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CASE REPORT

Murdered while under the influence of 3-MeO-PCP

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Abstract

The abuse of new psychoactive substances (NPS) has been dramatically increasing all around the world since the late 2000s. The availability of hundreds of NPS in the past decade is challenging for both public health and global drug policies. A 39-year-old woman, known as a multidrug addict, was murdered by her partner by ligature strangulation. A comprehensive toxicological screening by gas chromatography and ultra-high performance liquid chromatography with tandem mass spectrometry revealed the simultaneous presence of ethanol (1.37 g/L), diazepam (157 ng/mL) and nordiazepam (204 ng/mL), cocaine (25 ng/mL) and benzoylecgonine (544 ng/mL), and (3-methoxy-(1-(1-phenylcyclohexyl)piperidine) or 3-MeO-PCP, a dissociative hallucinogen anesthetic drug. Concentrations of 3-MeO-PCP were 63, 64, and 94 ng/mL in femoral blood, bile, and urine, respectively. Hair tested also positive for 3-MeO-PCP on 3 × 2-cm segments at 731, 893, and 846 pg/mg, indicating long-term abuse of the drug. This seems to be the first ever reported hair concentrations. Major impairment of the victim, including visual hallucinations and alteration of behavior, was attributed to the mixture of all the drugs, with a major contribution of 3-MeO-PCP. The toxicological findings were compared to the few reports available in the medical literature.

Keywords New psychoactive substances · 3-MeO-PCP · UPLC-MS/MS · Severe hallucinations

Introduction

For several years, new synthetic drugs appeared on the Internet and constituted a wide group called new psychoactive substances (NPS), which designate a wide range of molecules having the same pharmacological effects as various illegal substances such as ecstasy, amphetamines, benzodiazepines, opiates, or cannabis. Their chemical structures can be close to the original compound but can be also very far from it. These substances can skirt the narcotic laws because they are not listed as controlled drugs. Generally sold on the Internet, NPS are differentiated by their chemical names or trade names such as "bath salts," "plant for nutrients," and "incense." According to a survey of the *French Observatory Drugs and Drug Addiction* [1], more than 382 substances circulated freely in the European Union between 2008 and 2015, including 176 in France. NPS are becoming more prevalent in the world of teenagers and parties, given the ease of purchase and use.

Among NPS, a group derived from phencyclidine (1-(1-phenylcyclohexyl)piperidine or PCP) has gained importance in the recent period because it was proposed as legally available alternatives, although in some European countries (e.g., France or Germany), it is banned by the narcotics act. This group includes 2-MeO-PCP, 3-MeO-PCP, 4-MeO-PCP, and 3-methoxyeticyclidine. 2- and 4-MeO-PCP were first synthetized in 1965 [2], while 3-MeO-PCP was first described in 1979 [3]. Although there is limited information available on these compounds, their behavioral effects are closely related to those produced by dissociative anesthetics, such as ketamine, methoxetamine, and PCP with high affinity for the PCP site on the glutamate *N*-methyl-D-aspartate (NMDA) receptor. In addition, they present appreciable affinities for the serotonin transporter and high affinities for sigma receptors [4].

The compounds have numerous psychedelic effects which are characteristic of dissociative anesthetics and include dissociation from the physical body, visual and auditive hallucinations, altered time and space, and change of consciousness. They also have stimulating effects like euphoria or empathy. 3-MeO-PCP, like PCP, is active via oral, inhalation, and injection routes in the low milligram range (3–5 to 10–20 mg) and therefore can be hard to accurately measure, being prone to overdosage [5]. It produces many adverse effects, including psychosis, confusion, violent behavior, hypertension, tachycardia, suicidal impulses,

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and coma up to death. Dosage of 4-MeO-PCP is much higher, as the usual oral dose can be up to 250 mg. This difference in drug activity between isomers can be responsible of acute and severe intoxication in case of confusion by addicts [6]. Both drugs are available as powder or tablets.

