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Fetal death associated with the use of 3,4-MDPHP and α-PHP

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ABSTRACT

Introduction: The second largest group of new drugs monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is synthetic cathinones. Substances that are controlled by the law are immediately replaced by new uncontrolled derivatives that cause constant and dynamic changes on the drug market. Some of the most recent synthetic cathinones that have appeared on the "legal highs" market are 3,4-methylenedioxy-α-pyrrolidinohexanophenone (3,4-MDPHP) and α-pyrrolidinohexanophenone (α-PHP).

Case history: A 21-year-old woman in the 36th week of pregnancy presented with psychomotor agitation. Fetal demise was demonstrated and a caesarean delivery performed.

Methods: The analyses were carried out by liquid chromatography with mass spectrometry (LC–MS/MS). The analytes were isolated from the biological material by liquid–liquid extraction with n-butyl chloride.

Results: 3,4-MDPHP and α-PHP were detected and quantified in both the fetus' and the mothers blood, as well as in the mothers urine samples. The determined concentrations of 3,4-MDPHP and α-PHP were, 76 ng/mL and 12 ng/mL in the fetal blood sample, 16 ng/mL and traces in the mothers blood, and 697 mg/mL and 136 ng/mL in the mothers urine, respectively.

Discussion: The presented case demonstrates that 3,4-MDPHP and α-PHP transfers from maternal blood to fetal blood. Blood concentrations of these compounds were higher in the fetus than in the mother. Based on the known effects of these substances and the patient's presentation and clinical course, it would seem that these substances contributed to the fetal death.

Conclusions: The detected substances transfer from maternal to fetal circulation, and synthetic cathinone blood concentration can be higher in the fetus than in the mother. This along with the fact immature metabolic ability makes a fetus more vulnerable to cathinones intoxication than adults.

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Introduction

Since Spice's first appearance in 2006, the number of new psychoactive substances (NPS) introduced on the drug market increased over the last decade. The second largest group of new drugs monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) are synthetic cathinones. They are chemically related to cathinone, which is one of the components of a psychoactive plant called khat (*Catha edulis*). Synthetic cathinones have similar structures and effects to cocaine and amphetamines, including 3,4-methylenedioxymethamphetamine (MDMA). These psychostimulants are often used as alternatives to the above mentioned classic drugs [1].

3,4-Methylenedioxy-α-pyrrolidinohexanophenone (3,4-MDPHP; 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-yl-hexan-1-one) and α-pyrrolidinohexanophenone (α-PHP; 2-(pyrrolidine-1-yl)-1-(phenyl)hexan-1-one) are analogs of 3,4-methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopentiophenone (α-PVP), respectively. They differ simply by the addition of a single carbon to the alkyl side chains (Figure 1). 3,4-MDPHP and α-PHP were originally developed in the 1960s but have appeared in 2014 on the gray-market in some countries as novel designer drugs [2, 3].

3,4-MDPHP and α-PHP are sold through online research chemical vendors mainly in the form of white, beige, or brown powders or crystallized shards. They are generally odorless and tasteless or have an unpleasant chemical odor and taste. These substances are most often insufflated through the nose (snorted) or inhaled (vaporization). They are also sometimes administered orally, intravenously, rectally, smoked (with tobacco or in e-cigarettes). The doses of 3,4-MDPHP described on Internet forums by users were in the range of 5–50 mg. The doses of α-PHP were in the range of 1–25 mg. The larger doses of both compounds do not produce much stronger effects; however, some users repeat the doses. The strongest effects of 3,4-MDPHP are observed after about 20–60 min; they last up to 2–4 h, and finish after several or even a dozen hours. The effect of α-PHP begins after about 10–30 min, with the strongest effects being observed after about 20–45 min and lasting for about 2–5 h (however, the stimulation can last up to several hours) [4–6] .

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Supplemental data for this article can be accessed here.

