medications included fluoxetine, clonazepam, buprenorphine, lamotrigine, tramadol, and baclofen. To manage his anxiety, he admitted to using a “research chemical” he purchased from the Internet. He appeared lethargic and could not recall its exact name at the time of his initial interview. He was accepted for direct admission to the psychiatric facility for the management of sedative dependence and withdrawal. The next morning, he was noted to be “nearly obtunded” and was transferred to the emergency department (ED) for the evaluation of hypotension and bradycardia that had developed throughout the night.

Upon arrival to the ED he was lethargic, but he was responsive to verbal stimuli, with a heart rate (HR) of 49 beats/min and a blood pressure of 110/64 mm Hg. When interviewed in the ED he recalled that he had purchased flubromazolam and he usually took 0.4 mg to achieve anxiolysis. He did not experience the same relief this time, however, and believed he received a “bad batch.” Because his anxiety persisted he increased his dose to 3 to 4 mg in an effort to elicit the same effect. His last 3-mg dose was taken shortly before presenting to the psychiatric facility the previous evening.

On physical examination he was noted to have midrange pupils, active bowel sounds, supple muscle tone, and skin that was warm and dry. His laboratory evaluation was only remarkable for benzodiazepines detected in a routine urine drug screen. His electrocardiogram revealed sinus bradycardia with normal intervals. He was treated supportively with 1 L of normal saline and was placed

on continuous cardiac monitoring. Although he remained persistently bradycardic he was hemodynamically stable. Because of his known comorbidities the decision was made to not administer flumazenil. Because his HR remained in the 40s with mild hypotension, he was admitted to the intensive care unit for further monitoring. His intensive care unit admission was uneventful and required no lifesaving interventions. Approximately 72 hours into his hospital course his vital signs returned to baseline (HR, 72 beats/min; blood pressure, 137/83 mm Hg). He was medically cleared for transfer back to the inpatient psychiatric facility thereafter for management of his sedative dependence. No further adverse events were reported.

## Discussion

Although they exist within a legal gray area, designer benzodiazepines are readily available for purchase on the Internet despite the limited information known about them. A PubMed search limited to the English language and human data was conducted using the keywords *flubromazolam*, *designer benzodiazepine*, and *flumazenil*. Diclazepam, flubromazepam, flubromazolam, and clonazolam are some designer benzodiazepines reported in the literature.<sup>3</sup> Powders, injectable solutions, and blotters are a few examples of the many formulations available to online consumers.<sup>3</sup> The individual in this case reported using flubromazolam. Flubromazolam is the triazolone analog of another designer benzodiazepine, flubromazepam, and is structurally related to the prescription triazole benzodiazepines alprazolam and triazolam.<sup>2,4</sup>

Because flubromazolam has not been extensively tested, the exact dose at which clinical effects manifest following ingestion is unknown. On Internet forums mild anxiolytic and skeletal muscle relaxant effects have been reported with doses as low as 0.1 mg and significant sedation at doses of 0.5 mg.<sup>3-5</sup> Flubromazolam has been described as “hard to dose” because of its unpredictable dose-response effects.<sup>5</sup> Other clinical manifestations described in online forums include cognitive impairment, memory loss, ataxia, sleep paralysis, visual disturbances, heart palpitations, rapid onset of tolerance, and severe withdrawal lasting more than a month.<sup>5</sup> A summary of the symptoms reported in the medical literature can be found in the Table.

A unique clinical manifestation observed in this case was bradycardia. Although benzodiazepines are known to cause respiratory and central nervous system depression, they are rarely associated with a reduction in HR. Tachycardia, with concomitant hypotension, is more often reported.<sup>2,5</sup> The patient in this case denied taking any medications that would reduce his HR and he had no