To date, there are very few published reports on 3-MeO-PCP intoxications. Zidkova et al. [7] detected the drug in the serum of two subjects admitted to hospital for disorientation and hallucinations at 49 and 66 ng/mL. In Italy, Bertol et al. [8] found 180 and 350 ng/mL in the blood from two patients admitted to hospital in a comatose state. A nonfatal intoxication with a 3-MeO-PCP blood concentration at 140 ng/g at admission and seven deaths with femoral blood concentrations ranging from 50 to 380 ng/g were described by Johansson et al. [9]. Based on a multi collection of blood specimens from the nonfatal intoxication, the half-life of 3-MeO-PCP was estimated to 11 h. Finally, in two other papers [10, 11], 3-MeO-PCP peripheral blood concentrations were 3200, 630, and 139 ± 41 ng/mL from three postmortem cases. This demonstrates that there are no clear toxic and fatal concentrations established for 3-MeO-PCP, mainly because the drug is often associated to other recreative substances.

The objective of this publication is to present the analytical procedure established for assaying 3-MeO-PCP in postmortem specimens obtained from the victim of a murder while under the influence of the drug and to discuss possible aggressive behavior due to impairment.

Case history

A 39-year-old white woman (1.58 m tall, 61 kg) with a history of illicit drug use (heroin, cannabis, cocaine, GHB) was found dead at home after being assaulted by her partner. To the police, he immediately reported an altercation while under the influence of various drugs and he admitted having strangled her with a rope in order to constrict her neck. Various paraphernalia were also found at the scene, including spoons and plastic pipettes. External examination of the victim confirmed the presence of parched, horizontal ligature mark encircling the neck. A broad band-like red area, due to intense subcutaneous hemorrhage, and a clear ligature mark consisting of abrasions were visible. Autopsy showed fractures with associated hemorrhage of the superior horn of the thyroid cartilage and of the right greater horns of the hyoid bone, respectively. Intense multi viscera congestion was noticed. During the autopsy, femoral blood, bile, urine, and hair (10 cm, brown) were collected for toxicological investigations.

Blood from the partner, preserved with sodium fluoride and collected about 1 h after the event, was also tested for alcohol, pharmaceuticals, and drugs of abuse. The test revealed no alcohol, diazepam (2120 ng/mL), nordiazepam (2540 ng/mL), oxazepam (830 ng/mL), methadone (290 ng/mL), EDDP (54 ng/mL), Δ9-tetrahydrocannabinol (8.1 ng/mL), 11-OH-THC (2.8 ng/mL), and THC-COOH (190 ng/mL). All these drugs should have markedly impaired the subject. No 3-MeO-PCP was detected in his blood.

Toxicological analyses

Ethanol was tested by head space GC/FID on a Perkin Elmer system (TurboMatrix 40 & Clarus 580) using a standard validated procedure. Volatiles were tested by head space GC/MS on a Thermo system (Focus GC & DSQII) using a standard validated procedure. ELISA tests for illegal drugs were achieved using Alere Microplate kits using the recommendations of the manufacturer. Pharmaceuticals and drugs of abuse (including NPS) screenings were performed with ultra-performance liquid chromatography-diode array detection (Waters UPLC-PDA) and ultra-performance liquid chromatography tandem mass spectrometry (Waters UPLC-MS/MS).

During the initial screenings, 3-MeO-PCP or 4-MeO-PCP, which have the same chromatographic behavior (same retention time, same MRM transitions), was identified in the femoral blood. Discrimination of the positional isomer was obtained by GC/MS on a Perkin Elmer system (Clarus 680 and Clarus SQ 8T) as their retention times differ, i.e., 8.58 min for 3-MeO-PCP and 8.74 min for 4-MeO-PCP, while both have the same mass spectrum (*m*/*z* 230, 272, 273, 121, 216). The results were consistent with the presence of 3-MeO-PCP in the blood of the victim (one single chromatographic peak at 8.58 min).

As a consequence, a specific MRM method for 3-MeO-PCP testing in postmortem fluids and hair was developed.

3-MeO-PCP was extracted from 1 mL of fluid (blood, urine, bile) in presence of 2 ng of MDMA-d_5 used as internal standard, with 1 mL borate buffer pH 9.5 and 5 mL of a mixture of ether/dichloromethane/hexane/isoamyl alcohol (50/30/20/0.5). After extraction, centrifugation, and evaporation to dryness, the residue was reconstituted in 50 μL of ammonium formate buffer adjusted at pH 3.

