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A case study on MDMA. Two fatal cases involving young adults

Caterina Politi*, Andrea Gabbin*, Giovanni Cecchetto, Massimo Montisci, Guido Viel and Jennifer P. Pascali

Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padova, Padova, Italy

ABSTRACT

The introduction of new stimulants seems not to hamper the still widespread consumption of MDMA (3,4-methylenedioxymethamphetamine) among young people, especially in determined nightlife settings. Herein, we present two different MDMA-related deaths, providing pathological, histopathological and toxicological data integration. A hypothesis for the mechanisms of the deaths is also discussed. Case 1: an insulin-dependent 16-year-old girl died in a discotheque after the ingestion of MDMA. Before dying she presented seizure, bruxism, trismus, sweating and reduced consciousness. Biochemistry showed hyperglycaemia and hyponatraemia. Toxicological analyses revealed blood MDMA concentration of 1750 ng/mL. Autopsy, accompanied by histological examination, identified cerebral oedema due to hypotonic hyponatraemia as cause of death. Case 2: a 16-year-old girl collapsed during dancing at a rave party. She died 15 hours later in hospital. Autopsy and histology revealed epicardial haemorrhage, hepatitis and disseminated intravascular coagulation. Toxicological analyses revealed blood MDMA concentration of 3700 ng/ml. Cause of death was identified as fulminant liver failure. Since death is not strictly correlated with MDMA blood concentration, to better understand the aetiology of the death after MDMA consumption an integrated and multidisciplinary approach is strongly recommended.

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1. Introduction

Ecstasy is one of the street names for the synthetic compound 3,4-methylenedioxymethamphetamine (MDMA), a ring-derivative of amphetamines, with hallucinogenic and stimulant properties. It is generally used in the form of tablets, but forms such as crystals and powders are also available; tablets are usually swallowed, but crystal and powder forms of MDMA may be taken orally or snorted. According to the most recent EMCDDA (European Monitoring Centre of Drugs and Drug Addiction) report, young Europeans between 15 and 34 years of age consuming MDMA are a total 2.2 million, with an increasing trend observed [1]. The trend in number of users was defined as related to MDMA prices; the lower the cost, the greater the diffusion of the drug. They are mainly young adults, who perceive the drug as having low harm potential and use it to enhance

CONTACT Jennifer P. Pascali jennifer.pascali@unipd.it
*These authors have equally contributed to the manuscript and should be considered co-first authors

entactogenic behaviours especially in nightlife settings. However, MDMA represents one of the main intoxicants detected in the blood of drug addict fatalities [2] in European Nordic Countries. In fact, the introduction and spread of more 'exotic' drugs (i.e. new psychoactive substances), which should sound more appealing to young adults, has not limited MDMA from still playing a role in the sum of fatalities around the world [3–5]. Although the adverse effects of MDMA have been investigated, the pathophysiological mechanism of MDMA-induced death still needs to be fully understood. MDMA is in fact capable of causing both severe acute and chronic toxicity and the pattern of acute toxicity reflects the circumstances in which it is misused. In fact, circumstances associated with ingestion are thought to influence toxicity, which may lead to the death of healthy subjects at the first contact with the drug [6]. In this article, some key features of MDMA-related death are described in two young females. In both cases, MDMA was considered the underlining cause of the death, although a contributory role of pre-existing pathological conditions could not be excluded. A hypothesis for the mechanisms of the deaths is also discussed.

2. Case presentation

2.1. First case

An insulin-dependent diabetic (DM type 1) girl of 16 years old died in a discotheque after the reported consumption of two MDMA tablets. Her history did not include any alcohol and/or substance abuse. The witnesses reported she presented sweating, bruxism, trismus, seizure, and reduced consciousness before collapse. Upon arrival of the health personnel, she was unconscious (Glasgow Coma Scale 3). Biochemical blood analyses performed on site showed hyperglycaemia (305 mg/dL) and hyponatraemia (118 mmol/L). Suddenly the patient became cyanotic and developed cardiopulmonary arrest. Health personnel attempted cardiopulmonary resuscitation (CPR), which failed, and death was certified soon after.

