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Analysis and Clinical Findings of Cases Positive for the Novel Synthetic Cannabinoid Receptor Agonist MDMB-CHMICA

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Abstract

Context: MDMB-CHMICA is a synthetic cannabinoid receptor agonist which has caused concern due to its presence in cases of adverse reaction and death. *Method:* 43 cases of suspected synthetic cannabinoid ingestion were identified from patients presenting at an Emergency Department and from post-mortem casework. These were subjected to liquid-liquid extraction using tertiary-butyl methyl ether and quantitatively analysed by Electrospray Ionisation Liquid Chromatography – tandem Mass Spectrometry. For positive samples, case and clinical details were sought and interrogated. *Results:* 11 samples were found positive for MDMB-CHMICA. Concentrations found ranged from <1 – 22 ng/mL (mean: 6 ng/mL, median: 3 ng/mL). The age range was 15 – 44 years (mean: 26 years, median: 21 years), with the majority (82%) of positive results found in males. Clinical presentations included hypothermia, hypoglycaemia, syncope, recurrent vomiting, altered mental state and serotonin toxicity, with corresponding concentrations of MDMB-CHMICA as low as <1 ng/mL. Duration of hospitalisation ranged from 3 – 24 hours (mean: 12 hours, median: 8 hours). *Discussion:* The concentration range presented in this case series is indicative of MDMB-CHMICA having a high potency, as is known to be the case for other synthetic cannabinoid receptor agonists. The age range and gender representation were consistent with that reported for users of other drugs of this type. The clinical presentations observed were typical of synthetic cannabinoid receptor agonists and show the difficulties in identifying reactions potentially associated with drugs of this type. *Conclusion:* The range of MDMB-CHMICA concentrations in Emergency Department presentations (n=9) and post-mortem cases (n=2) was reported. No correlation between the concentration of this drug and clinical presentation or cause of death was reported in

this sample. However, the potential for harm associated with low concentrations of MDMB-CHMICA and the symptoms of toxicity being non-specific was highlighted.

Introduction

MDMB-CHMICA (methyl-2-(1-(cyclohexylmethyl)-1 H-indole-3-ylcarbonylamino)-3,3-dimethyl butanoate, Figure 1), is a novel indole-based compound in the 'synthetic cannabinoid receptor agonist' (SCRA) drug group. It has previously been erroneously referred to as MMB-CHMINACA. Based on SCRA nomenclature, however, 'CHMINACA' indicates an indazole – rather than indole – structure, and 'MMB-' indicates an isopropyl - rather than tertiary butyl - group.

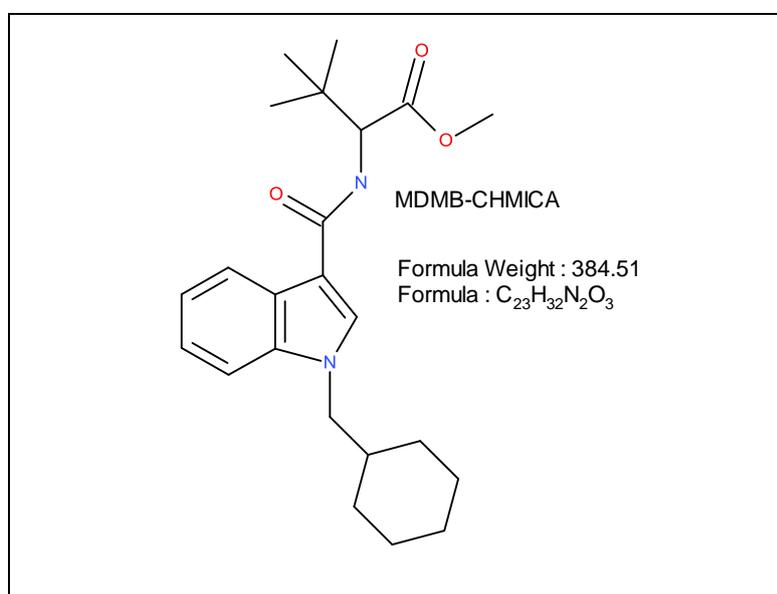


Figure 1 – Structure and chemical formula of MDMB-CHMICA

The potential dangers of MDMB-CHMICA were first highlighted by the European Monitoring Centre for Drug and Drug Addiction Early Warning System (EMCDDA EWS) in December 2014 when seven non-fatal intoxications were linked to the drug in Austria¹. Shortly after these adverse reactions, ten intoxications – four proving fatal – were reported in Sweden¹. A third alert was issued in April 2015 reporting two deaths and three non-fatal intoxications linked to the drug in Germany². Adverse reactions reported in the latter included seizures, severe motor impairment, and persistent vomiting; recorded causes of death included probable methadone intoxication and suffocation on aspirated gastric contents related to ethanol intoxication. In addition to this, details of seizures of the drug were given, including 40 kg en route from China to Spain seized in Luxembourg². As of the beginning of May 2016, MDMB-CHMICA is not controlled in the U.K., but has been confirmed as an ingredient in several products including 'AK47 Loaded', 'Manga Hot', 'Cloud 9-second