Hair analysis of 3-MeO-PCP was performed after decontamination with dichloromethane and segmentation into 3 × 2-cm segments to cover the last 6 months before death, assuming a growth rate of 1 cm/month. Twenty milligrams was incubated overnight at 50 °C in 1 mL borate buffer pH 9.5, in presence of MDMA-d_5, and then, the mixture was extracted as blood.

Chromatography was achieved using a Waters HSS C18 column (150 × 2.1 mm × 1.8 μm) maintained at 50 °C in a thermostatically controlled enclosure. A gradient elution was performed using formate buffer adjusted to pH 3 (mobile phase A) and 0.1% formic acid in acetonitrile LC-MS (mobile phase B) as mobile phases at flow rate of 0.4 mL/min. The initial gradient was 87% mobile phase A and the final gradient, at 7 min, was 5% mobile phase A. An injection volume of 10 μL was used in all cases. A Xevo triple quadrupole mass

spectrometer was used for the detection of the drugs. Ionization was achieved using electrospray in the positive ionization mode (ES+).

The following conditions were found to be optimal for the analysis of 3-MeO-PCP and the internal standard: capillary voltage at 1.5 kV, source block temperature at 149 °C, desolvation gas nitrogen heated at 600 °C and delivered at a flow rate of 1000 L/h. In order to establish appropriate multiple reaction monitoring condition, the cone voltage was adjusted to maximize the intensity of the protonated molecular ion, and collision-induced dissociation of both species was performed. Collision energy was adjusted to optimize the signal for the two most abundant product ions of 3-MeO-PCP, i.e., *m/z* 274.0 > 120.9 (CV, 10 V; CE, 28 eV) and 274.0 > 188.9 (CV, 10 V; CE, 35 eV), and the most abundant product ion of internal standard *m/z* 198.9 > 164.9 (CV, 22 V; CE, 14 eV). Transition *m/z* 274.0 to 120.9 was used for quantification of 3-MeO-PCP. These transitions have already been described in the literature [9, 11]. MassLynx 4.1 software was used for quantification.

Linearity was observed in blood for 3-MeO-PCP concentrations ranging from 10 to 1000 ng/mL, with a correlation coefficient of 0.998. QC samples (50 and 200 ng/mL), analyzed in duplicate in six independent experimental assays, were used for determination of a coefficient of variation for precision and accuracy. These CVs were lower than 20%. Linearity was observed in hair for 3-MeO-PCP concentrations ranging from 10 to 1000 pg/mg, with a correlation coefficient of 0.999. QC samples (50 and 200 pg/mg), analyzed in duplicate in six independent experimental assays, were used for determination of a coefficient of variation for precision and accuracy. These CVs were lower than 20%. Under the used chromatographic conditions, there was no interference with the analytes by chemicals or any extractable endogenous materials present in blood or in hair.

Results and discussion

The analysis by gas chromatography coupled to mass spectrometry allowed the unambiguous identification of 3-MeO-PCP (Fig. 1) in the femoral blood of the victim and ruled out a possible contribution of its positional isomer 4-MeO-PCP. Using a dedicated UPLC-MS/MS method, the concentration of 3-MeO-PCP in the femoral blood was 63 ng/mL. The drug tested also positive in other biological matrices (Table 1). The blood concentration is close to the toxic values reported in intoxicated patients [7]. It is therefore possible to anticipate that the victim was impaired due to 3-MeO-PCP abuse. The psychoactive effects of the drug were even enhanced by simultaneous consumption of other CNS depressants. Indeed, blood alcohol concentration was 1.37 g/L and diazepam (157 ng/mL) and its main metabolite, nordiazepam (204 ng/mL), and cocaine (25 ng/mL) and its metabolites, benzoylecgonine (544 ng/mL) and cocaethylene (43 ng/mL), were identified in blood. Other authors [6–11] have also reported combination of 3-MeO-PCP with other drugs in both fatal and nonfatal intoxications. Although metabolites of 3-MeO-PCP, including hydroxylated, carboxylated, and O-demethylated metabolites, have been identified in human liver preparations [12], there was no attempt to characterize them in urine, mostly because the reference standards are not commercially available.