2.1.1. Autopsy

An autopsy was performed 48 hours after death. The external inspection revealed sero-ematic liquid from nostrils and mouth at the passive mobilization of the head, a recent iatrogenic needle puncture in the antecubital fossa attainable to CPR and a wide area (10 × 17 cm) of necrobiosis lipoidica on the right leg surface. No evidence of trauma was found. The internal examination revealed diffuse cerebral oedema (Figure 1) with vessel congestion but no sign of tonsillar herniation, pulmonary oedema and congestion, and a mild increase of the liver volume, and consistency of mild greasiness due to hepatic steatosis (fatty liver). The remaining organs showed no obvious macroscopic anomalies, except for congestion. Histologic examination confirmed the autopsy macroscopic findings (i.e. cerebral oedema and congestion, pulmonary congestion with intra-alveolar oedema, slight hepatic steatosis, pluri-visceral congestion). It also showed focal brain areas of demyelination and gliosis (Figure 1(a,c)), reduction of the substantia nigra width in the brain stem (Figure 1(b)), and kidneys characterized by glomerulosclerosis with Kimmelstiel-Wilson lesions. Samples of femoral blood, vitreous humour and hair were collected for toxicological examination.

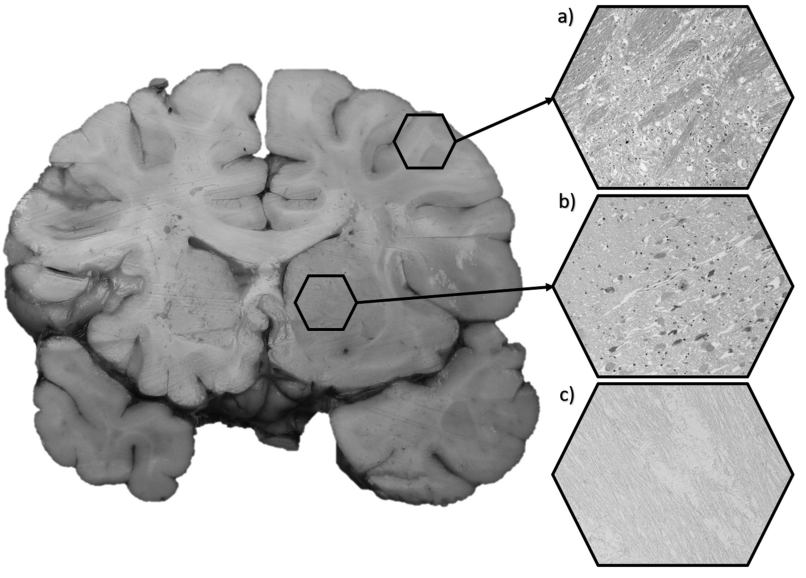

Figure 1. Brain oedema due to hyponatraemia. Microscopy documenting (a) pericellular and perivascular oedema and demyelination (H&E); (b) reduction of pigmented neurons in the substantia nigra (H&E); (c) focal reduction of myelin in the cerebellum (Luxol).

2.1.2. Toxicological analysis

Toxicological analysis for common drugs of abuse was performed by immunoenzymatic screening and gas or liquid-chromatography coupled with mass spectrometry (GC/LC-MS) confirmation. The LC-MS results confirmed the presence of MDMA and MDA in both blood and vitreous humour (Table 1). GC-MS toxicological hair analyses showed the presence of THC both in the proximal and in the distal fraction; neither MDMA nor MDA were found in the hair (limit of detection for MDMA and MDA in hair: 0.03 ng/mg). Ethanol determination was performed by head space gas-chromatography-flame ionization detection (HS-GC-FID, limit of detection 0.01 g/l). A target search on a home-made accurate mass spectral library for new psychoactive substances (NPS), accounting for synthetic cannabinoids, synthetic cathinones, synthetic fentanyls and phenetylamines (data not published) was negative (limit of detection 0.05–0.2 ng/ml).

In this case of a diabetic subject, to rule out fatal ketoacidosis (DKA), biochemical analysis on betahydroxybutirate (BHB) and acetone was performed on blood. BHB and acetone were thus determined post-mortem and were 4,8 mg/dL and 6 mg/dL, respectively.

Table 1. Blood, vitreous humour, and hair toxicological results in Case 1.

			Hair (ng/mg)	
Substance	Blood (ng/ml)	Vitreous Humour (ng/ml)	0–3 cm	3–10 cm
MDMA	1750	2000	–	–
MDA	80	95	–	–
THC	–	–	0.7	0.5

2.2. Second case

A 16-year-old girl, with known occasional use of hashish and ecstasy, collapsed at a rave party after the reported consumption of one ecstasy tablet diluted in a drink. When the ambulance arrived, she was unconscious (Glasgow Coma Scale 8), pale and sweaty. Doctors reported a metabolic acidosis (pH 7,22; pCO_2 = 42; HCO_3 = 24), hypoglycaemia (55 mg/dl), skin temperature of 40.5°C, cardiac rate of 149 beats per minute (bpm), and blood pressure of 135/65 mmHg. She was intubated in the field and immediately transported to the nearest hospital. She died 15 hours after admission due to important internal bleeding and severe metabolic acidosis.