generation-Mad Hatters-incense', 'Black Diamond', 'AKB48-F', 'PB-22-F', 'Sky High' and 'Sweet Leaf Obliteration' in Europe^{2,3}.

There is currently a paucity of data regarding the pharmacology and toxicology of MDMB-CHMICA, but case reports describe vomiting, seizures, and psychological distress as possible sequelae from ingestion. A case report from Norway implicates an ante-mortem serum concentration of 1.4 ng/mL MDMB-CHMICA as the probable cause of death, although mirtazapine (5.3 ng/mL), Δ^9 -tetrahydrocannabinol (Δ^9 -THC, 1.5 ng/mL), and cetirizine (not quantified) were also present⁴.

The first reports of adverse reactions to MDMB-CHMICA in the U.K. were reported in the summer of 2015 with one in North Wales and one in Glasgow^{5,6}. In response to this the authors developed and validated an LC-MS/MS method, with a simple liquid-liquid extraction for the quantification of MDMB-CHMICA in whole blood.

Materials and Methods

Materials

MDMB-CHMICA was purchased from Chiron (Trondheim, Norway) and JWH-200-d₅ was purchased from LGC Standards (Teddington, U.K.). Phosphate buffer (pH 6, 0.1M) was prepared in-house from disodium hydrogen orthophosphate anhydrous and sodium dihydrogen orthophosphate dihydrate from Fisher Scientific (Loughborough, U.K.) and deionised water produced from a Purite (Thame, U.K.) deionised water system. *Tertiary* methyl butyl ether (tBME) and ammonium acetate were purchased from Sigma Aldrich (Gillingham, U.K.). Methanol and acetonitrile, both HPLC grade, and formic acid were obtained from VWR (Lutterworth, Leicestershire, U.K.). Blood products were purchased from the Scottish National Blood Transfusion Service (SNBTS) based at Gartnavel Hospital (Glasgow, U.K.).

Methods

Sample Collection and Data Analysis

The laboratory at Forensic Medicine and Science (FMS) provides post-mortem (PM) toxicology services for the cities of Glasgow, Edinburgh and Dundee and their surrounding regions, as well as an ongoing research project analysing Emergency Department (ED) admission samples for Novel Psychoactive Substances (NPS). Between the 1st of September and the 9th of December 2015, 43 cases were submitted for MDMB-CHMICA analysis to the laboratory, comprising 17 PM submissions and 26 cases from the ED of Glasgow Royal

Infirmiry. The decision to conduct MDMA-CHMICA analysis on a sample was made on case circumstances suggestive of SCRA use. It is acknowledged that in some circumstances case details may have been misleading or lacking leading to incorrect inclusion or exclusion of cases.

Unpreserved blood samples were obtained either by collection at autopsy for PM cases, or during the clinical management of ED patients. The NHS Greater Glasgow and Clyde Research and Development Committee advised ethical approval was not required for this service development study. With regards to the PM cases, the medical histories of the deceased and basic PM findings were reviewed. Prior to toxicological analysis, only limited presenting symptoms and potential substances ingested were known for ED samples.

On receipt at Forensic Medicine and Science, the specimens were stored between 2 – 8 °C prior to analysis. These were submitted for MDMA-CHMICA analysis if the case circumstances suggested that SCRA may have been used prior to death or hospital treatment. The additional analyses conducted were dependant on case circumstances and available sample volume, and included alcohol and the most prevalent prescription and recreational drugs.

On completion of toxicological analysis, each case was reviewed in terms of gender and age of individual, other toxicological findings, drug product ingested (if noted) and any other relevant circumstantial information. Where the case was a PM investigation, the assigned cause of death was also noted.

