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CASE REPORT

Severe Toxicity to the New Psychoactive Substances 3-Hydroxyphencyclidine and N-Ethylhexedrone: an Analytically Confirmed Case Report

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Abstract

Introduction 3-Hydroxyphencyclidine (3-HO-PCP) is a new psychoactive substance (NPS) and a hydroxy derivative of phencyclidine (PCP), and N-ethylhexedrone (Hexen) is a synthetic cathinone. We describe an analytically confirmed case of acute toxicity related to the use of both 3-hydroxyphencyclidine and N-ethylhexedrone.

Case Report A 56-year-old male was brought to the Emergency Department by ambulance with hyperthermia (39.9 °C), sinus tachycardia (150 beats per minute), reduced consciousness, ocular clonus, and vertical nystagmus. He was treated with cooled intravenous (IV) fluids and IV benzodiazepines. Following 1 hour of treatment, his temperature fell to 37.7 °C, he developed rhabdomyolysis (creatine kinase peaked at 5999 IU (normal range < 229 IU)): he was managed with supportive measures and was discharged after 25 hours. The patient admitted regular use of Hexen and recent use of 3-HO-PCP. Analysis of urine and serum identified 3-hydroxyphencyclidine and metabolites, N-ethylhexedrone and metabolites, and clephedrone and metabolites.

Discussion This is a case of analytically confirmed toxicity to 3-HO-PCP and N-ethylhexedrone. The acute toxicity reported in this patient is consistent with the use of 3-HO-PCP, but there were sympathomimetic and serotonergic features potentially consistent with the cathinone N-ethylhexedrone. The description of the acute toxicity of NPS, such as these, is vital to aid medical toxicologists and emergency medicine physicians treating patients who use them.

Keywords 3-Hydroxyphencyclidine · N-Ethylhexedrone · NPS (novel psychoactive substance) toxicity · Cathinone · PCP

Background

3-Hydroxyphencyclidine (3-HO-PCP) is a hydroxy derivative of phencyclidine (known as PCP) [1, 2]. Although the synthesis of 3-HO-PCP was first described in 1982, it was not reported to be used recreationally as a new psychoactive substance (NPS) until 2009 following a report on the drug forum website www.bluelight.ru [2, 3]. In vitro studies have shown that 3-HO-PCP, like PCP, acts on the NMDA receptor and it is an uncompetitive antagonist at the NMDA receptor ion-channel complex [4]. 3-HO-PCP has a higher affinity for the NMDA receptor and greater μ-opioid receptor affinity than PCP [3, 5].

N-Ethylhexedrone, also known as Hexen, appears to have been first cited in a patent for aminoketone derivatives in the 1960s by Boehringer Ingelheim [6]. It is a pentedrone analogue synthetic cathinone and was first reported as an NPS in 2015–2016 when seizures of the compound were reported to the EMCDDA early warning system [6, 7]. N-Ethylhexedrone has been shown to have high affinity for norepinephrine, serotonin and dopamine receptors when compared with 22 other substituted cathinones, including the more widely available and used mephedrone [7, 8].

Information about the adverse (unwanted) effects associated with the use of 3-hydroxyphencyclidine and/or N-ethylhexedrone can only be found in grey literature websites

The authors declare this data has not been presented previously.

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and drug forums [6, 9], as there are no published cases of acute toxicity in the medical literature. We describe here an analytically confirmed case of acute toxicity related to the use of both 3-hydroxyphencyclidine and N-ethylhexedrone.

Case Report

A 56-year-old male was brought to the Emergency Department (ED) by ambulance. The patient had a past medical history of myocardial infarction with one coronary artery stent 11 years previously. His regularly prescribed medications included once daily clopidogrel, simvastatin, atenolol and lansoprazole; he also gave a history of occasional use of over the counter 'cough syrup'. His neighbours called the emergency services due to their concern about 'noises' coming from his home. He was found by the ambulance crew when they arrived to be drowsy, diaphoretic and pale, and was reported to be 'hot to touch'. The ambulance crew noticed after arrival that his limbs were briefly rigid; thereafter, the ambulance crew documentation noted that he had 'normal movement of all four limbs with no lateralising signs and his pupils were 3 mm and reactive bilaterally'. His initial Glasgow Coma Score (GCS) was 6 (E1, V1, M4), and vital signs were respiratory rate 40 breaths per minute, oxygen saturations 99% on 15 L of oxygen via a non-rebreather mask, heart rate 144 beats per minute, blood pressure 145/93 mmHg, temperature 39.9 °C. His capillary blood glucose was 187.2 mg/dL (10.4 mmol/L). An unknown white powder, weighing scales, and an empty bottle of beer were found nearby.

