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BRIEF COMMUNICATION

Case series: toxicity from 25B-NBOMe – a cluster of N-bomb cases

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ABSTRACT

Background A new class of hallucinogens called NBOMes has emerged. This class includes analogues 25I-NBOMe, 25C-NBOMe and 25B-NBOMe. Case reports and judicial seizures indicate that 25I-NBOMe and 25C-NBOMe are more prevalently abused. There have been a few confirmed reports of 25B-NBOMe use or toxicity. **Report** Observational case series. This report describes a series of 10 patients who suffered adverse effects from 25B-NBOMe. Hallucinations and violent agitation predominate along with serotonergic/stimulant signs such as mydriasis, tachycardia, hypertension and hyperthermia. The majority (7/10) required sedation with benzodiazepines. **Analytical method** 25B-NBOMe concentrations in plasma and urine were quantified in all patients using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. Peak plasma levels were measured between 0.7–10.1 ng/ml. **Discussion** The NBOMes are desired by users because of their hallucinogenic and stimulant effects. They are often sold as LSD or synthetic LSD. Reported cases of 25B-NBOMe toxicity are reviewed and compared to our series. Seizures and one pharmacological death have been described but neither were observed in our series. Based on our experience with cases of mild to moderate toxicity, we suggest that management should be supportive and focused on preventing further (self) harm. High doses of benzodiazepines may be required to control agitation. Patients who develop significant hyperthermia need to be actively managed. **Conclusions** Effects from 25B-NBOMe in our series were similar to previous individual case reports. The clinical features were also similar to effects from other analogues in the class (25I-NBOMe, 25C-NBOMe). Violent agitation frequently present along with signs of serotonergic stimulation. Hyperthermia, rhabdomyolysis and kidney injury were also observed.

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Background

Since 2010, there have been reports of a new class of hallucinogenic drugs called NBOMes being sold and used recreationally.[1,2] The class currently includes the analogues 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe, which vary by one halogenated side group. The 25-I and 25-C analogues appear the most prevalent agents available for recreational use.[2–5] In contrast, there are only 5 individual cases reported of 25B-NBOMe use or toxicity reported.[2,6,7,8,9] There are no prior reports of clusters of patients with 25B toxicity. There are isolated reports of 25C, 25D, 25E and 25G-NBOMe detection in drug market confiscations [10,11] however, there are no reports of toxicity in the peer reviewed literature yet.

Report

This report describes a case series of 10 patients with 25B-NBOMe toxicity confirmed in biological specimens. They presented to the Emergency Department (ED) in two clusters.

This is an observational case series. The authors attest that this study complies with the 2012 Guidelines for Observational Studies as specified by the National Ethics Advisory Committee, New Zealand.

In the first cluster, four violently agitated patients were brought to our ED by Police. We will also describe another cluster of six patients who presented to the same ED a month later over a 12 h period.

Cluster one (patients 1–4)

Police and ambulance were called to a party where four adult males were behaving bizarrely and aggressively. The patients had reportedly taken a white powder identified as 2C-B by nasal insufflation.

Patient one was a 24-year-old male who was agitated, aggressive and appeared to be hallucinating. Police described him running into walls and repeatedly head-butting a concrete floor. He could not be reasoned with so was restrained and handcuffed. He was given two 7.5 mg increments of intramus-

cular (IM) midazolam. On arrival at the Emergency Department he was grunting and struggling against his restraints. He had profuse sweating, temperature was 37.8°C, respiratory rate (RR) 25 rpm, heart rate (HR) 175 bpm, blood pressure (BP) 180/95 mmHg and pupils were 6 mm and reactive with nystagmus. An associate of the patient said the four men had snorted a fine white powder at the party that he thought was "2CB".

The patient received 5 mg of haloperidol and further increments of midazolam totalling 23.5 mg over 60 min. He continued to struggle aggressively. His heart rate remained high at 135 bpm, temperature 38.5°C and BP was elevated at 200/90 mmHg. The patient was anaesthetized and intubated to prevent self-harm and rhabdomyolysis.

