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Synthetic Cathinones in Belgium: Two Case Reports with Different Outcomes Observed in the Emergency Room

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Abstract

We herein report two cases of cathinone intoxication. The first case is about a drug addict who was admitted to the emergency room after the injection of an unknown compound. He presented with tachycardia, palpitations, mydriasis, dyspnea, dizziness, headache and nausea. After leaving the hospital against medical advice, he returned the next day with police escort, presenting aggressiveness and agitation signs. One month later, he returned one more time for sleeping disorders, hallucinations and anxiety. He was finally transferred for his 21st detoxification treatment. The second case concerns a man who was wandering the streets and tried to escape when police officers called him. He confessed the snorting of *N*-ethylpentedrone and was admitted with severe agitation including delusion of persecution, tachycardia, mydriasis and fever. Because of renal failure, rhabdomyolysis and metabolic acidosis, he was transferred to the intensive care unit where he manifested worsening of the symptoms, turning into coma. He was intubated for 3 days before a complete resolution of the symptoms. A screening was performed by high-resolution mass spectrometry followed by quantifications made by high-performance liquid chromatography coupled with a diode array detector. In the first case, alpha-pyrrolidinohexiophenone was identified only during the first two admissions. However, as plenty of other psychotropic substances were also found, the cathinone alone could not be held directly responsible for the symptoms. In the second case, more than 2,000 ng/mL of *N*-ethylpentedrone was found without any decrease in the next 17 h, underlining the long half-life of this compound. Unlike the first case, symptoms could be clearly attributed to the cathinone. In conclusion, cathinones can be found on the Belgian illicit drug market, with various routes of administration and clinical consequences. In these two case reports, some common points were observed initially. However, one patient was finally able to leave the hospital without any treatment, whereas the other would most likely have died without intensive care.

Introduction

With 162 synthetic cathinones monitored by the European Monitoring Centre for Drugs and Drug Addiction by the end of 2021, this is the category of new psychoactive substances (NPS) containing the most compounds after synthetic cannabinoids (1). The structure of synthetic cathinones derives from one parent compound, i.e., cathinone, a natural psychoactive compound found in the leaves of *Catha edulis*, a plant growing in eastern Africa and southern Arabia and locally consumed (2). As shown in Figure 1, cathinone is the beta-keto derivative of amphetamine.

Although some cathinone derivatives are registered as medicine (such as bupropion), others share the stimulant effects of cocaine or amphetamines and are present on the recreational drug market (3). They are sold as powders, crystals, capsules or tablets and can be ingested, injected or snorted. Considering the number of existing cathinones, their effects and intensity can vary depending on the chemical structure, even if some similarities are observed. Cathinones act by increasing the concentrations of monoamines (dopamine or noradrenaline or serotonin) in the synapse through reuptake inhibition or release stimulation (depending on the compound). In small doses, cathinones generate euphoria, excitation, increased energy, empathy and self-confidence (4–6). Side effects such as tachycardia, palpitations and hypertension are commonly reported and, with larger dose, hallucinations, delirium, acute psychosis, seizure, hyperthermia and multiorgan failure potentially leading to death have also been reported (4, 7–9). Cathinones were used as legal highs locally since the beginning of the 21st century (10), even if some of them were already synthesized a long time ago for medical purposes. They were sold under the appellation "bath salts" to avoid drawing attention. Mephedrone (4-methylmethcathinone) can be considered the leader of synthetic cathinones, as it has been widely used and is the most studied cathinone (11). Then, lots of other cathinones appeared on the market, some of them becoming very popular (for example, 3,4-methylenedioxy-*N*-methylcathinone, also known as methylone and 4-methylenedioxypyrovalerone). However, there is a lack of information concerning other derivatives. In this paper, we report two cases of patients intoxicated with cathinones that are less studied in the literature. These cases were analytically confirmed with the aim of ultra-high-performance liquid chromatography coupled with a time-of-flight detector mass spectrometer (UHPLC–TOF-MS), which represents the gold standard method for NPS identification.