Toxicological Analysis

MDMA-CHMICA was detected and quantified using an Agilent 1260 Infinity Liquid Chromatography (LC) system coupled with tandem Mass Spectrometry (MS; ABSciex 3200 QTRAP® instrument). A calibration range of 1 – 100 ng/mL MDMA-CHMICA was employed. Extraction of the analyte plus internal standard (I.S., JWH-200-d₅ at 25 ng/mL) was undertaken through a liquid-liquid extraction process, by adding tBME (2 mL) to 100 µL blood sample plus 2 mL pH 6.0, 0.1 M phosphate buffer. Chromatographic separation took place on a Phenomenex Gemini C18 column (150 mm x 2.0 mm, 5 µm) fitted with a guard column of the same packing material, held at 40 °C, and using a mobile phase flow rate of 300 µL/min. The mobile phase was run isocratically and was composed of 0.1% formic acid and 2 mM ammonium acetate in 20% deionised H₂O and 80% methanol. MS detection was conducted using positive Electrospray Ionisation (ESI) with multi-reaction monitoring (MRM). The transitions monitored for MDMA-CHMICA were m/z 385 → 240 for the quantification transition and m/z 385 → 144 and 116 (qualifier transitions), with m/z 390 → 155 for the I.S.

The method was validated according to the following criteria: linearity with 1/x weighting was assessed by analysing calibrators of 1, 5, 10, 25, 50 and 100 ng/mL, evaluating the linear model and correlation co-efficient. Selectivity was determined by the absence of a MDMA-CHMICA peak in MDMA-CHMICA-free samples. The lower limit of quantification (LLOQ) was defined as the lowest calibrator, ensuring a signal-to-noise ratio of at least 10:1. The limit of detection (LOD) was designated as the lowest concentration affording a signal-to-noise ratio of 3:1. Inter- and intra-day accuracy and precision were determined at 10 and 42 ng/mL, with accuracy defined by the ratio of the mean actual concentration of triplicate standards to their expected concentration multiplied by 100, and the %CV of the triplicate results taken as the precision. Process efficiency was determined at 50 ng/mL by comparison of the mean peak area of calibrators extracted from blank blood in triplicate to those of an unextracted solution of equivalent concentration. Matrix effects were assessed at 50 ng/mL using the Matuszewski method⁷ and 6 distinct sources of blank blood.

Results

Toxicological Analysis

Linearity was assessed over the calibration range 1 – 100 ng/mL and established ($R^2 > 0.99$) using 1/x weighted regression. The LLOQ was assigned as the lowest calibrator (1 ng/mL), with LOD determined to be 0.5 ng/mL. Mean inter-day accuracy was found to be 102 and 104% at 10 and 42 ng/mL respectively; and the mean precision at the same concentrations was $\leq 8.3\%$ and $\leq 5.3\%$ respectively. Mean intra-day precision was found to be $\leq 4.7\%$ at 10 ng/mL and $\leq 3.7\%$ at 42 ng/mL; and the mean accuracy was calculated as 96% and 108% for 10 ng/mL and 42 ng/mL respectively. Process efficiency was calculated as 90% at 50 ng/mL. Slight ion enhancement was observed when the matrix effects were assessed, the most significant of these being an extracted peak area at 116 % of the unextracted equivalent.

The ion transitions employed in MDMA-CHMICA analysis were found to be identical to those used for another SCRA, BB-22 (1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid 8-quinolinylnyl ester), which is similar structurally and shares the precursor ion m/z 385. In addition to this, these drugs were not resolved chromatographically on the MP system in use. In order to distinguish between the two drugs, the ratio of the quantitation transition (m/z 385 \rightarrow 240) to the qualifier transition (m/z 385 \rightarrow 116) was calculated and this value differed sufficiently to allow distinction. However, it is important to bear in mind the resemblance of these substances in terms of analytical behaviour.

Analysis of Case Samples

Between the 1st of September and the 9th of December 2015, 43 blood samples were submitted for MDMA-CHMICA analysis, comprising 17 PM cases and 26 ED cases, with a total of 11 found to be positive for the drug. Concentrations ranged from <1 to 22 ng/mL, with a mean of 6 ng/mL and median of 3 ng/mL. These cases are detailed in Table 1 and Table 2 for ED and PM cases respectively. With regards to the cases negative for this analyte, generally these were found positive for other drugs which would account for the observed symptoms. This, however, falls outside the scope of this study.

The age range was 15 – 44 years (mean: 26, median: 21). The gender split was 82% males to 18% females.

