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To cite this article: Magdalena Łukasik-Głębocka, Karina Sommerfeld, Artur Teżyk, Barbara Zielińska-Psuja, Paweł Panieński & Czesław Żaba (2016) Flubromazolam – A new life-threatening designer benzodiazepine, Clinical Toxicology, 54:1, 66-68, DOI: 10.3109/15563650.2015.1112907

To link to this article: http://dx.doi.org/10.3109/15563650.2015.1112907

Published online: 20 Nov 2015.
Flubromazolam – A new life-threatening designer benzodiazepine

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ABSTRACT

Context: In addition to designer benzodiazepines such as etizolam, deschloroetizolam, pyrazolam, diclazepam, nifoxipam, or clonazolam, a new psychoactive substance like flubromazolam, triazole of flubromazepam has become available. Flubromazolam is currently not marketed as a medication but rather as a research chemical and recreational drug. It mostly causes sedative effects but also has moderate anti-anxiety and muscle relaxant effects. A case of a severe intoxication of flubromazolam has been reported.

Case details: A 27-year-old man, presented with deep coma, bilateral pinpoint unreactive pupils, acute respiratory failure and hypotension, complicated by hypoxic ischemic changes in the central nervous system. A positive result of a urine screening test confirmed the presence of benzodiazepines, which resulted in administration of flumazenil and improved patient consciousness. Quantitative method of liquid chromatography indicated flubromazolam in the patient’s serum at 59 ng/mL and urine at 105 ng/mL about 19 h after ingestion of 3 mg dose. On admission, serum creatine kinase was 15 960 U/L. The patient was treated with mechanical ventilation, intravenous fluids, flumazenil and continuous infusion of norepinephrine at a dose of 0.12 µg/kg/min. The patient survived and on the ninth day of hospitalization he was transferred to the Department of Neurology.

Discussion: Flubromazolam is a new designer drug. Recreational use may be a cause of prolonged, severe intoxication associated with coma, hypotension, and rhabdomyolysis.

ARTICLE HISTORY

Received 17 August 2015
Revised 21 October 2015
Accepted 21 October 2015
Published online 19 November 2015

KEYWORDS

CNS; psychological; lung; respiratory support; other

Introduction

For several years a number of new psychoactive substances have been introduced into the market of illicit drugs. Being legally placed and generally available in Internet shops and online sales they become the cause of an increasing number of poisonings and represent an enormous challenge for clinical and forensic toxicologists, as well as policy makers in many countries. Those compounds have different effects: euphoric, stimulating, or hallucinogenic. This market also provides analogs of drugs that are benzodiazepine’s derivatives, sometimes used in combination with stimulants to reduce their side effects. It could be assumed that compounds from this group should not create serious toxicological problems, because benzodiazepines usually have relatively low acute toxicity. However, some new designer benzodiazepines such as etizolam, deschloroetizolam, pyrazolam, diclazepam, nifoxipam, clonazolam, and flubromazolam could pose a risk of severe life-threatening intoxications.[1–6]

This article presents a case of poisoning by a new designer benzodiazepine, flubromazolam, confirmed by serum and urine drug concentrations. Flubromazolam (8-bromo-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine) as a triazole analog of flubromazepam (7-bromo-5-(fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) presents extremely high affinity and efficacy for the benzodiazepine receptors. It is quickly absorbed with peak effects generally within an hour. The safety of flubromazolam is untested, and it can cause unexpected side-effects due to the lack of screening for off-target effects prior to marketing and that makes it a very potent and dangerous new designer drug.[2,3]

Case details

A 27-year-old man (height: 170 cm, weight: 70 kg) was found unconscious at home for an unknown time. The family denied any history of trauma or chronic diseases. The patient experimented with new psychoactive substances for several years. Recently he was using some psychotropic drugs, which he obtained from unknown sources. The patient was not known to be taking any prescribed medication. Upon arrival to...
the Department of Toxicology at Municipal Hospital, he was in a deep coma, score 3 in Glasgow Coma Scale (GCS). He was intubated and mechanically ventilated due to hypoventilation (respiratory rate of 6–8 breaths/min) and respiratory failure. There was no spontaneous voluntary or involuntary movement noted. A physical examination revealed paleness with livedo reticularis and cyanosis of hands and feet. The presence of bedsores on the right side of the body – on his cheek, shoulder, forearm and hip and on the inside of the knee and ankle joints, pointed to a prolonged immobilization in recumbent on the right side. Eyes were deviated upwards, with bilateral pinpoint unreactive pupils. The exam showed generalized hypotonia, diminish reflexes, and absent plantar response. Neither pathological neurological symptoms nor meningeal signs were noted.