A rapid sequence induction was performed using propofol, fentanyl and suxamethonium. He was transferred to the intensive care unit. He had an ECG which showed sinus rhythm. Initial investigations returned a creatinine kinase (CK) of 8255 IU and a troponin I of 399 ng/L (normal range 0–34).

After 9 h he was weaned off Propofol. He was calm and cooperative so was ex-tubated. He had no recall of events from the previous evening. He remained under observation. CK peaked at 18361 IU/L, troponins declined and serial ECGs were normal. Liquid chromatography-mass spectrometry of urine identified 25B-NBOMe. Drug screening revealed Carboxy-THC just above detection limit (15 µg/L) and nicotine but no detectable ethanol.

At the party three other patients were disoriented, combative and also appeared to be hallucinating. The three were handcuffed and brought to the ED.

Patient two was a 21-year-old male. He was given 10 mg midazolam IM at the scene. On arrival at the ED he had a temperature of 36.5°C HR 110 bpm, BP 150/90 mmHg, RR 24 rpm, dry warm skin and pupils both 6 mm. He was given midazolam increments totalling a further 35 mg over the subsequent hour. His airway was maintained and his behaviour was manageable. Plasma ethanol was 12 mmol/L. 25B-NBOMe was detected in the urine.

Patient three was a 22-year-old male. His arrival vital signs were temperature 38°C, HR 145 bpm, BP 160/89 mmHg, RR 24 rpm, and pupils both 7 mm. He received a total of 55 mg of midazolam and 4 mg of lorazepam parenterally. He was cooperative enough to allow removal of restraints 3 h after arrival.

Patient four was a 26-year-old male. He also received 10 mg of midazolam IM by an ambulance officer. On arrival at the ED he was diaphoretic, drooling and struggling against his handcuffs. He was covered in contusions and grazes. His initial vital signs were HR 135 bpm, BP 165/110 mmHg, RR 24 rpm and pupils were 7 mm. He was given 6 mg of midazolam IV and after 90 min was in a sedated and co-operative state. Five hours after arrival his vital signs had returned to normal.

Cluster two (patients 5–10)

Patient five was a 23-year-old man who had been drinking with friends. On the walk home, he became disorientated and aggressive then sustained a hand injury punching a window. Police were called. On arrival to ED he was agitated, combative and appeared to be hallucinating - reaching out at objects in

the air. His pupils were dilated that 8 mm. Vital signs were unobtainable until he had received a total of 35 mg of midazolam IM IV and 75 mg of ketamine IV. Seven hours later he was orientated and cooperative. He had no recall of drug use. He was discharged with planned definitive management of his injuries.

Patient Six was a 42-year-old man who told his friends that he has taken "acid". He was violently agitated and shouting. He was picked up and restrained by police then transferred to ED by ambulance. On arrival he was sweating profusely with dilated pupils, increased muscle tone, tremor and hyper-reflexia but no clonus. His behaviour settled after a total of 12 mg midazolam IV. He was discharged 13 h after arrival.

Patient seven was a 30-year-old male who had reportedly been drinking alcohol and snorting an unknown white powder. He started hallucinating and quickly became very agitated and combative. Police restrained the patient and transferred him to the ED. At 2½ h post insufflation he was still agitated, internally preoccupied and uncooperative. He was given a total of 15 mg midazolam IV and 2 mg of lorazepam IV. After another 3 h he was cooperative, conversant and orientated. He was later discharged from the ED with a family member.

Patient eight was a 30-year-old man picked up by police in a confused and agitated state. He was uncooperative so brought in handcuffed. He had a flushed face with dilated pupils and dry mucous membranes. He was sweating profusely. He had increased muscular tone, hyper-reflexia and inducible clonus. His heart rate 120 bpm and BP 160/100 mmHg. He was much calmer after 5 mg of midazolam IV. Later he disclosed he had taken his first is dose of 'N-bomb' earlier. His vital signs normalised and he was calm enough to be discharged 3½ h later.