**TABLE:** Summary of flubromazolam ingestion literature review

	Huppertz et al <sup>2</sup> (2017)	Łukasik-Głębocka et al <sup>4</sup> (2016)
Study type	Healthy volunteer study	Case report
Patient characteristics	44-year-old otherwise healthy male	27-year-old male with a history of psychoactive substance use
Flubromazolam dose ingested	0.5 mg	48 h PTA: 2 mg 19 h PTA: 3 mg
Known coingestant	None	Phencyclidine, unknown amount 48 h PTA
Clinical symptoms	Muscle relaxation Sedation (repeatedly fell asleep) Difficulty following and participating in conversation Partial amnesia	Deep coma Miosis (bilateral, unreactive) Acute respiratory failure Hypotension Tachycardia Transaminitis Leukocytosis Hyperglycemia Hypotonia, diminished reflexes Rhabdomyolysis
Onset of clinical effects	Muscle relaxation: 1.5 h Sedation: 3 h	Unknown
Duration of clinical effects	Sedation: 10 h (with reemergence at 30 h after ingestion) Amnesia: >24 h	Sedation: 4 d (fluctuating severity)
Laboratory detection	Serum value (hours after ingestion): 7.4 ng/mL (5) 8.6 ng/mL (8) 3.2 ng/mL (24) 5.2 ng/mL (30) Urine (days after ingestion): Flubromazolam (6.5) and its monohydroxylated metabolite (8) Hair: Detected up to 4 wk after ingestion	Serum value (hours after ingestion): 59 ng/mL (19) Urine value: 105 ng/mL (19) Benzodiazepines present in urine drug screen (19)
Laboratory method used	LC-MS/MS (serum, urine) Triple quadrupole mass spectrometry (hair)	LC-MS/MS (serum, quantitative urine) Lateral flow chromatographic immunoassay (qualitative urine)
Flumazenil used	No	Yes, multiple doses 19 h after ingestion: 0.5 mg every 3 min for 2 doses (transient response lasting 30 min) 48 h after ingestion: 0.5 mg (transient response lasting 30 min)
Other interventions	None	Naloxone Mechanical ventilation Norepinephrine (for 49 h)
Study conclusions	Terminal elimination half-life estimated to be 10-20 h	Extubated on d 4 and transferred to neurology on d 9 of admission

LC-MS/MS = liquid chromatography–tandem mass spectrometry; PTA = prior to arrival.

known cardiac history. It was concluded that the source of his bradycardia was more likely flubromazolam versus one of primary cardiac origin.

The persistent bradycardia in this case suggests that flubromazolam may have a prolonged half-life when taken orally. In vitro studies of flubromazolam showed a half-life of 182 minutes.<sup>7</sup> It is a known substrate of cytochrome P<sub>450</sub> 3A<sub>4/5</sub>.<sup>7</sup> The patient in this case was taking fluoxetine, an inhibitor of 3A<sub>4</sub>, at home. This drug

interaction may have contributed to the prolonged duration of toxicity observed. Flubromazolam's major metabolites are  $\alpha$ -hydroxy-flubromazolam and 4-hydroxy-flubromazolam.<sup>7</sup> Although other triazole benzodiazepines have active metabolites, it is uncertain whether flubromazolam's metabolites are pharmacologically active.<sup>7</sup> Its high degree of protein binding and low clearance suggest the potential for a long elimination half-life in vivo. This is consistent with the prolonged effects reported in clinical cases of flubromazolam intoxication.<sup>5</sup> Based on the data

obtained from a single healthy volunteer study, the terminal elimination half-life of flubromazolam following a single dose of 0.5 mg was estimated to be 10 to 20 hours.<sup>2</sup> Users of flubromazolam not only reported a quick onset of action (10 minutes) but also sedative effects that lasted several days.<sup>5</sup> The variable and prolonged clinical effects of flubromazolam highlight the high risk of unintentional overdoses with life-threatening consequences.<sup>4,5</sup>

Aside from its unpredictable clinical effects, another issue complicating the swift identification of flubromazolam is laboratory detection. Although flubromazolam has caused routine urine drug analyses to come back positive for benzodiazepines (Table), a method to measure exact urine and serum flubromazolam concentrations is not widely available for routine clinical use.<sup>2,4</sup> Both flubromazolam and its monohydrated metabolite have been measured in the urine via liquid chromatography–tandem mass spectrometry.<sup>2</sup> The same technique has also detected its monohydrated metabolite in the urine for up to 8 days after ingestion.<sup>2</sup> In the same healthy volunteer study, serum concentrations of flubromazolam were found to peak at 5 hours following the oral ingestion of a 0.5-mg dose. Interestingly, despite a downward trend of serum concentrations a second peak occurred at 8 hours after ingestion. A delay in the gastrointestinal absorption of flubromazolam, the effect of food on complete drug resorption, or the influence of enterohepatic recirculation was thought to explain the rise in repeat concentrations.<sup>2</sup>