Case History

Case 1

A 31-year-old man, known as a long-term drug addict, was admitted to the emergency room (ER) after the injection of an unknown hallucinogenic compound recommended to him by his drug dealer. He presented with tachycardia, palpitations, mydriasis, dyspnea, dizziness, headache and nausea, improving during the admission. After leaving against medical advice, he came back the next day with police escort (six policemen), presenting confusion, aggressiveness and agitation signs. Indeed, his grandmother had called the police because he had threatened her and broken some furniture in a fit of anger. He refused to comply so that pepper gas, rubber bullets and taser were used to calm him down and to bring him to the hospital with handcuffs. At the ER, he received ketamine and propofol to facilitate the examination. During his psychiatric evaluation, he admitted the intravenous injection of synthetic compounds for 2 days. His agitation disappeared after a few hours, and no mental illness was noticed by the psychiatrist.

He left the hospital to return a month later, reporting a withdrawal of 5 days. He said that he had pain everywhere, sleeping disorders, auditory hallucinations and anxiety. Finally, he was transferred to a psychiatric institution for his 21st detoxification treatment.

Case 2

A 27-year-old man was wandering the streets in the middle of the night, trying to escape when police officers tried to stop him for a routine control. He was admitted to the ER with severe agitation including delusions of persecution, tachycardia, mydriasis and fever. He had no previous known history of drug abuse but confessed the snorting of *N*-ethylpentedrone. A small bag containing a white powder was found in his pocket. In consequence of renal failure, rhabdomyolysis and metabolic acidosis, he was transferred to the intensive care unit where the symptoms got worse. He developed an acute heart failure, seizures and deterioration of consciousness, leading to coma. He was sedated and intubated for 3 days. Dialysis was performed before the gradual resolution of the symptoms. Levomepromazine and risperidone were used to control the agitation. Finally, he recovered and could leave the hospital after two more days of observation.

Materials and Methods

Blood alcohol determination

Blood ethanol determination was done by headspace gas chromatography with flame ionization detection (HS-GC-FID) using an in-house method developed on a HS-GC-FID 2014 (Shimadzu, Kyoto, Japan) on a VF-624 ms (60 m × 0.25 mm) column from Varian (Palo Alto, USA).

Drugs of abuse analysis

Detection of drugs of abuse in urine was done by UHPLC tandem mass spectrometry (UHPLC–MS-MS) on an Acquity® UPLC coupled with a Quattro Premier® mass spectrometer (Waters, Milford, USA). More details can be found in Supplementary material.

Screening for NPS and medicines

Sample preparation

Serum and urine were submitted to the same liquid–liquid extraction. After the addition of an internal standard (prazepam 10 mg/L) and basification (Na_2CO_3 1 M), 5 mL of a mix containing diethyl ether/dichloromethane/*n*-hexane/*n*-amylic alcohol (50/30/20/0.5:V/V) was added to 1 mL of the sample. After mixing for 15 min and centrifugation, the organic layer was evaporated to dryness and reconstituted in the mobile phase. Extracts were analyzed by high-performance liquid chromatography coupled with a diode array detector (HPLC-DAD) and UHPLC–TOF-MS.

Instrumental conditions

The HPLC-DAD equipment was an Alliance® 2695 combined with PDA 2996 from Waters; chromatographic parameters were inspired by the method developed by Gaillard and colleagues (12). More details can be found in Supplementary material.

The UHPLC–TOF-MS apparatus was an Eksigent® LC 100 XL combined with a Triple TOF 4600® (Sciex, Framingham, USA), and the screening method was advised by Sciex [inspired from (13)]. More details can be found in Supplementary material.

Results and Discussion

Case 1

Alpha-pyrrolidinohexiophenone (α-PHP or PV-7) was identified only during the first and second admissions. This is a cathinone belonging to the pyrovalerones subclass, as it can be seen in its chemical structure depicted in Figure 1. As reviewed in previous studies (14, 15), the intravenous route of administration, used by our patient, is uncommon for this compound compared to the oral or nasal route.