Patients 9 and 10 were two 26-year-old females who ingested one capsule containing white powder each - sold to them as '2C- B'. They became concerned when they realised that each capsule was intended for multiple doses so they self presented to the ED anticipating problems from over-dosage. On arrival both were agitated, tachycardic and hypertensive. Neither required sedation. Their agitation and vital signs settled and they were discharged 3 h later. Clinical features and management of patients 1–10 are summarised in Table 1.

Quantification and analytical method

25B-NBOMe (4-bromo-2,5-dimethoxy-N-(2-methoxybenzyl)-phenethylamine) concentrations in plasma and urine were quantified by a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. At the time of analysis no isotopically labelled internal standards for NBOMe's were available and instead 25D-NBOMe was used. The samples were screened first and none of them contained this compound. For both plasma and urine, 20 µl prepared samples were injected into the LC-MS/MS system (Agilent 1290 Infinity Series High Performance Liquid Chromatograph the connected to an Agilent 6460 Series Triple Quadrupole Mass Spectrometer; Agilent Technologies, Santa Clara, CA). A Poroshell 120 EC C18 2.7 µm, 50 mm × 3.0 mm column (Agilent Technologies) was used for separation under gradient elution with acetonitrile and 0.2% formic acid and 10 mmol/l ammonium formate in water. The mass spectrometric

Table 1. Patient demographics and clinical features.

Case	Age (years)	Sex (M/F)	Clinical features										Sedation given			Notes	Discharge (h)
			Hallucinating	Panic	Pupils Dilated	Tone increased	Inducible clonus	Sweaty	Police restraint	Temp	HR (bPM)	BP (mmhg)	Midazolam (mg IV)	Other agents			
Case 1	24	M	Y	Y	Y	Y	Y	Y	Y	Y	37.8	175	200/98	45	Haloperidol 5mg IV	Intubated, ICU	60
Case 2	21	M	Y	Y	Y	Y	Y	Y	Y	Y	36.7	110	150/90	10	Diazepam 10mg IV		15
Case 3	22	M	Y	Y	Y	Y	Y	Y	Y	Y	38.0	145	160/80	15			15
Case 4	26	M	Y	Y	Y	Y	Y	Y	Y	Y	38.0	135	170/110	6			15
Case 5	23	M	Y	Y	Y	Y	Y	Y	Y	Y	-	108	160/70	35	Ketamine 75mg IV	Self injury on broken glass	7
Case 6	42	M	Y	Y	Y	Y	Y	Y	Y	Y	37.0	120	120/60	0	Lorazepam 2mg IV	Patient sold 'synthetic acid'	13
Case 7	30	M	Y	Y	Y	Y	Y	Y	Y	Y	36.6	100	120/60	15		Patient sold 'synthetic acid'	3
Case 8	30	M	Y	Y	Y	Y	Y	Y	Y	Y	37.8	120	160/100	5		peak creatinine 120 µmol/L	3.5
Case 9	26	F	Y	Y	Y	Y	Y	Y	Y	Y	37.3	117	150/75	0		Patient sold '2CB'	2.5
Case 10	26	F	Y	Y	Y	Y	Y	Y	Y	Y	37.0	120	140/65	0		Patient sold '2CB'	3

detection was in the positive mode with 25B-NBOMe monitored at 380.1/121.1 and 380.1/91.1 eluting at 2.06 min and 25D-NB2OMe at 316.1/121.1 and 316.1/91.1 eluting at 2.01 min. Linear calibration curves were used for the range 0.1–10 µg/l in plasma and 1–200 µg/l in urine. Interday precision and bias for quality control samples (1 and 10 µg/l in plasma, 10 and 100 µg/l in urine) were within 8% and within 18% at the lower limit of quantification (0.1 µg/l in plasma, 1 µg/l in urine). Recoveries were complete and matrix effects were accounted for by the internal standard. Patient samples were analysed in duplicate. Plasma and urine samples were screened against a database of 150 prescription medications and drugs of abuse (including 18 different amphetamine-type substances). Results are reported in Table 2.

