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Case Report

A Case Review of the First Analytically Confirmed 25I-NBOMe-Related Death in Washington State

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This case was submitted to the Washington State Patrol Toxicology Laboratory in September 2014. A 15-year-old male went to a party where he ingested 25I-NBOMe and mushrooms. A short time later, he started to vomit and began seizing until he eventually passed out. Resuscitation efforts were made, but were unsuccessful. He was transported to a local hospital, where he died three days later of multi-system organ failure following cardiopulmonary arrest. The hospital admission samples were negative for ethanol and basic drugs and their metabolites. The hospital serum confirmed positive for delta-9-tetrahydrocannabinol (THC) and carboxy-THC at 4.1 and 83 ng/mL, respectively. On the basis of the case history, the hospital blood and urine were sent to NMS Labs for NBOMe and psilocin confirmation. The blood was positive for 25I-NBOMe, and the urine was positive for 25C-, 25H- and 25I-NBOMe, as well as, psilocin. Antemortem and postmortem blood were also sent to AIT Laboratories for NBOMe confirmation. The antemortem blood confirmed positive for 25I-NBOMe with a concentration of 0.76 ng/mL. The manner of death was ruled an accident as a result of combined 25I-NBOMe and psilocin intoxication.

Introduction

NBOMe drugs are novel, substituted derivatives of the 2C class of phenethylamines with hallucinogenic and stimulant properties (see Figure 1). They are potent full agonists of the serotonin 5-HT_{2A} receptor. NBOMe refers to the *N*-benzoylmethoxy moiety of the structure; methoxy is 'OMe' in shorthand notation (1).

25I-NBOMe is 4-iodo-2,5-dimethoxy-*N*-(2-methoxybenzyl) phenethylamine, where the 2C substructure contains an iodine atom. The other NBOMe compounds are derived by exchanging the iodine with bromine (25B-), chlorine (25C-) or hydrogen (25H-). The 2-methoxybenzyl group significantly enhances the activity at the 5-HT_{2A} receptor, which means very low doses are needed to achieve the powerful hallucinogenic effects, compared with LSD or ecstasy (2). The World Health Organization cautions that they pose '. . . especially serious risk to public health and society and are of no recognized therapeutic use by any party' (1), yet they remain accessible through continued clandestine manufacturing.

NBOMe drugs have been developed over the past 10 years—they first appeared in the scientific literature in 2011 and have been available over the Internet since 2010 (3). From November 2011 to June 2013, the System to Retrieve Information from Drug Evidence (STRIDE) reported 43 cases that included 25I-, 25C- and 25B-NBOMe. The National Forensic Laboratory Information System (NFLIS) had not reported findings before June 2011, but since then there have been 959 reports of NBOMe usage spanning 35 states. On 15 November 2013, the Drug Enforcement Administration issued a final order to temporarily schedule 25I-, 25C- and 25B-NBOMe into the Controlled Substances Act (CSA). NBOMe is normally seen as uncut powder or diluted into micro doses and applied to blotter paper (4). The DEA reports that NBOMe has been identified in 'powders and liquid solutions' as well as in 'food items laced with these substances'.

Previous case reports have described the following symptoms: agitation, aggression, confusion, visual and auditory hallucinations, tachycardia, hypertension, seizures, vomiting, rhabdomyolysis, organ failure and death (1, 3). NBOMe is often marketed as legal LSD, a 'research chemical', and sometimes misidentified as ecstasy (1, 5, 6). This poses a significant safety concern when consumers think they are taking LSD or ecstasy but are actually ingesting NBOMe because the symptoms can prove to be more severe and require a higher level of care from medical professionals. This also means there would be an increased likelihood of overdose, due to the larger than intended dosage taken by an individual who believes they are about to experience an LSD trip. Unlike NBOMe, LSD is rarely directly attributable to death. The following report documents the first analytically confirmed death involving 25I-NBOMe in Washington State.