On arrival in the ED, approximately 90 minutes after the initial call from the neighbors, his level of consciousness had improved (GCS 14: E4, V4, M6). Although he was confused, he was able to say that he had used a drug named 'Hexen' which he purchased from the Internet. He appeared to be hallucinating and remained diaphoretic. His observations at that time were respiratory rate 24 breaths per minute with oxygen saturations of 100% on high-flow oxygen, heart rate 148 beats per minute with a regular rhythm, blood pressure 154/102 mmHg and tympanic temperature of 39.0 °C. Clinical examination revealed normal cardiovascular, respiratory, and abdominal system; his pupils were 3 mm and reactive bilaterally, with ocular clonus and vertical nystagmus. All four limbs had Medical Research Council (MRC) Scale for Muscle Strength grade 5 throughout (maximum/normal score is 5) with no spontaneous or inducible ankle clonus, flexor plantar responses and normal upper limb coordination bilaterally. His ECG showed sinus tachycardia with no ischemia and normal QTc and QRS durations. His initial blood investigations are shown in Table 1 below. A non-contrast CT head scan was reported by the radiologist to be normal with no evidence of any cerebral edema or intracranial hemorrhage.

He was treated with 4.3 L of crystalloid solution, which had been cooled in refrigerator at between 2 and 6 °C, intravenously (IV) over a period of 4 hours and a total of 7.5 mg of IV diazepam over 2 hours. The ED physicians felt sepsis could be contributing to his clinical syndrome and so he was initially treated with IV amoxicillin/clavulanic acid. Antibiotics were discontinued after one dose when the treating physicians determined the clinical symptoms/signs and physiological and laboratory findings were instead consistent with acute drug toxicity rather than sepsis. His plain chest radiograph showed no evidence of focal consolidation. His temperature fell to 37.7 °C and heart rate to 125 beats per minute after 1 hour of treatment. His temperature remained < 38.0 °C for the duration of his stay without any additional cooling. Once his vital signs stabilised, he was transferred to the high-dependency unit (level 2 facility) for ongoing care.

On the second day of admission, the patient was less confused and a more detailed history was available. The patient had smoked cannabis once many years ago but had more recently become interested in exploring recreational drug use on internet discussion forums since his retirement from work. As a result, 6 months prior to the admission, he had purchased 25 g of N-ethylhexedrone from an internet supplier. He claimed to have been using the drug every day for 3 months by nasal insufflation and/or rectal insertion and that he had developed a 'psychological addiction' to it. After this, he did not use any further recreational drugs for 3 months until the night preceding his admission to the hospital. He had purchased a further 25 g of N-ethylhexedrone, along with 5 g of 3-HO-PCP. At 23:00 on the night prior to his admission to the hospital, he had used 100 mg of N-ethylhexedrone; he did not report any unwanted effects following use. The following morning he felt like he had a viral upper respiratory tract infection and therefore mixed some cough syrup, of which the ingredients were unknown, with the 3-HO-PCP. He said that he had attempted to measure the 10-mg dose 'recommended' on the packaging but this was difficult with the weighing equipment he had available. He was unaware of what had happened after use of the mixture until his second day in hospital, in the high-dependency unit (level 2 facility).

He developed rhabdomyolysis with associated mild acute kidney injury (AKI) (creatine kinase values are reported in Table 1). His acute kidney injury (AKI) improved following IV fluid maintenance (creatinine values are reported in Table 1). As his rhabdomyolysis and AKI were resolving, he was discharged home 25 hours after presentation to the ED and his pre-discharge blood results are shown in Table 1. He

Table 1 Blood results on presentation to the ED, 7 h after presentation and pre-discharge from hospital

Test	Level on admission	Level 7 h after admission	Pre-discharge bloods	Normal range
pH	7.379	7.372	7.386	7.350–7.450
Bicarbonate	21.4	25.6	26.0	22–28 mEq/L
Base excess	− 3.2	0.1	0.6	− 2–+ 2 mEq/L
Lactate	3.25	1.7	1.1	0.20–1.80
Creatinine mg/dL (μmol/L)	1.35 (119)	0.96 (85)	0.84 (74)	0.67–1.18 mg/dL (59–104 μmol/L)
Creatine kinase	485	5999	4805	0–229 IU/L

was followed up in our outpatient clinic 9 days later; he had remained clinically well since discharge from hospital and at that time, his creatine kinase was 104 IU/L and creatinine was 1.04 mg/dL (92 μmol/L). The results of his viral swab respiratory panel were available for review at that outpatient appointment and were noted to be positive for enterovirus/rhinovirus RNA.