Some users compare the actions of 3,4-MDPHP and α-PHP to those induced by MDPV and α-PVP, but they are less euphoric and with much less side effects. The effects induced by 3,4-MDPHP mentioned on online forums included the following: stimulation, insomnia, thought acceleration, focus enhancement, increased concentration and motivation. The action of α-PHP is similar when compared to 3,4-MDPHP,; however, it is much more euphoric. The negative effects of these cathinones include anxiety, nervousness, paranoia, suspiciousness, tachycardia, increased blood pressure, hypopnea (overly shallow breathing), vasoconstriction, elevated temperature, delusions and hallucinations. The hallucinations and psychoses occurred more frequently after large doses [4–6].

The use of 3,4-MDPHP and α-PHP, as well as other synthetic cathinones, is often associated with health and life risks. Currently there is no data related to the impact of these compounds on pregnancies. This paper describes the circumstances and toxicological findings of a case involving an intrauterine fetal death, where the aforementioned substances were detected and quantified in biological materials.

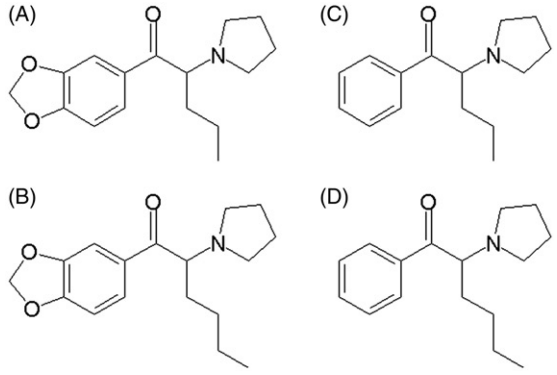

Figure 1. Chemical structures of MDPV (A), 3,4-MDPHP (B), α-PVP (C), and α-PHP (D).

Case history

A 21-year-old female estimated to be 36 weeks pregnant felt bad and started to vomit. One hour later her partner found her unconscious in the apartment. By the time the ambulance arrived 2 h later the woman was conscious and showing signs of psychomotor agitation. On admission to the Emergency Department, psychomotor agitation, anxiety and mumbled speech were observed. A psychoactive substance overdose was suspected; however, there were no independent confirmation of the drug(s) of abuse.

During the pregnancy, the woman smoked tobacco and drank alcohol. Her medical history was limited, with only one obstetric examination performed 2 weeks before admission (on ultrasonographic examination no fetal malformations were seen and a vaginal swab and cytological examination from the uterus cervix proved negative,the mother's blood pressure and glucose blood were also normal). Because of the presence of vaginal spotting and what appeared to be an intrauterine fetal death, the patient was admitted to the Perinatology Department and stayed in the Intensive Care Unit. Her initial vitals were BP 160/90 mmHg, pulse 130/min, blood saturation 98%, body temperature 36.8 °C, and blood glucose 97 mg/dL. Increased psychomotor agitation was observed, and she required sedation with benzodiazepines (diazepam and midazolam), and propofol. Intubation and respiratory support were ultimately performed. Radiographic examination of her chest revealed inflammation in the lungs. Empiric antibiotic therapy (ceftriaxone and metronidazole) was started. On the second hospital day, a caesarean delivery was done, delivering a 2380 g female infant with an Apgar of 0. No fluid was found in the peritoneal cavity.

Blood and urine samples were collected from the patient 1 h post-admission on the first day. The blood of the infant was collected for further toxicological analyses during the autopsy that was performed 4 days after the death. These materials were sent for further toxicological analyses. The post-mortem examination of the infant showed no significant pathological findings. The medical examiner concluded that the newborn baby was stillborn and that her death was