Discussion

NBOMes

Over the last two years, a new class of psychoactive drugs known as NBOMes (or "N-bomb") has emerged. 25I-NBOMe was first detected in 2012 in a drug confiscation by Swedish Police.[12] Since then, availability and use of these analogues have steadily increased. These drugs are desired for their hallucinogenic properties.

The term NBOMe describes a group of drugs modified from a class of hallucinogens called the 2C-X family (of which 2C-B is the prototype). The attachment of a modified phenyl ring to the base 2C-X molecule creates the NBOMe structure. The most common analogues are 25I-NBOMe 25C-NBOMe and 25B-NBOMe which vary by one halogenated functional group.[13]

The NBOMe series were first synthesized in 2003 by Elz, Heim and colleagues at Free University, Berlin for use as tools to activate 5-HT_{2a} (serotonin) receptors. [14,15]. Of these analogues, Cimbi-36 (25B-NBOMe), was shown to have a high agonistic affinity for the 5-HT_{2a} receptor *in vitro*. [16,17] 25B-NBOMe has higher affinity for the 5-HT_{2a} receptors than for other N-benzyl-substituted phenethylamines which may indicate relatively higher potency. [16,18] Stimulation of the 5-HT_{2a} receptor within the cerebral cortex can evoke hallucinations and severe behavioural disturbances. [19]

Potency of the NBOMe drugs is reportedly in the same range as that for Lysergic acid diethylamide (LSD). [12] Based on information derived from drug forums, the effect threshold following sublingual administration of 25C-NBOMe is reported to range from 100 to 250 µg. [4,10] Duration of effect reported by users is between 3 and 13 h (modal duration was 6 h). [2]

The diagnosis of NBOMe intoxication can be difficult but suspected when a patient's history is of 'NBOMe', 'synthetic LSD' or 'synthetic speed' use. Associated clinical features include internal preoccupation, violent agitation and hallucinations. Serotonergic effects such as mydriasis, sweating, agitation, tachycardia hypertension, hyperreflexia, increased muscle tone and clonus can be present but difficult to distinguish from sympathomimetic excess. [20–22] The most common adverse clinical effects reported to a poison centre by users were tachycardia, agitation, hallucinations, hypertension and confusion. [5,23] The most common users are male (74%) with a median age of 18 years. [5]

Table 2. Quantification of 25B-NBOMe and toxicology screening from biological specimens.

Case	Age (Y)	Sex M/F	Plasma			Urine		
			Time from ED arrival (minutes)	25B-NBOMe (ng/ml)	Ethanol (mmol/l)	Time from ED arrival (minutes)	25B-NBOMe (ng/ml)	Urine drug screen by mass spectrometry (excluding treatment drugs)
Case 1	24	M	75 395 660 1440	1.9 0.3 <0.1	0	690 765	178 55	Nicotine, tetrahydrocannabinol carboxylic acid (THC-COOH)
Case 2	21	M	30655	10.7	12.0	660	4.4	Ethanol. No other drugs detected
Case 3	22	M	50585	5.1 0.2	0.0	675	2.6	No other drugs detected
Case 4	26	M	15655	6.1 0.5	9.0	660	4.3	Ethanol. No other drugs detected
Case 5	23	M	5	1.0	Not done			No urine specimen available
Case 6	42	M	20	3.5	Not done	495	17	Amphetamine, nicotine, metamphetamine, THC-COOH
Case 7	30	M	30	2.3	Not done	220	29	Caffeine, midazolam, tramadol, butylone
Case 8	30	M	10	1.0	12.0	50	7.6	Caffeine, nicotine, THC-COOH
Case 9	26	F	4	2.0	0			No urine specimen available
Case 10	26	F	4	0.7	0			No urine specimen available