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Drug Analysis

Serum samples were collected from the patient on admission and urine samples were collected on the day of discharge. The samples were analysed by the LCG group, Cambridgeshire. The urine sample was prepared for analysis using solid-phase extraction following enzymatic hydrolysis of any glucuronidated phase II metabolites. The serum sample was prepared in the same manner but omitting the hydrolysis step. The prepared samples were analysed on a Thermo XRS ultra high-performance liquid chromatography (UHPLC) system, interfaced to a Thermo Q Exactive Focus HRAM mass spectrometer, operating in heated positive ion electrospray mode. Chromatographic separation was achieved in 5.0 minutes on Waters Atlantis T3 HPLC column maintained at 40 °C using a gradient consisting of a mixture of 0.1% acetic acid and acetonitrile containing 0.1% acetic acid. Data were acquired in full scan mode operating at a mass resolution of 70,000 across a mass range of 50–750 amu. Data-dependent scanning was enabled in 'confirmation' mode utilising an inclusion list of over 800 compounds derived from the in house accurate mass database. A second scan event using 'all ion fragmentation' (AIF) was performed with a stepped HCD setting of 15, 35 and 50 at a mass resolution of 35,000 across a scan range of 80–500 amu. Acquired data were processed using Thermo Toxfinder software against an in-house database containing over 800 NPS and other pharmaceutical drugs. The presence of reported drugs is confirmed in the data through full scan accurate mass determination of molecular ions, identification of accurate mass qualifier ions in AIF and the automatic generation of accurate mass MS/MS data for comparison with mass spectral libraries.

Results of Drug Analysis

Qualitative toxicological analysis of the serum samples identified 3-hydroxy PCP and metabolites, N-ethylhexedrone and metabolites, and clephedrone and metabolites. The urine showed 3-hydroxy PCP and metabolites, carboxy THC, N-ethylhexedrone and metabolites, clephedrone and metabolites, and 3-methoxy PCP.

Paracetamol, atenolol, and diazepam and metabolites were found and are considered present due to therapeutic use.

Discussion

The toxidrome reported in this patient involved visual hallucinations, reduced level of consciousness, diaphoresis, tachycardia, hypertension, hyperthermia, and vertical nystagmus. These features are akin to those seen in acute PCP toxicity [10]. This aligns with studies showing 3-HO-PCP to have very similar binding sites to that of PCP [2, 4]. Some of these features, such as tachycardia, hypertension, and hyperthermia, are shared with sympathomimetic and serotonergic toxidromes that would be expected with the N-ethylhexedrone that had been used the previous night [7, 11]. As the patient had described, the dose for 3-HO-PCP is very small and it is possible that he took many times more than the 'recommended' dose of 10 mg listed on the packet. However, some drug information websites including drugs.tripsit.me and psychonautwiki.org report that a normal dose should range from 2 mg for a light effect to 8 mg for the heaviest effect with user reports on Erowid.org describing use of up to 25 mg giving pleasurable effects [6, 9, 12]. N-ethylhexedrone has been reported to be sold in pale white powder form and is usually used by nasal insufflation and/or ingested orally [6, 9]. It is possible that the effects reported in this patient on presentation were due to a combination of both drugs used, although the vertical nystagmus and visual hallucinations, along with the timing of use related to the onset of

acute toxicity would suggest that 3-HO-PCP toxicity predominates in this case. Furthermore, toxicological analysis did not identify any active ingredient of any potential cough syrup, suggesting that this did not contribute to the acute toxicity reported. To improve completeness of our understanding of the toxidrome seen in this patient, knowledge of the ingredients of the cough syrup would have been valuable.

The patient was treated with benzodiazepines and cooled IV fluids in order to manage the hyperpyrexia and other features of toxicity that he had developed. He was also treated initially with broad-spectrum antibiotics to cover for possible sepsis as would be expected in a case where initially the diagnosis is unclear. When the history revealed that our patient had indeed used both 3-HO-PCP and N-ethylhexedrone, the physicians managing his care discontinued antibiotic treatment with the knowledge that infection was no longer to cause for his hyperthermia. Following treatment, the patient made a full recovery allowing him to be discharged from the hospital the following day.

This single case report is the first documented toxicity to the drug 3-hydroxyphencylidine or N-ethylhexedrone in the medical literature. Case reports and case series often provide an initial signal about new outbreaks or potential acute toxicity related to the use of recreational drugs and NPS. However, in case reports and case series, there are a number of confounding factors that should be acknowledged as seen in this case, where the individual uses more than one recreational drug and/or NPS that could contribute to the clinical symptoms and signs reported. However, it is possible for an experienced medical toxicologist to use the self-reported drug or NPS used alongside the analytical data and the clinical symptoms and signs to determine which drug/NPS is most likely to be responsible for the acute toxicity described. A limitation with the case presented here is our presumed understanding of the dose consumed by the patient. As discussed, reports on Erowid have described 25-mg doses to give positive effects. The patient stated an aim to consume 10 mg of 3-HO-PCP but may have inadvertently taken a massive dose. If he did take the intended dose, this may have been due to purity or individual sensitivity. Further study looking at quantitative analysis and analysis of the drug itself may help to understand this issue.

This case of toxicity to 3-HO-PCP demonstrates a toxidrome similar to that of PCP with the patient's presentation perhaps also influenced by N-ethylhexedrone. In all patients presenting with a similar presentation, it is important that we consider the differential of acute drug toxicity.

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Compliance with Ethical Standards Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Conflict of Interest None.

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