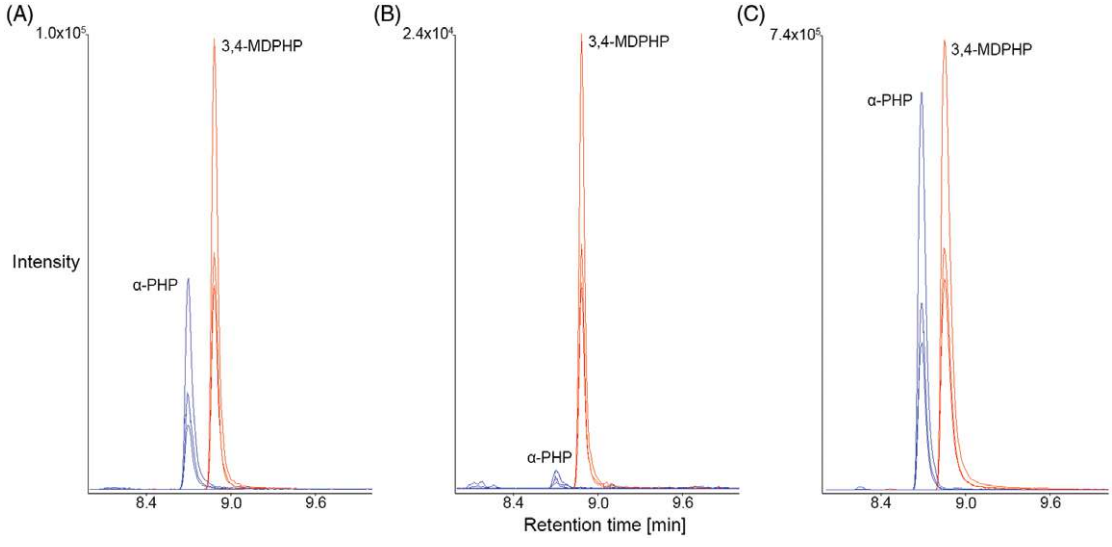

Figure 2. MRM chromatograms of 3,4-MDPHP and α-PHP in blood of fetus (A), blood of mother (B), and urine of mother (C).

Table 1. Concentrations of 3,4-MDPHP and α-PHP in the described case.

		3,4-MDPHP	α-PHP
Mother	Blood	16 ng/mL	Traces (estimated on below 1 ng/mL)
	Urine	697 ng/mL	136 ng/mL
Fetus	Blood	76 ng/mL	12 ng/mL

intrauterine as a result of asphyxia. The reason of the asphyxia could not be explained by autopsy. Fetal age and lack of fetal defects suggested that fetus would have been able to live independently outside the mother's body.

Methods

The blood and urine samples collected at the hospital were analyzed for the presence of alcohol, common drugs of abuse, and wide range of prescription drugs and toxic substances. The screening analyses for the presence of NPS were carried out using a modified previously published method [7]. This method included 198 compounds. The analyses revealed the presence of 3,4-MDPHP and α-PHP in both the blood and urine samples. These cathinones were isolated from the biological material by liquid–liquid extraction with *n*-butyl chloride. The analyses were carried out by liquid chromatography with mass spectrometry (LC–MS/MS). Analyses were performed on an Agilent Technologies 1200 series liquid chromatograph connected to a 6460 Triple Quad mass spectrometer. Separation was achieved on a Kinetex C18 column (Phenomenex).

The detailed description of the extraction, chromatographic and spectrometric conditions as well as reagents and materials used is presented in Supplemental online material.

Results

As a result of the performed analyses, the presence of 3,4-MDPHP and α-PHP in all blood and urine samples were shown (Figure 2). The determined concentrations of the detected substances are presented in Table 1. The analyses did not reveal any other substances (including alcohol, classic drugs as well as other almost 200 NPS).

Discussion

Numerous reports of illicit substance abuse during pregnancy have been documented. In recent years, many NPS have appeared on the drug market and consequently, incidents of synthetic derivates of cathinone abuse by pregnant women are increasingly reported [8, 9].