The most prevalent substance found in combination with MDMA-CHMICA in the samples tested was alcohol, which was present in 60% of MDMA-CHMICA-positive cases at concentrations from 79 to 237 mg/dL (mean: 163, median: 178). It should be noted that alcohol analysis was not conducted in case 10, as it was not requested by the pathologist. The main active component of cannabis, Δ^9 -THC, or its metabolite, 11-nor- Δ^9 -THC-COOH, was also present in 27% of cases.

The predominant clinical features on presentation at ED were syncope, present in 67% of ED cases, and recurrent vomiting, present in 33% of ED cases. With the exception of cases 1, 5 and 8 body temperatures were indicative of hypothermia with mean and median body temperatures of 35.1 °C and 34.8 °C respectively (range: 33.0 – 38.5 °C). Blood glucose concentrations, where noted, ranged from 3.3 – 8.5 mmol/L (mean and median both 5.5) with 75% within the range indicative of fasting. Heart rates ranged from 54 – 150 bpm (mean: 112, median: 120) with sinus tachycardia being the most common presentation (78%). Systolic blood pressure (SBP) ranged from 100 – 148 (mean: 118, median: 116), with the diastolic equivalent (DBP) ranging from 57 – 91 (mean: 71, median: 65). Glasgow Coma Scores (GCS) ranged from 4/15 – 15/15 with the mean and median being 12/15 and 14/15 respectively. Duration of hospitalisation varied, ranging between 3 – 24 hours (mean: 12 hours, median: 8 hours).

The cause of death noted for case number 10 was suicidal hanging; the individual had a history of poor mental health.

With regards to case 11, the cause of death was recorded as complications of chronic alcohol abuse and acute alcohol toxicity.

Discussion

The age range and gender representation is in-keeping with other studies where 'young' males or males in their early 20s have been the most common demographic to be encountered by medical staff treating symptoms of synthetic cannabis use^{8,9}. Of note is the consumption of the drug by an individual under 16 (case 4); there is a lack of understanding as to how MDMB-CHMICA use may affect development either physiologically or mentally.

It is not possible to compare the positivity rate between PM samples and ED admissions due to the non-standardised inclusion criteria for MDMB-CHMICA analysis. The effects of the interval between death and PM, PM sampling and analysis, and the degraded nature of PM blood on MDMB-CHMICA concentrations is unknown, and these complications were unlikely to be present to the same extent in the ED cases. An additional concern is the limited information available regarding potential metabolites of MDMB-CHMICA and no potential metabolites were included in the analytical method presented here.

The presence of alcohol in 60% of cases is unsurprising given its prevalence in Scottish society. Case numbers 6, 7 and 11 exhibit notably high alcohol concentrations; the symptoms of which may themselves require medical intervention. Literature has suggested that users of SCRA are likely to have been or be current cannabis users, and SCRA may be co-administered with cannabis by being smoked in the same 'joint'¹⁰. The presence of cannabinoids or SCRA in cases 2, 3, 6, 8 and 9 is indicative of these substances having been ingested within a similar timescale to or concurrently with MDMB-CHMICA.

With regards to cases 1, 8 and 9, no benzodiazepines were prescribed or used in the treatment of these individuals. The presence of diazepam and/or desmethyldiazepam was due to illicit consumption.

The drug products named, where provided, have largely been found to contain MDMB-CHMICA³. However it is not uncommon for drug product packaging to be misleading or incorrect in terms of ingredients, so this information should be treated with caution.

While little is known currently about the potential short- and long-term psychological effects of SCRA, there is evidence of new psychotic phenomena exhibiting after SCRA use in individuals already undergoing treatment for psychiatric disorders^{8,11}. Known effects of SCRA use are hallucinations, psychosis, anxiety and panic attacks,

and it has been suggested that these may be due to disturbed dopaminergic neurotransmission; also a hypothesis for the aetiology of schizophrenia¹².

Recent media reports have focussed on the apparent prevalence of use of “legal highs” - specifically SCRA - within prisons, and the Prison and Probation Ombudsman for England and Wales has recently issued a report into fatal cases of “legal high” use¹³⁻¹⁵. Some of these incidents included the use of SCRA, although no deaths mentioned in this report suggest SCRA intoxication as a direct cause of death, and the specific drug is not mentioned. The types of behaviours associated with SCRA use, some of which were observed in these cases, would be a troubling occurrence in prison settings, both in terms of safety of the individual under the influence of the drug and those managing the situation. Indeed, the U.K. Government intends to make possession of MDMB-CHMICA and other drugs covered by the Psychoactive Substances Bill an offence whilst in a custodial institution; possession of such a drug out in any other setting will not be prohibited¹⁶.