25B-NBOMe

The full chemical name for 25B-NBOMe is 4-bromo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine. We searched English-language scientific articles for reports of 25B-NBOMe exposure. MED-LINE (PubMed) database was searched using medical subject headings "NBOMe," "25B," "N-benzylmethoxy" and "N-bomb" through to August 2014. There were only four known peer-reviewed reports describing five patients with toxicity following use of 25B-NBOMe.

Poklis described a 19-year-old man who was found in status epilepticus.[9] The patient had other serotonergic features: hyperthermia (40 °C), tachycardia and hypertension (152 bpm, 145/90 mmHg). He required intubation and active cooling but appeared to make a full recovery with supportive management. The presence of 25B-NBOMe was confirmed in both serum and urine samples.

Two additional cases were reported by Tang and co-workers in 2014.[6] The first was a 17-year-old male patient with a similar presentation: seizures, tachycardia (140 bpm), hypertension (215/94 mmHg), hyperthermia (38.4 °C) and sweating. The second, a 31-year-old male, presented with 'sympathetic crisis': agitation, tachycardia (162 bpm), hypertension (160/123 mmHg), hyperthermia (39.6 °C), sweating and mydriasis. The second patient did not require intensive care treatment but developed rhabdomyolysis (creatinine kinase peak 1107 U/L) and renal failure (urea 6.2 mmol/L creatinine 170 µmol/L). In both patients, 25B-NBOMe 25I-NBOMe was identified in urine samples.

Laskowski reported a 15-year-old male who presented with agitation after taking a blotter of '25I-NBOMe'. He had dilated pupils with a heart rate 111 bpm, blood pressure 177/93 mmHg and a temperature of 99.80 F (37.70C) He had two generalised tonic clonic seizures. With supportive management he recovered over 8 h. 25B-NBOMe was detected in serum but not 25I-NBOMe.[1]

Yoshida reported a 20-year-old male who ingested a blotter paper laced with NBOMe and became agitated and violent. An hour after ingestion he was stuporous with hypotension (systolic BP 90 mmHg), tachycardia (156 bpm), tachypnea (48/min) and severe hyperthermia (41.5 °C). He was admitted for intensive care and active cooling. His condition deteriorated. He developed rhabdomyolysis, a bleeding diathesis and multi-organ failure. He died 3 days after admission.[8]

Our patients were physiologically similar to these 25B-NBOMe cases. Autonomic signs such as mydriasis, tachycardia, hypertension and hyperthermia were seen consistently. Neuromuscular signs such as increased tone and inducible clonus were seen in only 3/10 cases. These clinical features could easily be interpreted as sympathomimetic toxicity. One of our cases required intubation and active cooling however, none of our cases had toxic seizures. The other major presenting features were behavioural agitation, hallucinations and panic. Eight of our cases were so agitated and demonstrably violent that they required police restraint and escort to hospital.

From our data, and the reported cases, 25B-NBOMe appears to cause similar physiological and psychoactive effects compared to 25I and 25C NBOMe analogues.[23–25]

The management of patients with mild to moderate NBOMe intoxication is often focussed on controlling agitation and preventing physical harm. Many users get injuries arising from their violent agitation or attempts at restraint.[25–27] Patients with only minor agitation may be managed without pharmaceutical intervention, by providing a quiet, non-stimulating environment and a nursing attendant. More severely agitated patients require physical restraints to prevent self-harm; rapid pharmacological sedation with benzodiazepines should be commenced concurrently.

As demonstrated in our series, large doses of benzodiazepines may be required to overcome agitation, tachycardia and hypertension. One patient was still combative after a large cumulative dose of IV midazolam (35 mg). The addition of titrated ketamine appeared effective in controlling the patient's agitation.

