CASE REPORT

Acute Stimulant Toxicity from the Use of Ocean Burst and Lunar Wave Bath Salts: Detection of 3-Chlorophenmetrazine and the Cathinones N-ethylpentedrone and Alpha-pyrrolidinoisohexanophenone (alpha PHiP)

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Abstract

Background: In this study, we report on a patient with acute stimulant toxicity following the use of two bath salt products purchased over the Internet in the UK, where two novel cathinones and a substituted phenylmorpholine were detected on toxicological screening.
Case Report: A 52-year-old male with ADHD presented to ED with chest pain, shortness of breath, sweating, and agitation after nasal insufflation of Internet purchased 'bath salt' products "Ocean Burst" and "Lunar Wave". He was anxious and agitated, but did not have delusions, paranoia or delirium. On examination, he was tachycardic (113bpm), hypertensive (171/115mmHg), and normothermic (36.0°C). He was tremulous, but his tone and reflexes were normal and there was no clonus. Initial blood tests were normal and initial Troponin I was 32.2ng/L; reduced to 28.3ng/L on repeat (low risk for ACS if ≤34 ng/L on repeat). ECG showed sinus rhythm (99bpm) left axis deviation, QTc 462msecs, QRS 100msecs, with no ischaemic changes. He was treated with oral diazepam (total 25mg) and IV fluids in the ED. Following the admission, he required a further 60mg of oral diazepam for ongoing agitation. His symptoms resolved within 24 hours and he was discharged.
Analytical Results: Serum, urine and drugs samples analysed using ultra performance liquid chromatography interfaced to high resolution accurate mass spectrometry:
- 'Ocean Burst': N-ethyl pentedrone, alpha PHiP;
- 'Lunar Wave': 3-chlorophenmetrazine, 4-methylmethamphetamine, alpha PHiP;
- Serum/urine: the cathinones N-ethylpentedrone and alpha-PHiP were detected, along with the substituted phenylmorpholine 3-Chlorophenmetrazine.
Conclusion: The novel cathinones detected in this patient, related to the use of 'bath salts', were associated with acute stimulant toxicity. Analytical confirmation of NPS products in patients presenting with acute NPS toxicity is important in the surveillance of the NPS currently available and to inform public health interventions.

Keywords: New Psychoactive Substances, Acute Drug Toxicity, Cathinones, Bath Salts

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INTRODUCTION

Since the early 2000s, there has been an increase in the availability and use of new psychoactive substance (NPS) and these products were often sold as products advertised as 'not for human consumption' to circumvent existing national and international drug legislation.[1] In the past, NPS containing synthetic cathinones such as mephedrone and methylenedioxypyrovalerone (MDPV) were marketed, particularly in the USA, as "bath salts".[2,3] Over time, there has been a change in the NPS found within different products. In Europe, there has been a change from the synthetic cathinones to the synthetic cannabinoid receptor agonists, as noted from the analysis of samples seized by border and law enforcement agencies, products purchased from internet and other suppliers, and in cases of acute toxicity presenting to Emergency Departments (EDs) .[4,5] The UK 2016 Psychoactive Substances Act means that it is illegal to "*produce, supply, offer to supply, possess with intent to supply, possess on custodial premises, import or export psychoactive substances; that is, any substance intended for human consumption that is capable of producing a psychoactive effect*".[6] Despite these changes, NPS containing products marketed as "bath salts" containing NPS

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are still available, and we present a case report of prolonged "bath salt" acute toxicity in 2023 related to use of an unknown product, later found to contain synthetic cathinones and other new psychoactive substances.

CASE REPORT

A 52 year old male, with underlying attention deficit hyperactivity disorder (ADHD) and previous cocaine use (stopped one week previously), nasal insufflated 10 sachets of Ocean Burst and Lunar Wave 'bath salt' products purchased from an Internet supplier over a period of 15 hours. He developed chest pain, shortness of breath, sweating, and severe agitation, which he tried to self-manage with 5mg of Internet purchased 'Xanax' (Alprazolam); he subsequently presented to the ED within 6 hours after onset of symptoms. His regular medications included Atomoxetine 50mg twice a day and Venlafaxine modified release 150mg twice a day.

On initial examination, he was sweaty, tachycardic (106 bpm), hypertensive (175/112 mmHg), and tachypnoeic (respiratory rate 22 breaths/minute) with oxygen saturations of 94% on 1L of oxygen via nasal cannula and a temperature of 37.0°C. He was agitated, but alert and oriented and there was no evidence of delusions, paranoia or delirium. Although he was tremulous with dilated pupils, he had normal tone and reflexes with no spontaneous or inducible clonus. His initial routine bloods (full blood count, renal function, liver function), venous blood gas including lactate and chest x-ray were normal. His initial Troponin I was 32.3 nanograms/L which reduced to 28.3 nanograms/L on repeat testing 7 hours later (low risk for ACS if ≤34 ng/L on repeat). Creatinine Kinase was 131 units/litre. An ECG showed sinus rhythm with left axis deviation and a QTc interval of 462ms and no other abnormalities. In ED, he was initially treated with 5mg oral diazepam, followed by 10mg 1 hour later and a further 10mg after 2 hours. He was also given a 2L of intravenous crystalloid (Hartman's Solution) over 3 hours. He was admitted for ongoing observation; he remained agitated and required a further 60mg oral diazepam over the next 12 hours (10mg doses every 2-3 hours). His agitation resolved approximately 18 hours after presentation to ED, and he was discharged the following day with contact details for self-referral to local community drug and alcohol treatment services.