Thanks to high-resolution MS, the identification of α-PHP could be done with a sufficient confidence. Indeed, the mass spectrum of the sample perfectly matched the library mass spectrum (Figure 2).

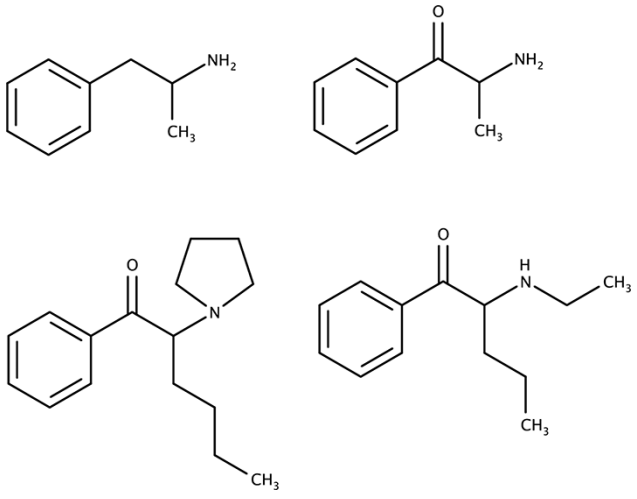

Figure 1. Chemical structures of amphetamine (on the top left), cathinone (on the top right), α-PHP (on the bottom left) and *N*-ethylpentedrone (on the bottom right).

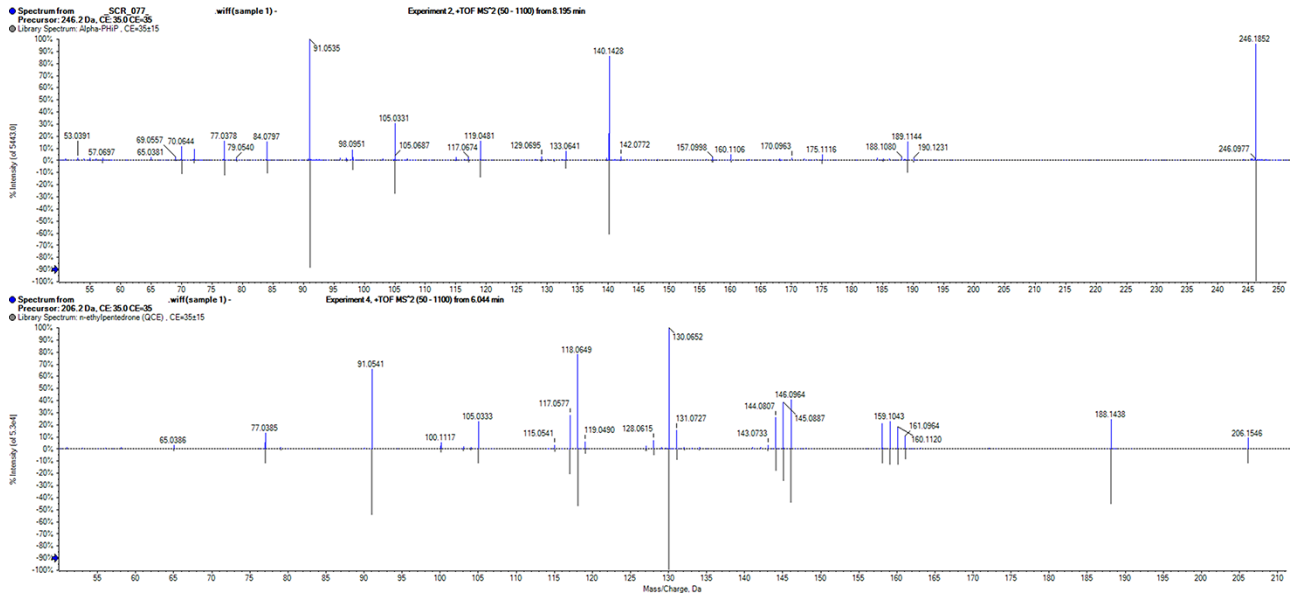

Figure 2. MS-MS spectra of α-PHP (top) and *N*-ethylpentedrone (bottom) compared with the library MS-MS spectra.