Background

A 15-year-old male went to a party in August 2014. From witness reports, there were drugs being sold by the DJ of the party, which included mushrooms and '25I (acid)'. The decedent was seen taking mushrooms and drinking an unknown clear liquid from a sealed vial. About an hour later, he started to vomit and convulse but was still coherent enough to tell people, 'This is awesome!' He was laughing and telling people he was fine, however, he continued to have more convulsions until he eventually passed out. He was transported to a nearby fire station, where resuscitation efforts were made, but were unsuccessful. He was ultimately relocated to a local hospital where he was intubated. He presented with acute renal failure with a serum creatine concentration of ~4 mg/dL, liver failure with aspartate aminotransferase and alanine aminotransferase in the tens of thousands and was coagulopathic with disseminated intravascular coagulation (DIC)-like presentation. He also had a creatine phosphokinase concentration of ~66,000 mcg/L. He ultimately died from multi-system organ failure following cardiopulmonary arrest 3 days after drug ingestion.

Methods and results

The following hospital samples were submitted for testing to the Washington State Patrol Toxicology Laboratory: hospital blood, hospital serum, hospital urine and postmortem peripheral blood. All of the hospital samples were collected at the time of

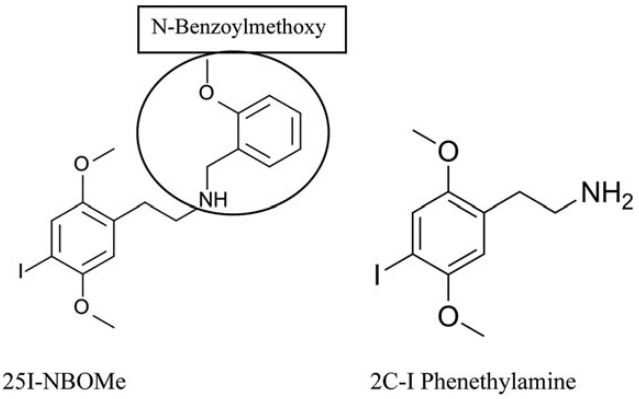

Figure 1. Chemical structure of 25I-NBOMe compared with 2C-I phenethylamine.

admission and the peripheral blood at the time of the autopsy. The hospital blood was tested by Headspace-Gas Chromatography for the presence of volatiles and was negative for acetone, ethanol, isopropanol and methanol. An enzyme multiplied immunoassay technique was employed to test the hospital blood for nine different drug classes, which includes amphetamines (cutoff concentration: 200 ng/mL), barbiturates (cutoff: 100 ng/mL), benzodiazepines (cutoff: 100 ng/mL), cannabinoids (cutoff: 10 ng/mL), cocaine metabolite (cutoff: 100 ng/mL), methadone (cutoff: 100 ng/mL), opiates (cutoff: 20 ng/mL), phencyclidine (cutoff: 10 ng/mL) and tricyclic antidepressants (cutoff: 100 ng/mL). The hospital blood tested presumptive positive for cannabinoids. Liquid chromatography/tandem mass spectrometry (LC–MS-MS) was utilized to confirm the presence of delta-9-tetrahydrocannabinol (THC) and carboxy-THC in the submitted serum at concentrations of 4.1 and 83 ng/mL, respectively. The hospital blood was also tested by gas chromatography/mass spectrometry for the presence of alkaline drugs and their metabolites, and no drugs were detected.

The hospital blood and urine were sent to NMS Labs in Willow Grove, PA, to be analyzed for the presence of NBOMe and psilocin. The blood was tested by LC–MS-MS and was positive for 25I-NBOMe. The reporting limit is 0.50 ng/mL. The urine was also examined by LC–MS-MS and was positive for 25C, 25H and 25I-NBOMe. The reporting limit was 0.50 ng/mL. In addition, the urine was screened by liquid chromatography/time of flight-mass spectrometry and LC–MS-MS for psilocin and confirmed its presence using both methods. The reporting limits are 10 and 20 ng/mL, respectively.