Due to hypotension (blood pressure of 80/40 mmHg) with tachycardia (heart rate of 102 beats/min) intravenous fluid reuscitation (1500 ml of 0.9% NaCl and 500 ml of Gelofusine – 4% solution of succinyllated gelatine) was started, without any improvement. Intravenous administration of 25 mg of epinephrine did not increase the blood pressure. As the medical history suggested the possible abuse of some drugs and clinical symptoms insinuated an opioid toxidrome, naloxone 0.4 mg intravenously was administered twice every 3 min. There was no response to antidote administration. Therefore, a central port was inserted into the right subclavian vein and the continuous infusion of norepinephrine at 0.12 µg/kg/min was started, which resulted in blood pressure increasing to 120/80 mmHg.

Diagnostic and laboratory tests were performed in parallel to treatment. Head computed tomography and the chest X-ray were normal. Electrocardiography showed a regular sinus rhythm of 102/min without any conduction delay, QT prolongation, or signs of ischemia. Laboratory studies showed leukocytosis, respiratory acidosis and increased serum glucose, creatine kinase (CK), aminotransferase alanine (ALT) and aspartate aminotransferase (AST). The serum creatine and potassium levels were slightly elevated. The other results of the lab tests were in the reference ranges (Table 1).

After a positive benzodiazepines result in urine obtained on admission in the 19th hour after flubromazolam ingestion, 0.5 mg flumazenil was injected intravenously twice, every 3 min. The patient woke up and opened his eyes, made localized movement in response to painful stimulus but did not respond to voice, reaching score 10 in GCS. His pupils dilated and vertical nystagmus was observed. A spontaneous, insufficient breathing with respiratory rate of 4–6/min returned. After about 30 min the consciousness of the patient deteriorated to GCS score 3.

Due to the positive reaction after the flumazenil administration, benzodiazepine derivative poisoning was diagnosed. The following day the patient was still unconscious, made non purposeful movement in response to noxious stimulation, reaching score 6 in GCS. His pupils dilated to about 2 mm and responded to the light. He was still mechanically ventilated. A slight improvement in circulatory parameters was observed – blood pressure was maintained at the level 110–120/70–80 mmHg at the dose of noradrenaline reduced to 0.04 µg/kg/min. The temperature increased to 38.3°C. An increase of CRP to 129.45 mg/L was noted and chest X-ray showed double pneumonia (in the lower right lobe and the left side). Therefore, amoxicillin with clavulanic acid was administered. After a dose of 0.5 mg of flumazenil intravenous the patient awoke (GCS 9–10) for ~30 min.

On the third day of the treatment, due to persistent disturbances of consciousness, a second computed tomography was performed that revealed hypoxic-ischemic changes within the internal capsules bilaterally in both frontal and left temporal region. Neurological examination revealed bilateral hyperreflexia of a knee and an ankle, a weaker defense reaction of the right leg and the presence of Babinski sign on the right side. In the following hours, a further rise in blood pressure led to discontinuation of the infusion of norepinephrine, which had been administered for 49 h. A significant improvement of the state of consciousness took place only after the fourth day of treatment, when it was possible to extubate the patient. He rehabilitated physically and continued antibiotic therapy (8 d). On the ninth day of the treatment he was moved to the Department of Neurology for further treatment.

After establishing logical verbal contact with the patient, the clinical interview was completed. The patient reported that he bought flubromazolam from an online store and consumed about 3 mg the previous evening, around 19 h before hospitalization. He stated that 48 h before admission, he also ingested 2 mg of flubromazolam in combination with phenycyclidine. At that time he felt very sleepy and woke up after about 10 h, without any unexpected symptoms.