However, as plenty of other psychotropic substances were also found (cocaine, cannabis, opiates and benzodiazepines), cathinones could not be held directly responsible for the symptoms. The complete results of the toxicological analysis are detailed in Table I.

Supratherapeutic levels of bromazepam were found during the first and second admissions (therapeutic range: 80–170 ng/mL), whereas clonazepam, diazepam and nordiazepam quantifications were always within the therapeutic range (respectively, 20–70, 125–500 and 200–800 ng/mL). High levels of methadone were found in blood, especially during the last two admissions. This did not prevent opiates use as it can be deduced from the numerous derivatives observed in the samples. Except for diazepam, nordiazepam and methadone, the concentrations of all of the compounds were lower during the third admission, confirming the probable withdrawal and explaining the unpleasant symptoms felt by the patient.

Unfortunately, α-PHP reference standard was not available within a reasonable period of time (delivery time longer than 6 months) for quantification. However, considering the polydrug intoxication, quantification of the compound would be of limited interest due to the tricky interpretation. However, a high level of α-PHP could mean a relative safety of this compound, even when it is consumed with other NPS. This long delivery time gives rise to a stability issue: will the quantification still be right after 6 months of storage? The stability of α-PHP itself in biological samples is not described in the literature. As shown by Adamovicz and Malczyk (16), the stability of synthetic cathinones in biological samples is of crucial importance. Indeed, some of them are highly unstable (for example, 4-chloromethcathinone or 4-CMC), especially at room temperature. On the other hand, Glicksberg et al. showed that tertiary amines (which is the case of α-PHP) are more stable than secondary amines (17). One has to keep in mind this stability issue when quantifying a compound in a biological sample. Indeed, samples are sometimes stored at room temperature in hospital laboratories or in the fridge of forensic institutes before toxicological analysis.

Intoxication with α-PHP has already been described in the literature (15). Notably, it was one of the most frequent derivatives in the STRIDA (acronym of the Swedish project name) project that described patients presenting to Swedish hospitals for cathinone intoxication (18). Although most of the cases were polydrug intoxications, one of their patients was admitted for an intoxication by α-PHP alone, with a serum concentration as low as 1.9 ng/mL.

Case 2

N-ethylpentedrone or α-ethylaminopentiophenone (the chemical structure in Figure 1) was found in an admission plasma sample (2,234 ng/mL), and no decrease was observed 17 h later. We can underline the long half-life of this cathinone—leading to long-lasting psychotic effects—which was observed with other lipophilic derivatives, including α-PHP (19, 20).

N-ethylpentedrone also showed a specific mass spectrum (Figure 2).

Nordiazepam (1,299 ng/mL), which is available in Belgium as a medicine, and oxazepam (94 ng/mL) were also found in blood. Unlike Case 1, the symptoms could clearly be attributed to *N*-ethylpentedrone here. The symptoms and results are summarized in Table II. In this case, the patient declared the NPS consumption. However, when it is not the case (for example, with an unconscious patient), laboratory methods able to detect NPS are mandatory to explain some symptoms. Only two other cases involving *N*-ethylpentedrone were described in the literature; lethal blood concentrations were 3,100 and 932 ng/mL, respectively (21, 22). In the first publication, it was detected along with the synthetic cannabinoid mepirapim. The second publication described 57 intoxication cases with cathinones: only one case concerned *N*-ethylpentedrone and ethanol was also detected. In his review on concentrations of synthetic cathinones in blood, Adamovicz states that a postmortem concentration of 1,000 ng/mL can easily be considered as lethal, irrespective of the cathinone (23). Indeed, we can easily imagine that Case 2 would have died in the absence of medical care. The renal