Currently, there is no information available about the impact of synthetic cathinones in both acute and chronic exposures during pregnancy or their effects on the fetus. Most dopamine promoting drugs, when administered to pregnant mouse mothers tended to impair motor functions in the newborn pups. Neurotoxic effects of prenatal methamphetamine exposure on serotonergic neurons are thought to be associated with learning impairment, behavioral deficits, increased motor activity, and enhanced conditioned avoidance responses [10, 11]. In a study on the monoamine receptor and transporter interaction profiles of various NPS, among others MDPV, no cytotoxicity was found even at the highest concentration, when tested with functional assays [12]. However, in other studies, cytotoxic effects of MDPV have been observed: in human DA-ergic SH-SY5Y cells MDPV caused apoptosis through the rise of reactive oxygen species (ROS), mitochondrial dysfunction and autophagy, which clearly shows the neurotoxic potential of MDPV [13, 14].

The case presented here is noteworthy for three main reasons: first, no prior cases of infant death with 3,4-MDPHP and α-PHP intoxication could be found. Second, these substances cross the maternal fetal blood barrier. Third, fetal blood levels of synthetic cathinones may be higher than maternal levels, although that finding here may reflect maternal metabolism and clearance following fetal demise. Fourth, these substances are associated with fetal death when used during pregnancy, and synthetic cathinone abuse among pregnant women is rising.

Toxicology analyses suggest that fetal death was associated with and may have been causally related to 3,4-MDPHP and α-PHP use. Simultaneous abuse of other psychoactive drugs or the presence of any other pathological conditions both on the mother's and the fetus' side which could be independent causes of the fetus' death were not found.

Determining the effects of these substances on a fetus is difficult. Reports on the use of synthetic cathinones by pregnant women have been presented; however, there is still a lack of data on the influence of these substances on the fetus [9]. Additionally, differences in the toxic effects of cathinones between infants and adults are not well known. Therefore, data on amphetamine derivatives, whose effects and structures are similar, could also be helpful.

There are known factors contributing to possibly increased vulnerability of the fetus to synthetic cathinones intoxication compared to adults. High concentrations of the cathinones in the fetus blood show that the detected substances cross the placenta. It is known that methamphetamine transfers from maternal blood to fetal blood via the placenta due to its low molecular weight and the high lipophilicity of this compound [15]. Synthetic cathinones have low molecular weights, and their ketone group confers a greater polarity and a predicted increased lipophilicity [16, 17]. It is also known that MDMA administered during pregnancy passes, along with its metabolite 3,4-methylenedioxyamphetamine (MDA), to the uterus [18]. However, several pyrrolidine derivatives, including MDPV and MDPPP (3,4-methylenedioxy-α-pyrrolidinopropiophenone), have lower polarity and have shown high solubility in organic solvents [19]. Methylone, mephedrone, and MDPV also cross the placenta and are present in the fetus' brain [20]. Furthermore, recent in vitro studies of mephedrone, MDPV, methylone, ethylone, butylone, and naphyrone demonstrated high blood–brain barrier permeability of all these cathinones [17]. Considering the similar structure and the molecular masses, it can be assumed that 3,4-MDPHP and α-PHP also cross the placental barrier and enter the fetus. These features of synthetic cathinones also favor their accumulation, and prolonged exposure in the fetal central nervous system. This

could be also explained by the ion trapping theory [21]. Synthetic catinones are basic compounds, and in more acidic fetal blood they are in their ionized form and become trapped within the fetal blood system and may produce fetal concentrations higher than maternal concentrations. A low fetal metabolic rate of cathinones due to immature metabolic ability (low activity of cytochrome P450 enzymes) could also result in higher concentration in fetal blood than the mother's. These factors may make infants more vulnerable to synthetic cathinones intoxication than adults [20, 22–25].

Methamphetamine use during pregnancy has several risks to the health of the fetus. Maternal amphetamine addiction can cause preterm birth and perinatal death [15, 22]. Maternal use of methamphetamine can result in an increased heart rate and increased maternal blood pressure what can lead to premature separation of the placenta from the uterus wall. It consequently usually leads to spontaneous abortion or premature delivery. Acutely elevated blood pressure in the fetus can also cause a fetal stroke. On the other hand, an increase in maternal blood pressure following methamphetamine abuse causes a decreased blood supply and consequently decreased oxygen supply to the placenta and fetus which in turn can delay fetal development [22].

