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CASE REPORT

A fatal case of 3-methylmethcathinone (3-MMC) poisoning

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Summary Synthetic cathinones are one of the major pharmacological families of new psychoactive substances (NPS). We report a case of a young man who was found dead a couple of hours after sniffing substances bought on the Internet from Spain. 3-methylmethcathinone (3-MMC) was identified during general unknown screening by liquid chromatography with diode array detector and gas chromatography coupled to mass spectrometry. Quantification of 3-MMC was performed by gas chromatography tandem mass spectrometry after solid-phase extraction. Toxicological analysis of postmortem peripheral blood, cardiac blood, vitreous humor, bile and urine revealed 3-MMC in concentrations of 249 ng/mL, 609 ng/mL, 2988 ng/mL, 1291 ng/mL and 29,694 ng/mL, respectively. Powder and crystals seized at victim's home contained 32.9% and 36.9% of 3-MMC, respectively. No other xenobiotics were detected in postmortem samples. The cause of death was 3-MMC intoxication and the manner was accidental.

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Introduction

Synthetic cathinones are related to the main psychoactive compounds of the khat plant. Since the 2000s, substances derived from cathinone have appeared on the European recreational drug market as alternatives to amphetamines [1]. The most widely encountered is 4-methylmethcathinone (4-MMC), also called mephedrone. To circumvent narcotic legislation, cathinone isomers and analogs were synthesized; more than 50 derivates were identified in Europe [2]. Two position isomers of mephedrone, 2-methylmethcathinone (2-MMC) and 3-methylmethcathinone (3-MMC), are available on the market. In France, mephedrone was classified as an illegal narcotic in 2010, and the generic cathinone family has been forbidden since July 2012 [3]. However, the French Observatory of Drugs and Drug Addiction (*Observatoire français des drogues et des toxicomanies* [OFDT]) reported 3-MMC and 2-MMC seizures in France, in 2014 and 2015, respectively [4]. Between 2012 and 2014, Cheze et al. [5] analyzed 64 cathinone seizures in France; two were identified as 3-MMC. Several fatal intoxications were reported in the literature involving 3-MMC associated to other drugs, such as 5-(2-aminopropyl)benzofuran (5-APB) [6] or gamma-hydroxybutyric acid (GHB) [7]. We here report a case of death exclusively involving 3-MMC, with quantification in the available postmortem matrices.

Case report

A 32-year-old man found dead at his home. According to some witnesses, after sniffing one or two lines of a white powder, the man suffered from headache and warm sensations. He lay down on a sofa at about 2:00 AM and was found dead at 7:00 AM. Some packets identified as 3-MMC containing crystals and a white powder, purchased on the Internet from Spain, were discovered in the victim's home. The deceased's personal history showed recreational GHB consumption. An autopsy was performed, and no sign of violence or any obvious cause of death was found. Full examination showed some non-specific indicators compatible with toxic death: major pulmonary edema associated with sero-hematic lung, and vascular congestion and edema, which spread to various organs. Several biological samples were collected for toxicological analysis: peripheral blood, cardiac blood, urine, vitreous humor (VH) and bile. Blood samples were collected in tubes with preservative (sodium fluoride). Samples were stored at 4 °C prior to analysis.

Material and methods

Standards and reagents

Certified stock solutions of mephedrone (4-MMC) at a concentration of 1 mg/mL, mephedrone-d3 and hydroxybutyric acid-d6 (GHB-d6) at 0.1 mg/mL were purchased from Euromedex (Souffelweyersheim, France). 2-MMC and 3-MMC at a concentration of 1 mg/mL were provided by LGC Standard (Molsheim, France). Methanol (MeOH), hydrochloric acid 1 M (HCl), ethyl acetate (EA), isopropanol (IPA), acetonitrile (ACN), sulfuric acid 95—97%, and ammonia 25% (NH_4OH) at HPLC grade were obtained from V.W.R (Fontenay-sous-Bois, France). *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) 1% chlorotrimethylsilane (TMCS) was purchased from Sigma Aldrich (Saint-Quentin Fallavier, France). DrugScreen® immunochromatographic assay for amphetamine, methamphetamine, opioids, cannabinoids, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), and buprenorphine were purchased from Nal Von Minden (Regensburg, Germany). Strata X Drug B solid-phase extraction (SPE) cartridges (3 mL, 60 mg) were purchased from Phenomenex (Le Pecq, France). Water was dispensed by a PurelabElga® purifier (Veolia Water, Solutions & Technologies, Décines, France). Mephedrone-d3 was used as internal standard (IS) at a concentration of 10 ng/μL in methanol. For calibration standards and quality control (QC), appropriate dilutions were made from the solutions of 4-MMC, 3-MMC and 2-MMC at 1 mg/mL.

Routine toxicological analysis

Immunological screening was performed on urine. Quantitative analysis for ethanol was performed on peripheral blood and urine, using a headspace (Triplus) gas chromatograph (Trace GC) coupled to a mass spectrometer (DSQ II) (Thermo Electron, Courtaboeuf, France). General unknown screening (GUS) was performed after liquid-liquid extraction on urine by gas chromatography (7890B, Agilent Technologies, Massy, France) coupled to mass spectrometry (5977A, Agilent Technologies) (GC-MS), and on cardiac blood by liquid chromatography with a diode array detector (LC-DAD) (1100 Series, Agilent Technologies). LC-DAD conditions were previously described [8]. For GC-MS assay, the injector in splitless mode was set at a temperature of 280 °C. Separation was performed on an HP-5MS capillary column (length 12 m, 0.18 mm ID, film thickness 0.18 μm; Agilent). The initial oven temperature of 90 °C was held for 0.85 min, then increased by 21.5 °C/min to 200 °C, followed by a rate of 16 °C/min to 300 °C, held for 11 min; total run time was 23.2 min. Helium was used as carrier gas at a constant flow of 0.7 mL/min. The transfer line was set at 300 °C. Molecules were identified using homemade and commercial libraries: SWGDrug 2015, Pfleger 2011, and Wiley 2007 for GC-MS using macro-command [9].

Quantitative analysis of GHB

Blood, urine, and bile samples (200 μL) were spiked with 15 μL GHB-d6 at 100 ng/μL as IS. A total of 100 μL sulfuric acid (0.05 M) was added, followed by 3 mL EA. After 10 min agitation, the mixture was centrifuged for 10 min at 2000 g. The supernatant was evaporated to dryness under nitrogen stream at room temperature. Dry residues were derivatized by adding 30 μL BSTFA 1%TMCS (30 min at 80 °C). One microliter of sample was injected in splitless mode in a GC-MS using a 6890 N GC system coupled to a 5975 MS detector (Agilent Technologies). The injector was set at 250 °C. Separation was performed on an HP-5MS capillary column (30 m × 0.25 mm i.d. × 0.25 μm film thickness; Agilent). The initial oven temperature of 60 °C was held for 2 min, then increased by 20 °C/min to 260 °C; total run time