Toxicological Analytical Confirmation

The patient gave informed consent for the analysis of a urine and blood sample collected at the time of admission, as well as the powder remaining in the drug packets that he had purchased online. The biological samples were prepared for the analysis using reversed phase solid phase extraction. The powder in the drug packets was prepared by dissolving approximately 1mg in 1ml of liquid chromatography mass-spectrometry (LCMS) mobile phase. All samples were then analysed using ultra performance liquid chromatography (UPLC) interfaced to high resolution accurate mass spectrometry. Estimates of drug concentrations in urine and serum were determined based on a calculation against the deuterated EDDP internal standard used in the mass spectrometry.

The analysis of the remaining powder in the two 'bath salt' products detected:

i) 'Ocean Burst': N-ethyl pentedrone, alpha-pyrrolidinoisohexanophenone (alpha PHiP); and

ii) 'Lunar Wave': 3-chlorophenmetrazine (3-CPM), 4-methylmethamphetamine (4-MMA), alpha PHiP

The recreational drugs and NPS detected in the serum and urine analysis, along with calculated concentrations are shown in Table 1 below. In addition, diazepam metabolites (nordiazepam, oxazepam and temazepam), dihydrocodeine, and venlafaxine related to therapeutic use were detected in the urine and serum.

DISCUSSION

We report a case of a patient presenting with acute stimulant drug toxicity (agitation, tachycardia, and hypertension) following the analytically confirmed use of the cathinones N-ethyl pentedrone and alpha PHiP, along with the substituted phenylmorpholine 3-chlorophenmetrazine (3-CPM), the amphetamine type stimulant 3 or 4 methylmethamphetamine (4-MMA) and the novel benzodiazepines bromazolam and flualprazolam.

The observed toxicity is unlikely to be due to the novel benzodiazepines, as these would not be expected to be associated with stimulant-like toxicity.[7,8] Whilst there are no published case reports of acute toxicity with analytical concentrations for flualprazolam or bromazolam, the concentrations reported here are lower than that previously reported in post-mortem detection of bromazolam (96 UK

Table 1. Recreational drugs and NPS detected in the serum and urine analysis with calculated concentrations

Drug/NPS Detected	Urine concentration (ng/mL)	Serum concentration (ng/mL)
N-ethyl-pentedrone	435 ng/mL	10 ng/mL
3-Chlorophenmetrazine	285 ng/mL	14 ng/mL
Alpha PHiP	38 ng/mL	5 ng/mL
Bromazolam	3 ng/mL	0.5 ng/mL
Flualprazolam	4 ng/mL	0.25 ng/mL
3 or 4-methyl-methamphetamine	385 ng/mL	5 ng/mL
Benzoylecgonine (cocaine metabolite)	290 ng/mL	2 ng/mL

deaths: mean concentration 65 ng/mL; 41 Canadian deaths: 11 ng/mL) and in 203 US driving under the influence cases (mean concentration 23 ng/mL).[9-11] There have been reports of individuals mis-sold bromazolam as alprazolam in the US, and as no alprazolam was detected in this case, it is likely that they had unknowingly purchased bromazolam instead of alprazolam from the Internet.[12]

A study reported the detected of N-ethyl-pentedrone in routine toxicological analysis undertaken on 5,001 cases (868 women, 4133 men) of acute drug toxicity by the Department of Forensic Medicine and Toxicology of the Medical University of Silesia in Katowice, Poland. [13] They reported in detail on 28 cases, where one or more novel synthetic cathinone was detected. N-ethyl-pentedrone was detected in 6 cases between 2016 and 2019 and blood concentrations ranged from 7 to 137 ng/mL with mean concentration of 44 ng/mL and median of 18 ng/mL. Five cases where N-ethyl-pentedrone was detected were deaths (1 female aged 35; 4 males aged 22 to 35); one 23 year old male was admitted to hospital with syncope and subsequently died although no further information is available; the other individuals were found deceased. One detection was in a male stopped as part of a roadside check and found to be in possession of drugs with an intent to supply; blood analysis detected N-ethyl-pentedrone at a concentration of 137 ng/mL along with 4-CMC, 4-MEAP, MDMA and MDA. There have been no other published case reports of fatalities or acute toxicity involving N-ethyl-pentedrone. In an animal study, intra-peritoneal administration of single doses of N-ethyl-pentedrone (1, 3 or 10 mg/Kg) to mice led to anxiolysis with reduced social exploration and slight hyperthermia. However, in mice administered doses of N-ethyl-pentedrone twice a day for five days, on cessation of administration the mice no longer had anxiolysis, but the reduced social exploration persisted and the mice had increased aggressive behaviour. Additionally, there increased plasma corticosterone and decreased striatal dopamine levels in those mice treated with repeated dosing.[14]