Only a few cases of fetal deaths associated with maternal methamphetamine use have been described in the literature. In the case presented by Sakai et al., the concentration of methamphetamine in the blood was 1600 ng/mL. Amphetamine was also detected but below the limit of quantification, which was 100 ng/mL [15]. In other similar cases, the concentrations of methamphetamine and amphetamine in blood ranged from 30 to 1200 ng/mL and from 10 to 80 ng/mL, respectively. However, not all cases where methamphetamine was detected led to the conclusion that the death was attributed to intoxication. Only in the case where methamphetamine and amphetamine at concentrations of 1200 and 60 ng/mL were determined, the cause of death could be determined as intoxication. In other cases asphyxia, prematurity, chorioamnionitis, and pneumonia were estimated to be associated with the infant deaths in addition to methamphetamine intoxication [22].

Stewart and Meeker described eight cases of fetal and infant deaths associated with maternal methamphetamine abuse. In two cases, concentrations were determined in both the maternal and fetal blood. The maternal and fetal methamphetamine concentrations in these cases were 210 and 400 ng/mL and 180 and 1200 ng/mL. In the first case, amphetamine was also determined at a concentration of 60 ng/mL in the fetal blood while this substance was not detected in the maternal blood. In the second case, the amphetamine was found in both blood samples at concentrations of 60 (fetal) and 30 ng/mL (maternal), respectively [22].

The toxicity of 3,4-MDPHP and α-PHP have not been studied and an exact toxic dosage and concentrations are unknown. The obtained results in the presented case can, however, be compared to the concentrations of MDPV and α-PVP because the doses and action of these compounds are similar. Concentrations of MDPV determined in blood in fatal cases were mostly in the range of 440–1090 ng/mL. Fatalities with lower concentrations, even at the level of 20 ng/mL, were also reported. Nevertheless, often this compound was not the sole cause of death and other substances were also present in these cases [26]. Similarly, in the majority of fatalities involving α-PVP, other substances were also present. The blood concentrations of α-PVP in the fatal cases were in the range of 1.1–6200 ng/mL; however, in most of these cases this compound was not the cause of death [27].

On analysis of the circumstances, autopsy findings, and substance concentrations, it cannot be unambiguously stated that the death of the fetus was caused by drug intoxication. Fetal concentrations were lower than those that have been typically associated with fatalities. Another limitation of the work is the lack of knowledge of the timing of drug intake and the death of the fetus with regard to substance concentrations.

Conclusions

3,4-MDPHP and α-PHP cross the placental barrier into fetal circulation. Factors are present that may concentrate these substances in the fetus and known effects of cathinones might be expected to produce potentially fatal effects. These substances should be considered as potentially dangerous in pregnancy.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2018: Trends and Developments. Publications Office of the European Union, Luxembourg; 2018.

[2] Koeppe H, Zeile K, Ludwig G. Patent DE1545591 – Verfahren zur Herstellung von α-Aminoketonen mit heterocyclischer Aminogruppe. 1965.

[3] European Monitoring Centre for Drugs and Drug Addiction. Europol 2014 Annual Report on the implementation of Council Decision 2005/387/JHA. Publications Office of the European Union, Luxembourg; 2015. http://www.emcdda.europa.eu/attachements.cfm/att_240380_EN_TDAN15001ENN.pdf.

[4] https://hyperreal.info/. [Accessed 2018 May 15].

[5] http://bluelight.org/. [Accessed 2018 May 15].

[6] https://psychonautwiki.org/. [Accessed 2018 May 15].

[7] Adamowicz P, Tokarczyk B. Simple and rapid screening procedure for 143 new psychoactive substances by liquid chromatography-tandem mass spectrometry. Drug Test Analysis. 2016;8:652–667.

[8] Gray BA, Holland C. Implications of psychoactive "bath salts" use during pregnancy. Nurs Womens Health. 2014;18:220–230.