### Toxicological analysis and results

Serum and urine used in toxicological and biochemical tests were collected at the same time, 19 h after intoxication. Gas chromatography–flame ionization detector (GC–FID) method did not reveal the presence of ethanol, methanol, isopropanol, acetone, or glycols (ethylene and propylene) in the blood. Moreover, the enzyme multiplied immunoassay technique (EMIT, Syva, Siemens Healthcare Diagnostics Inc., Deerfield, IL) did not confirm the presence of carbamazepine, tricyclic antidepressants, and valproic acid in serum either. Urine analysis (baclofen, chlorprotixen, phenotiazines, opiates, tramadol and...
barbiturates) using preliminary qualitative immunochemical methods and thin layer chromatography (TLC) was negative, except for benzodiazepines, which revealed its presence in the urine with a cut-off level of 300 ng/mL. The test used in the procedure was a lateral flow chromatographic immunoassay for the qualitative detection of benzodiazepines in urine.

Specimens collected from the patient (serum and urine on admission 19 h after intoxication) were investigated by high-pressure liquid chromatography coupled with triple quadrupole mass spectrometer (LC-MS/MS) working in multiple reaction monitoring (MRM) mode and two reactions for each compound, equipped with electrospray ionization source. The applied procedure confirming the presence of benzodiazepine was the same as the one routinely used in detecting the benzodiazepine presence in biological material. Extraction of flubromazolam was performed using liquid–liquid extraction method at an alkaline pH. The samples were alkalized with Tris(hydroxymethyl)aminomethane buffer pH 9.0, mixed with acetonitrile and extracted with ethyl acetate. For quantitative analysis of flubromazolam, the samples of blood and urine were mixed with internal standard (D5-oxazepam).[7] A calibration curve for flubromazolam sample was prepared in the range of 10–200 ng/mL. Toxicological testing of patient’s serum and urine showed the presence of flubromazolam. There were identified 59 ng/mL in the serum and 105 ng/mL in the urine.

Discussion

New life-threatening designer benzodiazepines such as flubromazolam represent an alternative to benzodiazepines issued only by prescription. Benzodiazepines are known to be safer than barbiturates by causing less respiratory depression in overdose settings. Though cases of serious and fatal benzodiazepine overdoses such as alprazolam intoxication have been reported with significant respiratory depression, it usually occurs in co-ingestion with another central nervous system depressant such as alcohol.[8] This case suggests that respiratory depression could have been due to the high dose of flubromazolam (about 3 mg). According to accounts given by users of new psychoactive substances presented in Internet forum, flubromazolam has tranquilizing, anxiolytic and hypnotic effect and acts as a skeletal muscle relaxant even at such a low oral dose as 0.1–0.2 mg, the effective dose has not been calculated.[9] This case indicates that the reported oral dose of 3.0 mg (about 0.043 mg/kg b.w.) could cause severe, long-lasting depression of the central nervous system with cardio-respiratory failure, complicated with brain hypoxic-ischemic changes.

Flumazenil reverses the effects of benzodiazepines by competitive inhibition at the benzodiazepine binding site on the GABA A receptor. Administered at the dose of 1.0 mg, it improved patient’s consciousness for about 30 min. In the presented case the injection of flumazenil was used as a test, which was to confirm that the benzodiazepines found in patient’s urine were responsible for his clinical condition. After the temporary improvement of patient’s consciousness, symptomatic therapy was continued. Neither the antidote dose was increased nor was the continuous infusion of this medicine applied.

New designer benzodiazepines like flubromazolam are also taken together with other psychoactive substances in order to decrease unpleasant symptoms of overstimulation, which can modify the clinical signs. As the efficacy and safety of these substances have not been thoroughly evaluated in animal and human trials, the use of these drugs may result in unexpected side effects. Free access to these derivatives entails the risk of poisoning and potential dead for consumers of these strongly sedative new and unevaluated benzodiazepines.[1,2,10]

Conclusion

Flubromazolam is a designer benzodiazepine with a strong and long-lasting depressive effect on central nervous system representing a high risk of severe poisoning complicated by hypoxic ischemic changes in the central nervous system. At the serum concentration of 43 ng/mL, flubromazolam can induce a deep coma with cardio-respiratory failure. It gives positive screen in qualitative benzodiazepine urine test. Flumazenil, a specific antidote used in benzodiazepines overdose may be effective in the treatment of flubromazolam intoxication.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References