The hospital and postmortem peripheral blood were also sent to AIT Laboratories in Indianapolis, IN, to quantitate NBOMe. The samples were extracted using a protein precipitation/solvent extraction with acetonitrile. The organic supernatant was evaporated to dryness under nitrogen gas flow and reconstituted in deionized water for analysis by LC–MS-MS. The column was a Waters Acquity BEH C18, 2.1 × 100 mm, 1.7 µm at 50°C with a constant flow rate of 0.5 mL/min. The gradient was 95–5% solvent B (0–4 min), 60–40% B (4–4.7 min), 100% B (4.7–4.8 min), 95–5% B at 4.8 min. Refer to Table I for UPLC parameters. For the mass spectrometer, the desolvation gas flow was set to 850 L/h at a temperature of 450°C. The source temperature was set at 140°C. The capillary voltage was set at 0.60 kV and the collision gas flow to 0.30 mL/min. The cone voltage was set at 16 V for 25I-NBOMe and 30 V for the internal standard.

Table I
Waters Acquity UPLC Parameters

Total time (min)	Flow rate (mL/min)	% *A*	% *B*
Initial	0.500	95.0	5.0
0.50	0.500	95.0	5.0
4.00	0.500	60.0	40.0
4.70	0.500	0.0	100.0
4.80	0.500	95.0	5.0
Mobile phases	*A* (0.1% formic acid in DI water); *B* (0.1% formic acid in acetonitrile)		
Column	Waters Acquity BEH C18, 2.1 × 100 mm, 1.7 µm at 50°C		
Retention time (min)	25I-NBOMe (4.5) 25I-NBOMe-d3 (4.5)		

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Table II
Waters TQD MS Parameters

Analyte	Ion transition	Type	Dwell time (ms)	Cone voltage (V)	Collision energy (eV)
25I-NBOMe	428.0 > 121.0	Quantifying	0.02	16	24
25I-NBOMe	428.0 > 91.0	Qualifying	0.02	16	58
25I-NBOMe-d3	431.1 > 92.1	Internal standard	0.02	30	60
Capillary voltage (0.60 kV)	Extractor voltage (3 V)	Source temperature (140°C)	Desolvation temperature (450°C)	Desolvation gas flow (850 L/h)	Collision gas flow (0.30 mL/min)

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Table III
Method Validation Results

Parameter	25I-NBOMe
Limit of detection (LOD)	0.2 ng/mL
Limit of quantitation (LOQ)	0.5 ng/mL
Linearity	0.5–20 ng/mL
Coefficient of determination (R^2)	0.9987–0.9999
Accuracy	
1.5 ng/mL	
Intrarun	94.1–100.2%
Interrun	97.4%
6 ng/mL	
Intrarun	95.9–102.0%
Interrun	99.8%
Imprecision	
1.5 ng/mL	
Intrarun	1.1–6.7%
Interrun	4.6%
6 ng/mL	
Intrarun	0.4–3.7%
Interrun	2.5%
Ion suppression	
1.5 ng/mL	
Matrix effect	1.05 (6.9% CV)
Response effect	1.08 (9.4% CV)
10 ng/mL	
Matrix effect	1.03 (6.9% CV)
Response effect	1.00 (9.8% CV)
16 ng/mL	
Matrix effect	1.04 (4.2% CV)
Response effect	1.02 (7.7% CV)
Carryover	None detected at 200 ng/mL
Exogenous interferences	None detected

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Refer to Table II for MS parameters. The limit of quantitation for this method is 0.5 ng/mL. Refer to Table III for method validation data.

The hospital blood confirmed positive for 25I-NBOMe with a concentration of 0.76 ng/mL. The peripheral blood was negative for all NBOMe drugs. The autopsy showed no remarkable findings at all, and the manner of death was ruled an accident as a result of combined 25I-NBOMe and psilocin intoxication.

Discussion

The NBOMe drugs are abused for their strong hallucinogenic impact on the brain. They are commonly characterized as 'contemporary LSD' and are even being marketed as such. The frequency of abuse has rapidly increased over the past couple of years as supported by various nonfatal and fatal intoxications around the world. Routes of administration include sublingual ('blotter' paper), buccal, nasal, oral, intravenous, intramuscular, rectal and smoking.