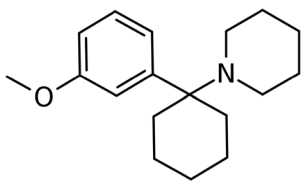

Fig. 1 Structural formula of 3-MeO-PCP

Segmental hair analysis is used to verify both previous drug history and recent enforced abstinence. Hair analysis is mostly suitable for accurately monitoring relative changes in drug intake by the same individual [13]. The hair test result for 3-MeO-PCP was the following: 731 (0–2 cm), 893 (2–4 cm), and 846 pg/mg (4–6 cm), supporting repetitive consumption of the drug over the last 6 months. Methadone (+ EDDP), cocaine and metabolites, and 6-acetylmorphine as specific marker of heroin were also identified in hair, clearly confirming the addiction to drugs of the donor. The toxicological significance of the measured concentrations is difficult to establish because this is the first case describing hair analysis for 3-MeO-PCP in the medical literature. Also, there is no controlled study about pharmacokinetic parameters of 3-MeO-PCP incorporation into hair. It is therefore not possible to interpret the data in terms of dosage and frequency of abuse. In a recent article, Salomone et al. [14] have highlighted the difficulties in interpreting results of hair analysis for NPS. In particular, little is known about the incorporation into the keratin matrix after intake and the correlation between dosage frequency of use and hair concentrations. The authors also considered different scenarios such as passive exposure vs. active consumption, mindful vs. unaware intake, and sporadic vs. chronic use. Due to these actual limitations, the authors

Table 1 Distribution of 3-MEO-PCP in the biological specimens collected during autopsy

Specimen	3-MeO-PCP concentration
Femoral blood	63 ng/mL
Bile	64 ng/mL
Urine	94 ng/mL
Hair, 0–2 cm	731 pg/mg
Hair, 2–4 cm	893 pg/mg
Hair, 4–6 cm	846 pg/mg

concluded that NPS hair results should be interpreted with caution by experienced forensic toxicologists.

The key point of this case report is the involvement of 3-MeO-PCP in the behavior of the victim. Blood and hair findings have demonstrated long-term abuse of several drugs. Among them, 3-MeO-PCP seems the most active to produce vivid hallucinations, typed auditory, visual, and tactile. There is a paucity of data on 3-MeO-PCP and its clinical effects and only one paper [15] reports an attempted murder by a subject under the influence of the drug. Unfortunately, no biological specimen was collected at the time of the event. In comparison, aggressive behavior, violence, and physical assault have been frequently described for PCP since 1979 [16–19]. It has been shown that PCP users have different characteristics from other drug users and that female PCP use is more common than use among males. Furthermore, there is evidence that those who respond to PCP with violence may differ from those who do not. In particular, female PCP using subjects reported more dysphoria and aggressiveness when not using PCP, while male subjects were more likely to report aggressive behavior and dysphoria under the influence [19]. However, the assumption that PCP provokes violent behavior in humans with predictable regularity has been challenged by some authors [20] who concluded after examination of hundreds of patients that clinical and forensic assumptions about PCP and violence are not warranted. Based on limited literature [6–9] on analytically confirmed nonfatal intoxications, there is little doubt that the measured 3-MeO-PCP concentration in the blood of the victim was responsible of strong behavior alteration. Thus, this, in combination with other drugs, should be considered as possible enhancers of the aggressive situation which has promoted the homicide.

Conclusion

3-MeO-PCP is a highly attractive drug for abusers seeking an alternative to PCP or for those who want to experiment new sensations (drug testers). It is one of the most potent known NMDA antagonists. The drug is easily accessible via the Internet at affordable prices. According to users, abuse dosages are usually in the range 3 to 20 mg and the duration of the effects has been reported to be 4 to 5 h. It is not detected by most routine drug screening tests and can be mixed up with the less potent 4-MeO-PCP. Confusion between both positional isomers can have serious health consequences and there is no way for users to know exactly what they are consuming. This work has presented a murder case where the victim was under the influence of 3-MeO-PCP and, according our knowledge, for the first time hair concentrations from a repetitive user.

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