A recent study analysed the urine of ED patients for Novel Psychoactive Substances (NPS), but acknowledged a limitation that SCRA drugs were not included within the scope of testing¹⁷.

The observation of hypothermia was believed to be reflective of the drug’s action, as all cases occurred during the summer months, when the ambient temperature was around 12 °C, and the patients were brought to hospital relatively quickly after ingestion of the drug.

With regards to case 2, the relatively high concentration of MDMB-CHMICA, along with other SCRA, appeared to have contributed to the recurrent hypoglycaemia, necessitating an intravenous infusion of dextrose, with additional boluses. This pharmacological action is supported, as the patient was found to be smoking the product within the hospital ward during the episodes of profound hypoglycaemia whilst on a dextrose infusion. The overall majority of ED cases (75%) exhibited blood glucose concentrations indicative of fasting. Whilst this could be a symptom of generally poor self-care among drug users, it is an interesting finding as previous studies have linked the ingestion of synthetic cannabinoids to hyperglycaemia^{18,19}.

Heart rates were generally tachycardic (78%) while BP were generally unremarkable. Case number 1 exhibited a heart rate of 150 bpm and was hypertensive. Case 5 also exhibited hypertension, with a BP of 148/91. Case 7 was the only other case outside of the normal BP range, at a pre-hypertensive level of 134/76.

It was of concern that very low concentrations of MDMB-CHMICA were capable of inducing acute toxicity manifesting as a dissociative state (case 9) and clinical features of serotonin toxicity (case 7), suggestive of high

potency. Additional drugs or alcohol present in these cases, idiosyncratic reactions, and/or the presence of active MDMA-CHMICA metabolites must be acknowledged as potential contributing factors to adverse effects. It is not surprising, therefore, that overall the concentrations of MDMA-CHMICA observed do not appear to have any correlation to blood glucose concentration, GCS score, heart rate, blood pressure, or duration of hospitalisation in this case series. However, there does seem to be evidence of the drug causing a decrease in body temperature, which may be of interest in further studies.

With regards to treatment of individuals presenting at the ED, this was administered on a symptomatic basis and guided by local policy. Necessary treatment included the administration of antibiotics due to aspirated vomitus (case 1), intravenous dextrose administration (case 2), urinary catheterisation (case 7), sedation and the administration of cooled fluids (both case 5).

Neither of the PM cases in this case series had causes of death attributable to MDMA-CHMICA toxicity. It is expected that further elucidation of MDMA-CHMICA pharmacology will increase understanding of the potential for this drug to contribute to mortality.

Limitations

The authors acknowledge the small scale of the case series, which was determined by the number of cases submitted for MDMA-CHMICA analysis and the resulting positive cases. The number of cases submitted for analysis was determined by case information, which was limited in some cases and may have been inaccurate due to the illicit nature of the drug and mental state of the individual undergoing emergency treatment. It is possible that the inclusion of metabolites of MDMA-CHMICA would have increased the window of detection for the drug, and additional positive cases may have resulted. The metabolism of this drug is, however, not understood and no reference standards for potential metabolites are commercially available. This is therefore acknowledged as a limitation of this study.

Conclusion

We have presented a series of cases positive for MDMA-CHMICA and the relevant clinical findings, confirming that this drug was used within the Scottish population. Whilst no correlation of MDMA-CHMICA concentration to clinical effects can be confirmed from this limited case series, it was noted that adverse

symptoms were present in a case (case 5) exhibiting an MDMB-CHMICA concentration of <1 ng/mL where no other drugs or alcohol were detected.

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Declarations of Interest

The authors report no declarations of interest.

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Table 1 – Details of ED cases positive for MDMB-CHMICA