Users describe subjective 'positive' effects to include: euphoria, mental/physical stimulation, strong open and closed eye visuals, increased awareness and appreciation of music, increased associative and creative thinking, feelings of love and empathy and life-changing spiritual experiences (7). 'Neutral' effects are described as pupil dilation, unusual body sensations, difficulty focusing, slight increase in heart rate, change in time perception, general change in consciousness and yawning; while the 'negative' effects include confusion, thought repetition, nausea, scrambled communication, insomnia, paranoia, fear, panic, unwanted and overwhelming feelings, vasoconstriction, peripheral numbness and the swelling of extremities. These negative effects are similar to serotonergic hallucinogens but users reported greater 'negative effects while high' (1, 7).

In 2013, Belgium reported three nonfatal intoxications due to 25I-NBOMe to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (1). All three were admitted to the hospital having consumed synthetic LSD. Their symptoms included lowered consciousness, insufficient breathing, tachycardia, hypertension, and dilated pupils. Their treatment included sedation, intubation and ventilation. In all three instances, 25I-NBOMe was confirmed analytically.

In the UK in 2013, seven nonfatal cases were reported where 25I-NBOMe was confirmed analytically (8). In one case, a 29-year-old male injected 3 mL of the liquid he bought as 25I-NBOMe. He was discharged from the hospital after 43 days. His symptoms included agitation, aggression, seizures, self-harming behavior associated with tachycardia, hypertension, oxygen desaturation and rhabdomyolysis. He was treated with resuscitation with intubation, ventilation, intravenous sedation, antibiotics and fluids. He had ongoing jerking seizure-like movements that were treated with atracurium infusion, a skeletal muscle relaxant. The other six subjects took the drug at a house party. 25I-NBOMe was purchased from the Internet in capsules that contained the powder. Three of the six swallowed the capsules and the other three nasally insufflated the powder from the capsules. The quantity taken is unknown. One of the six subjects had to be hospitalized for 5 days. The others were discharged the same day as admission or within 15 h of admission. All were treated with benzodiazepines.

From 2012 to 2014, there have been 19 nonfatal cases reported in the United States due to NBOMe alone or with other drugs, including ethanol, THC, ketamine and 2-CE (9–13). Additionally, there have been 16 reported deaths in the United States since 2012. Eleven of these cases included acute toxicity. Three of the cases included unpredictable, violent behavior due to 25I-NBOMe toxicity and ultimately led to death. The average age of the individuals was 20 years old (range, 15–29 years). Walterscheid *et al.* reported two of the 16 deaths, where both subjects had attended raves (14). The first was a 21-year-old male who took 'acid' while driving and had a sudden onset of violent behavior where he pulled over and destroyed the interior of the car. He then became unresponsive. His autopsy was unremarkable internally, similar to the case presented in this article. The second subject was a 15-year-old female who became ill outside of the rave and rapidly deteriorated as she was transported to the hospital. Her autopsy showed superficial internal injuries, but otherwise unremarkable, as well.

In January 2014, Poklis et al. (15) reported quantitative values for 25I-NBOMe in fluids and tissues for a death where the decedent suffered from bizarre behavior that led him to fall/jump from his apartment balcony. The 19-year-old male had ingested blotter paper that contained the NBOMe, and it was reported that this was his first experience taking the drug. The postmortem peripheral blood concentration was 0.405 ng/mL, and the urine concentration was 2.86 ng/mL.

Psilocin is the pharmacologically active, hallucinogenic metabolite of psilocybin. Effects include anxiety, paranoid delusions, hyperreflexia, dilated pupils, disorientation, hallucinations, tachycardia, vomiting and paresthesia (16). Psilocin presence was confirmed in this case by NMS Labs, and the medical examiner ruled death was caused by acute combined NBOMe and psilocin toxicity. It is interesting to note the presence of multiple hallucinogenic substances in the decedent's system. Psilocin acts on the $5HT_{2A}$ receptor, as well, with the principal effect being perceptual distortion (17). It is unknown at this time whether interactions occur between psilocin and NBOMe substances.

Conclusion

As shown in the case review above, the NBOMe drugs are powerful hallucinogens that continue to pose a danger to society. These novel substances are sold as LSD and many times, wrongly identified as ecstasy, which has made identification and treatment of intoxication a difficult task. There have been nonfatal and fatal cases observed around the world, but this is the first confirmed death in Washington State; and to our knowledge, is the first reported quantitative antemortem blood concentration of 25I-NBOMe which resulted in a death.

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