Journal of Analytical Toxicology, 2016;40:86–87
doi: 10.1093/jat/bkv110
Advance Access Publication Date: 9 September 2015
Letter to the Editor

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Sudden Cardiac Death Following Use of the Synthetic Cannabinoid MDMB-CHMICA

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Synthetic cannabinoids first appeared in Europe in 2008, and by 2014 a total of 134 different compounds belonging to this class of drugs had been described (1). Their pharmacological effects are highly unpredictable and range from a mild cannabis-like 'high' to death (2). We report our first case of a fatal intoxication by a drug which has allegedly been implicated in an increasing but hitherto not comprehensively reported number of cases of deaths and intoxications (3); the indole-based synthetic cannabinoid MDMB-CHMICA (methyl-(*S*)-2-(1-(cyclohexylmethyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate) (Figure 1).

A 22-year-old male with an unremarkable medical history was found lifeless by friends after being alone for ~15 min after smoking a brown organic powder alleged to be a synthetic cannabinoid. Upon arrival of ambulance personnel, he was found to have asystole. He received emergency treatment on site, spontaneous circulation was reestablished and he was subsequently transferred by helicopter to an intensive care unit at the St. Olav University Hospital. The following day the patient was declared dead due to brain hypoxia. He underwent organ donation and medico-legal autopsy, where changes commensurate with anoxic brain damage and pneumonia were present. No signs of injury or illness that could explain the circulatory collapse or brain damage were present.

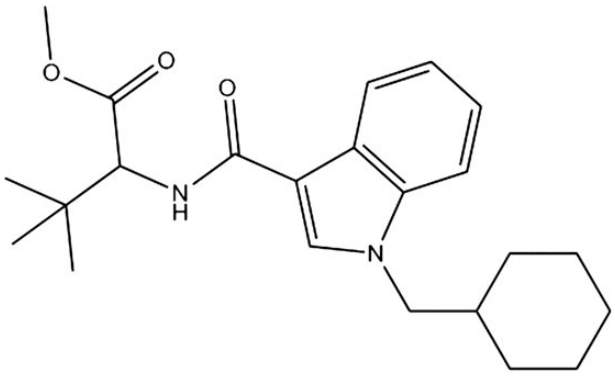

Figure 1. The structure of MDMB-CHMICA.

In the brown powder, MDMB-CHMICA was identified by accurate mass and MS–MS-spectra, later confirmed with reference material, using an Agilent 1290 Infinity liquid chromatograph coupled to an Agilent 6550 quadrupol time-of-flight mass spectrometer (LC–QTOF–MS). A method for quantification of MDMB-CHMICA in serum, blood and spleen was developed. In brief, 1 mL aliquots of calibrators and controls were fortified with MDMB-CHMICA (from Cayman Chemicals, AH Diagnostics, Oslo, Norway) to relevant levels, followed by addition of the internal standard d3-diazepam and precipitation with acetonitrile (ACN). The supernatants were evaporated to dryness and reconstituted in 50 µL 30% ACN in water. Analysis was performed with the LC–QTOF–MS using the mobile phase in a gradient from 98% A (5 mM ammonium formate in 0.025% formic acid) to 100% B (0.05% formic acid in ACN) during 15 min on an ACE EXCEL 2 C18-AR (100 × 2.1 mm, 2 µm) column. All other quantitative analyses in serum and urine were done according to accredited laboratory routines.

A serum sample obtained ~2 h after the victim was found in his flat was screened against a database of ~10,000 known substances using an LC–QTOF–MS method, and the positive findings were confirmed with specific methods. The serum sample contained MDMB-CHMICA (1.4 ng/mL), mirtazapine (5.3 ng/mL), tetrahydrocannabinol (1.5 ng/mL) and cetirizine (not quantified). The measured serum level of mirtazapine is subtherapeutic, and the serum level of tetrahydrocannabinol of a magnitude frequently encountered the first hours after cannabis exposure. A low level of ethanol was measured in urine, but not in the serum sample. Toxicological analyses

were also performed in postmortem splenic tissue (blood was not available because of organ donation), using screening and confirmation procedures similar to the serum analyses. The findings in splenic tissue reflected the measured serum levels and subsequent intensive care treatment. The spleen postmortem level of MDMB-CHMICA was 0.1 ng/mL. In the absence of other causes, it was concluded that the death was most probably caused by an overdose of MDMB-CHMICA.

To our knowledge, this is the first reported case where a fatality after exposure to MDMB-CHMICA has been linked to a serum level of the drug obtained a short time after the victim lost consciousness. Although no MDMB-CHMICA cases have so far been reported in the medical literature, regular media have reported at least six MDMB-CHMICA deaths in Europe in 2015 (3), and some very similar compounds have been linked to several overdoses and fatalities (2). As yet, there is no information corroborating that a level of the drug of 1.4 ng/mL may be fatal, and the pharmacokinetic and pharmacodynamic properties of the drug are, to say the least, obscure. In lieu of the short time span and the fact that serum was obtained from a living (but, by all indications, seriously brain damaged) individual may nevertheless shed some light on the acute toxicological profile of MDMB-CHMICA.

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