Case	Gender	Age (years)	MDMB-CHMICA Conc. (ng/mL)	Ethanol Conc. (mg/dL)	Other Substances Present (mg/L)	Estimated time from use to sampling	Circumstances/Clinical Presentation
1	F	20	5	130	Diazepam (0.075)	1 hour	Ingestion of 'Sweet Leaf' product. GCS [§] 4/15. Temp. 37.5 °C. Glucose 7.1 mmol/L. Heart rate 150 bpm sinus tachycardia, BP 130/90. Persistent vomiting, syncope, respiratory acidosis (Venous blood gases: [H ⁺] 67 [#] , [La ⁻] 1.9 ^{**} , [HCO ₃ ⁻] 25 ^{††} , BE -4.7 ^{††}). 8 hours hospitalisation.
2	M	41	22	ND	5F-AKB48 (present), 5F-PB-22 (present), 5F-PB-22 3-carboxyindole metabolite (present)	1 hour	Ingestion of 'Black Mamba' product. GCS [§] 15/15. Temp. 33 °C. Glucose 3.3 mmol/L. Heart rate 40 bpm sinus bradycardia, BP 110/60. Syncope, recurrent hypoglycaemia (12 hours), background of alcoholism, routine bloods normal. 24 hours hospitalisation.
3	M	25	<5*	80	5F-AKB48 (present), 11-nor- Δ^9 -THC-COOH [‡] (4 ng/mL)	>3 hours	Ingestion of 'Sweet Leaf' and 'Saint Row' products. GCS [§] 15/15. Temp. 35.2 °C. Glucose 3.9 mmol/L. Heart rate 94 bpm sinus tachycardia, BP 102/65. Syncope, vomiting, routine bloods normal. 3 hours hospitalisation.
4	M	15	<2*	ND	ND	1 hour	Ingestion of 'Red Exodus'. GCS [§] 13/15. Temp. 36 °C. Glucose 4.3 mmol/L. Heart rate 54 bpm sinus bradycardia, BP 100/57. Persistent vomiting, syncope, routine bloods normal. 22 hours hospitalisation.
5	M	21	<1	ND	ND	>24 hours	Admitted to ED with acute behavioural disturbance and drug-induced psychosis. Spontaneous urinating/defecating, thought disorder, aggression. Temp. 38.5 °C. Heart rate 150 bpm, BP 148/91. Routine bloods normal. 2 hours hospitalisation.
6	F	16	<1	225	11-nor- Δ^9 -THC-COOH [‡] (9 ng/mL)	1 hour	Ingestion of 'Red Exodus'. GCS [§] 14/15. Temp. 33.9 °C. Glucose 5.6 mmol/L. Heart rate 130 bpm sinus tachycardia, BP 118/74. Combative, acute behavioural disturbance, routine bloods normal. 3 hours hospitalisation.
7	M	18	2	229	ND	40 min.	Ingestion of 'Damnation'. GCS [§] 7/15. Temp. 34.8 °C. Glucose 5.9 mmol/L. Heart rate 120 sinus tachycardia, BP 134/76. Serotonin toxicity (clonus, hyperreflexia), acute behavioural disturbance, mild metabolic acidosis (Venous blood gases: [H ⁺] 54 [#] , [La ⁻] 3.2 ^{**} , [HCO ₃ ⁻] 23 ^{††} , BE -4.8 ^{††}). 19 hours hospitalisation.
8	M	24	1	ND	Δ^9 -THC [¶] (5 ng/mL), 11-nor- Δ^9 -THC-COOH [‡] (35 ng/mL), diazepam (0.2), desmethyldiazepam (0.13), morphine (<0.05)	4 hours	Ingestion of 'Obliteration'. GCS [§] 14/15. Temp. 37.2 °C. Glucose 5.3 mmol/L. Heart rate 108 sinus tachycardia, BP 116/61. Syncope, routine bloods normal. 17 hours hospitalisation.
9	M	20	4	79	Diazepam (0.28), desmethyldiazepam (0.34), 11-nor- Δ^9 -THC-COOH [‡] (23 ng/mL)	2 hours	Ingestion of 'K2'. GCS [§] 12/15. Temp. 34.2 °C. Glucose 8.5 mmol/L. Heart rate 130 sinus tachycardia, BP 100/63. Syncope, dissociative state, confused. 7 hours hospitalisation.

ND Non-Detected; NA Not analysed

* LOD amended due to limited sample volume † β -hydroxybutyrate ‡ 11-Nor- Δ^9 -Tetrahydrocannabinol carboxylic acid ¶ Δ^9 -Tetrahydrocannabinol § Glasgow Coma Scale || Blood Pressure

Hydrogen ions (nmol/L) ** Lactate (mmol/L) †† Bicarbonate (mmol/L) †† Base Excess (mmol/L)

Table 2 - Details of PM cases positive for MDMA-CHMICA

Case	Gender	Age (years)	MDMA-CHMICA Conc. (ng/mL)	Ethanol Conc. (mg/dL)	Other Substances Present (mg/L)	Circumstances/Clinical Presentation
10	M	44	1	NA	Amitriptyline (0.13)	Found dead by hanging.
11	M	38	<1	237	Acetone (<100), BHB [†] (249)	History of alcoholism: found dead at home.

NA Not analysed [†]β-hydroxybutyrate