Hyperthermia may be present due to serotonergic and adrenergic excess. Fuelled by agitation, core temperature may rise precipitously resulting in rhabdomyolysis, acute kidney injury then multi-organ failure.[8] Large doses of benzodiazepines again should be first line treatment with early paralysis and active cooling if required.

Seizures are frequently reported after 25I-NBOMe and 25B-NBOMe use. In a retrospective review of 148 cases of NBOMe use (mostly 25I-NBOMe), 8.8% had associated seizures.[5] Poklis et al. reported a case of 25B-NBOMe intoxication that went into status epilepticus. Lorazepam IV and a phenytoin infusion were required to terminate seizure activity.[9]

Patients in our series suffered mild to moderate toxicity without seizures and had measured 25B-NBOMe values between 0.1 and 10.7 mg/ml. One patient developed rhabdomyolysis with a peak creatinine kinase of 18362 U/L. Three patients had elevated serum creatinine (113–130 $\mu\text{mol/l}$) without CK rise. All improved with supportive fluid management.

Quantification of 25B-NBOMe in biological samples has been reported in two cases.[8,9] Both suffered hyperthermia, rhabdomyolysis and renal injury. The Poklis case with status epilepticus had serum levels of 180 ng/l.[9] The case reported by Yoshida et al. had features of serotonin toxicity and died from multi-organ failure. Peak plasma levels were 3.15 ng/ml 25B-NBOMe and 0.43 ng/ml 25C-NBOMe.

By comparison only six cases of 25I-NBOMe intoxication have been reported with quantitative confirmation. Levels of 28 and 36 ng/ml were measured in two patients who suffered seizures and required mechanical ventilation in intensive care. [25]. A patient with a level of 7.5 ng/ml had seizures but improved quickly and made a full recovery within 5 h. Patients with levels measured of 0.76 and 0.034 ng/ml respectively suffered moderate toxicity with presumed full recovery. One patient took one blotter of 'acid' and in an agitated delirium fell from a multi-storey building. Plasma 25I-NBOMe at post mortem was 0.405 ng/ml. [25]

The users in our series were sold or given 25BNBOMe as 'Synthetic LSD', 'synthetic speed' and "2C-B". NBOMes also appear to be commonly sold as LSD which is unfortunate as sellers are substituting LSD with a more potent and potentially lethal counterfeit drug.[2,28] The minimum psychoactive dose of NBOMes is so small that the risk of measurement error is high. If users think they are using a less potent drug then the risk of inadvertent over-dosage is compounded.

Of most concern is the potential for fatal toxicity with recreational use. The U.S. Drug Enforcement Agency has reported 19 cases where medical examiners have linked 25I-NBOMe, 25C-NBOMe or 25B-NBOMe to the deaths of individuals, aged 15 to 29 years, between March 2012 and August 2013 in the U.S.[29] The Advisory Council on the Misuse of Drugs (U.K.) reported a further 8 fatalities associated with the NBOMe drugs.[12] In some cases 25I-NBOMe appears to have caused death through pharmacological toxicity.[31–33]

NBOMe user deaths have also been reported where drug induced psychosis has led to falls, violence or other trauma [3,34] or caused suicidal behaviour.[28] 25B-NBOMe specifically has been implicated in one pharmacological death [8] and three other drug related deaths reported in general media.[35–37]

Conclusion

There have been few reports of 25B-NBOMe toxicity to date. In our series, 25B-NBOMe intoxication caused hallucinations with violent agitation. Serotonergic/sympathetic signs were observed; mydriasis, tachycardia, hypertension and hyperthermia. These effects were also similar to numerous reports

involving other analogues in the class; 25I-NBOMe and 25C-NBOMe. 25B-NBOMe was detected and quantified in blood and/or urine in all our cases. 25B-NBOMe has lethal potential however, no deaths occurred in our series.

Declaration of interest

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

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