Unfortunately, there are no standard “therapeutic” concentrations of flubromazolam that can be correlated with clinical manifestations in a predictable manner. One case report<sup>4</sup> has suggested that serum flubromazolam concentrations of 43 ng/mL can lead to cardiorespiratory failure. This individual, however, reported ingesting multiple doses of flubromazolam and phencyclidine in the 48-hour period preceding his respiratory failure, which may not represent the true clinical effects from flubromazolam alone.<sup>4</sup> Flubromazolam concentrations were not obtained in the case we describe because this test is not available at the small, community hospital to which he was admitted. The routine urine drug analysis was positive for benzodiazepines; however, it was not clear whether this was due to flubromazolam, prescribed clonazepam, or both.

Based on its pharmacology, flumazenil theoretically remains an option for managing designer benzodiazepine overdoses. Flumazenil reverses the effects of benzodiazepines via antagonism of their binding site on the GABA-A receptor.<sup>8</sup> It is intended to be used as an adjunct to proper airway management and circulatory support for benzodiazepine overdose.<sup>8</sup> Typical doses for this indication start at 0.2 mg given intravenously, with repeat doses administered as clinically indicated. The onset of reversal

occurs within 1 to 2 minutes of administration, with a peak effect in 6 to 10 minutes. Following extensive distribution to the extravascular space, flumazenil has a terminal half-life of 40 to 80 minutes.<sup>8</sup> Although initially considered to be a safe antidote lacking intrinsic activity, serious adverse events, such as seizures, cardiac arrest, and death, have been reported following the use of flumazenil.<sup>9–13</sup> Despite these risks, flumazenil has been used following one reported flubromazolam overdose. In the case by Łukasik-Głębocka et al,<sup>4</sup> respiratory insufficiency returned 30 minutes after receiving flumazenil. Because the half-life of flubromazolam far exceeds that of flumazenil, the reemergence of symptoms once flumazenil is eliminated can be expected.

The risk-benefit ratio of using flumazenil in benzodiazepine overdose is influenced by the presence of an underlying risk of seizures and the dose used. Administering flumazenil in the presence of proconvulsant coingestants (eg, anticholinergics, stimulants, cyclic antidepressants) can be potentially harmful because it will reverse the seizure protective effects of benzodiazepines.<sup>14</sup> In a retrospective review<sup>14</sup> of 904 benzodiazepine overdoses reported to the California Poison Control System, the authors found a significant association between exposure to proconvulsant drugs and seizures with flumazenil use (odds ratio, 3.41; 95% confidence interval, 1.13–10.72). In clinical practice flumazenil is avoided in patients who have or are suspected to have coingested a proconvulsive substance, are chronically taking benzodiazepines, and/or have a known history of seizures.<sup>14,15</sup>

Unlike the case presented by Łukasik-Głębocka et al,<sup>4</sup> flumazenil was not administered in this case because of multiple concomitant proconvulsant medications (eg, tramadol, baclofen), a history of seizures (on lamotrigine), and chronic use of clonazepam. Additionally, bradycardia lasting nearly 72 hours suggests a prolonged half-life of flubromazolam consistent with the literature. Considering the short half-life of flumazenil, comparatively, multiple repeat doses would have been necessary to elicit only a temporary effect.

## Conclusion

Designer psychoactive substances have become popular drugs of abuse in recent years. Flubromazolam is a designer benzodiazepine with strong and long-lasting central nervous system depressive effects that increases the risk of life-threatening consequences. This case describes prolonged bradycardia, highlighting a unique and formerly unreported clinical effect of flubromazolam use. It appears that it is detectable on routine urine drug analyses, but routine serum concentrations are not yet

widely available. Unfortunately, because these substances are not regulated by the US Food and Drug Administration, a paucity of safety and efficacy data exists in either animal or human models. Given the inconsistent side effects coupled with the possibility of proconvulsant coingestants, the role of flumazenil should be carefully evaluated. It is possible that repeat doses of flumazenil will be required given that the half-life of flubromazolam exceeds that of flumazenil.

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