[9] Pichini S, Rotolo MC, García J, et al. Neonatal withdrawal syndrome after chronic maternal consumption of 4-methylethcathinone. Forensic Sci Int. 2014;245:e33–e35.

[10] Ross EJ, Graham DL, Money KM, et al. Developmental consequences of fetal exposure to drugs: what we know and what we still must learn. Neuropsychopharmacol. 2015;40:61–87.

[11] Smith LM, Diaz S, LaGasse LL, et al. Developmental and behavioral consequences of prenatal methamphetamine exposure: a review of the infant development, environment, and lifestyle (IDEAL) study. Neurotoxicol. Teratol. 2015;51:35–44.

[12] Rickli A, Hoener MC, Liechti ME. Monoamine transporter and receptor interaction profiles of novel psychoactive substances: para-halogenated amphetamines and pyrovalerone cathinones. Eur. Neuropsychopharmacol. 2015;25:365–376.
[13] Valente MJ, Amaral C, Correia-da-Silva G, et al. Methylone and MDPV activate autophagy in human dopaminergic SH-SY5Y cells: a new insight into the context of β-keto amphetamines-related neurotoxicity. Arch Toxicol. 2017;91:3663–3676.
[14] Valente MJ, Bastos ML, Fernandes E, et al. Neurotoxicity of β-Keto amphetamines: deathly mechanisms elicited by methylone and MDPV in human dopaminergic SH-SY5Y cells. ACS Chem Neurosci. 2017;8:850–859.
[15] Sakai K, Iwadate K, Maebashi K, et al. Infant death associated with maternal methamphetamine use during pregnancy and delivery: a case report. Leg Med (Tokyo). 2015;17:409–414.
[16] Gibbons S, Zloh M. An analysis of the "legal high" mephedrone. Bioorg Med Chem Lett. 2010;20:4135–4139.
[17] Simmler LD, Buser TA, Donzelli M, et al. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol. 2013;168:458–470.
[18] Campbell NG, Koprich JB, Kanaan NM, et al. MDMA administration to pregnant Sprague-Dawley rats results in its passage to the fetal compartment. Neurotoxicol Teratol. 2006;28:459–465.
[19] Coppola M, Mondola R. Synthetic cathinones: chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as "bath salts" or "plant food.". Toxicol Lett. 2012;211:144–149.
[20] Strange LG, Kochelek K, Keasling R, et al. The pharmacokinetic profile of synthetic cathinones in a pregnancy model. Neurotoxicol Teratol. 2017;63:9–13.
[21] Garite TJ. Intrapartum fetal evaluation. In: Gabbe SG, Niebyl JR, Simpson JL, Landon MB, Galan HL, Jauniaux ERM, Driscoll DA, editors. Obstetrics: normal and problem pregnancies. 6th ed. Philadelphia, PA: Saunders Elsevier; 2012.
[22] Stewart JL, Meeker JE. Fetal and infant deaths associated with maternal methamphetamine abuse. J Anal Toxicol. 1997;21:515–517.
[23] Kalapos MP. 3,4-methylene-dioxy-pyrovalerone (MDPV) epidemic? Orv Hetil. 2011;152:2010–2019.
[24] Pedersen AJ, Reitzel LA, Johansen SS, et al. In vitro metabolism studies on mephedrone and analysis of forensic cases. Drug Test Analysis. 2013;5:430–438.
[25] Peters J, Keasling R, Brown S, et al. Quantification of synthetic cathinones in rat brain using HILIC-ESI-MS/MS. J Anal Toxicol. 2016;40:718–725.
[26] Adamowicz P, Gil D, Skulska A, et al. Analysis of MDPV in blood-determination and interpretation. J Anal Toxicol. 2013;37:308–312.
[27] Adamowicz P, Gieroń J, Gil D, et al. Blood concentrations of α-pyrrolidinovalerophenone (α-PVP) determined in 66 forensic samples. Forensic Toxicol. 2016;34:227–234.