Table I. Main Symptoms and Results of the Toxicological Analysis for Case 1

	First admission (J0)	Second admission (J1)	Third admission (J + 1 Month)
Symptoms	Tachycardia Palpitations Mydriasis Dyspnea Dizziness Headache Nausea	Confusion Aggressiveness Agitation	Pain everywhere Sleeping disorders Auditory hallucinations Anxiety
Plasma			
Bromazepam	438 ng/mL	524 ng/mL	127 ng/mL
Clonazepam	55 ng/mL	52 ng/mL	Not detected
7-Aminoclonazepam	85 ng/mL	65 ng/mL	Not detected
Diazepam	218 ng/mL	175 ng/mL	245 ng/mL
Nordiazepam	364 ng/mL	335 ng/mL	383 ng/mL
M3G	84 ng/mL	193 ng/mL	Not detected
M6G	Not detected	18 ng/mL	Not detected
C6G	Not detected	32.5 ng/mL	Not detected
Methadone	406 ng/mL	754 ng/mL	1,006 ng/mL
EDDP	Not detected	74 ng/mL	75 ng/mL
α-PHP	Present	Present	Not detected
Urine			
Benzodiazepines	NA	7-Aminoclonazepam, bromazepam, 3-OH-bromazepam, nordiazepam, oxazepam, temazepam	Bromazepam, nordiazepam, oxazepam, temazepam
Neuroleptics	NA	Olanzapine	Levomepromazine Olanzapine
Cannabis	NA	THC-COOH > 350 ng/mL	THC-COOH: 98 ng/mL
Cocaine	NA	Cocaine: 313 ng/mL BZE > 2,400 ng/mL	Cocaine: 12 ng/mL BZE: 83 ng/mL
Opiates	NA	Codeine: 279 ng/mL C6G: 2,260 ng/mL Morphine > 800 ng/mL M3G > 2,400 ng/mL M6G > 800 ng/mL Methadone > 2,400 ng/mL EDDP > 2,400 ng/mL Meconine: 507 ng/mL	Codeine: 22 ng/mL C6G: 399 ng/mL Morphine > 800 ng/mL M3G: 47 ng/mL Methadone: 779 ng/mL EDDP: 2,120 ng/mL

EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; NA: not assessed; THC-COOH: 11-nor-9-carboxy-delta-9-tetrahydrocannabinol; BZE: benzoylecgonine; C6G: codeine-6-glucuronide; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide.

Table II. Main Symptoms and Results for Case 2

	Admission
Symptoms	Severe agitation Delusions of persecution Tachycardia Mydriasis Fever
Biochemical results	Creatinine: 2.7 mg/dL CPK (Creatine Phosphokinase): 827 UI/L → 31,197 (H + 6) pH: 7.26 Lactic acid: 0.9 mM
N-ethylpentedrone (plasma)	2,234 ng/mL
Other toxicological results	Nordiazepam: 1,299 ng/mL Oxazepam: 94 ng/mL

failure, already described for other derivatives (24–26) can be consecutive to rhabdomyolysis.

The symptoms observed in both cases are part of sympathomimetic toxidrome (agitation, hallucination, aggressive behavior, delusions, mydriasis and tachycardia). They are often noticed in cathinones intoxication even if some of them, such as rhabdomyolysis, are only observed in the most serious cases (7, 9, 18, 27, 28).

The most common symptom associated with cathinone intoxication is acute psychosis (7). Case 1 (Case 2 to a lower extent) showed an excited delirium as described by Penders et al. (29), with extreme agitation and violence that can be treated by parenteral benzodiazepines and antipsychotic agents next to general supportive care (7).

Hair analysis would have been interesting in both cases to assess their drug habits.

Conclusion

Cathinones are present in the Belgian illicit drug market, with various routes of administration and clinical consequences. We herein report symptoms recorded in hospital. Initially, some common points were observed between the two cases; however, if one patient was able to leave the hospital without treatment, the other one would probably have died without intensive care, such as the other cases described in the literature.

Supplementary Data

Supplementary data are available at *Journal of Analytical Toxicology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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