Alpha-PiHP is a structural isomer of α-PHP (alpha-Pyrrolidinohexiophenone), and therefore it could be considered to be an analogue of α-PVP (alpha-Pyrrolidinopentiophenone), which is a Schedule I drug under the United Nations Convention on Psychotropic Substances. Alpha-PiHP was first reported to the European Monitoring Centre for Drugs and Drug Addiction in December 2016 having been detected in Slovenia. Since then, there have been an increasing number of detections in the illicit drug market in Poland, and the Polish Sanitary Inspector issued a warning about the increase on July 2022. [15] There have been two fatalities reported, where alpha-PiHP has been identified in post mortem analysis of blood and other samples. In the first case, an 18 year old male was found dead in his apartment. [16] Post-mortem analysis of femoral blood and urine detected alpha-PiHP at concentrations of 69 ng/mL and 2072 ng/mL respectively. It was also detected in the analysis of bile, liver, kidney, gastrointestinal tissue (stomach and small intestine), lung, and brain. The second case was of a 37 year old individual, who was agitated and acting strangely, then lost consciousness and was unable to be resuscitated and subsequently died. A bag of white powder labelled "α-PiHP" was found next to the deceased.[17] Subsequent post-mortem analysis of biological samples detected alpha-PiHP in femoral, cardiac and dural venous sinus blood at concentrations of 2,377 ng/mL, 1,133 ng/mL and 966 ng/mL respectively. It was also detected in CSF, brain, bile, liver, kidney, heart, pancreas, and lung sample analysis. There has been one non-fatal case of alpha-PiHP acute toxicity in a 29 year old male, who was found collapsed and unconscious on a bed with pin-point pupils, a heart rate of 116 bpm, blood pressure of 110/75 mmHg, pyrexia of 39.4°C, and intermittent muscle tremors. [18] He was managed with supportive care, including the administration of naloxone over 15 hours, and his symptoms settled and he was discharged 4 days later. Subsequent toxicological analysis of blood and urine collected at the time of admission detected alpha-PiHP at concentrations of 5.0ng/mL and 722.2ng/mL respectively. In addition, 4-fluoroisobutyryl fentanyl (4-FiBF) was detected in blood and urine at concentrations of 87.7 ng/mL and 2291.0 ng/mL respectively. At the time he was found, a woman was found deceased in the bed next to him; post-mortem toxicological analysis of biological samples obtained from her did not detect alpha-PiHP, but did detect 4-FiBF in a range of different biological matrices

3-chlorophenmetrazine is a substituted phenylmorpholine derivative, and therefore it is closely related to drugs such as 3-fluorophenmetrazine. There have been no published reports of acute toxicity or fatalities were 3-chlorophenmetrazine has been reported to have been used and/or detected. We were unable to find any case reports on the use of 3-chlorophenmetrazine in animal or human case reports.

In terms of the detection of the cocaine metabolite benzylecgonine and the potential for its contribution to the clinical features seen, firstly, it should be noted that there was no parent cocaine detected. Additionally, the concentration of the benyzlecgonine detected was not thought to be contributory as the threshold concentration of 50 ng/mL for a drug driving offence in the UK [19]. The venlafaxine was unlikely to be contributory to the presentation as the estimated serum concentration was 6 ng/mL, which is a sub-therapeutic concentration.

Typically, the screening of biological samples in patients with acute recreational drug toxicity focuses on individual cases and/or small cluster outbreaks. In Sweden, the STRIDA project tried to address this by screening biological samples in all cases of acute recreational drug toxicity, where the clinicians contacted the Swedish Poisons Information Centre between 2010 and 2016. [19,20]. Subsequently, in the UK, the Identification of Novel psychoActive substances (IONA) project looked at targeted consented screening of biological samples in patients presenting to sentinel centres with recreational drug and NPS toxicity until 2023; initially this was patients suspected NPS toxicity, but this was then extended to suspected opioid toxicity and/or severe recreational drug toxicity.[21,22] There have also been studies in sentinel centres, such as in London, UK, that have looked at anonymised screening of routinely collected blood

samples in patients with acute recreational drug and/or NPS toxicity.[23] Whilst these projects have provided useful information on trends on acute recreational drug and NPS toxicity and the patterns of toxicity within individual substances, the main limitation is the time-limited funding for these projects and the capacity of analytical laboratories to undertake the analysis. Additionally, these projects tend to be city and/or country focused, rather than projects that collect co-ordinated analytical screening data from multiple countries. It is important that clinical and analytical toxicologists, are supported not only financially to undertake the studies, but also to deal with the logistics of national and/or multi-national studies.

CONCLUSION

Historically, NPS has been reported to contain synthetic cathinones. Over time, there was a switch towards NPS containing synthetic cannabinoids and more recently to synthetic opioids. However, there continue to be new synthetic cathinones emerging on to the drug market, as described in the present case report. It is important that clinical toxicologists support not only the screening of individual cases, but also the development of wider systematic screening of patients presenting with acute recreational drug and NPS toxicity to determine trends in the NPS responsible for acute drug toxicity and to inform public health interventions.

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