2.2.1. Autopsy

An autopsy was performed 40 hours after death. The external examination revealed the presence of purple circular ecchymosis at the left leg and foot. No evidence of trauma was found. The internal examination revealed pronounced cerebral oedema with congestion of the cerebral vessels, sero-haematic bilateral pleural effusions, diffuse haemorrhagic petechiae on the epicardium surface (Figure 2), pulmonary oedema and congestion, hyperaemia and haemorrhagic petechiae on the stomach and intestinal lining, red streaks and yellow confluent spots on the liver surface and a flaccid consistency (Figure 3).

Histology examination confirmed oedema and congestion of the brain, the cerebellum, and the brain stem. The lungs showed acute septal stasis with the presence of endo-alveolar fibrinous material, macrophages, and red blood cells. Haemorrhagic purpura infarctions of the epicardial surface and areas of diffuse myocardiosclerosis and myocarditis outbreaks were found at heart level (Figure 2). Ischaemic necrosis in the zona reticularis of the adrenal glands and acute tubular necrosis of the kidneys were also

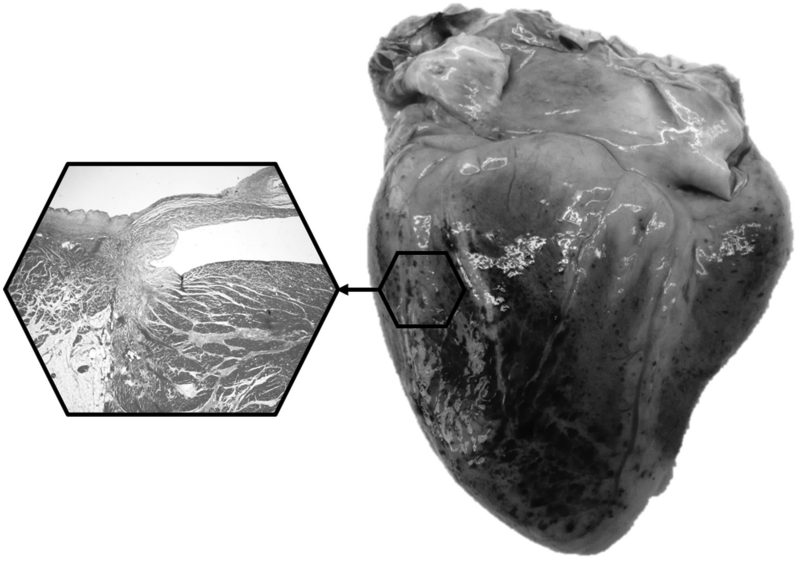

Figure 2. Diffuse haemorrhagic petechiae on the epicardium surface. Microscopy of haemorrhagic purpura infarctions of the epicardial surface and areas of diffuse myocardiosclerosis.

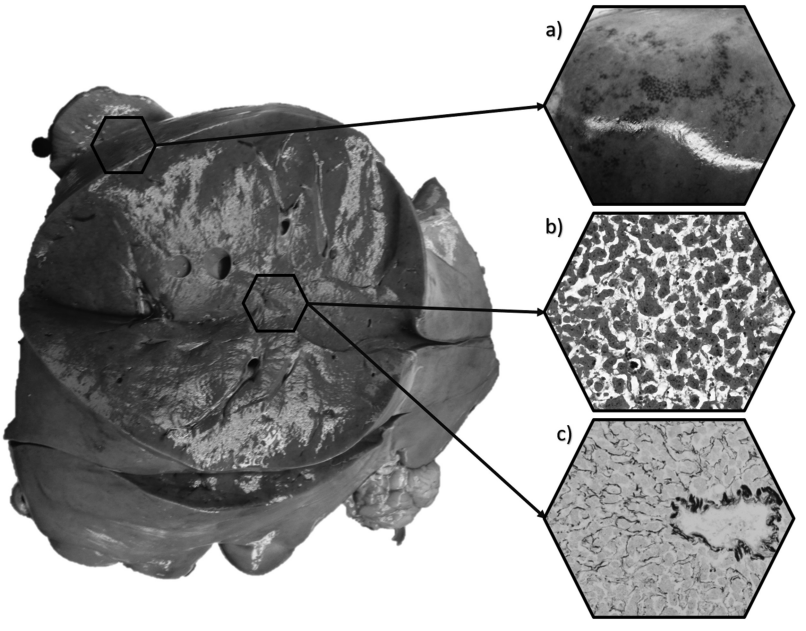

Figure 3. (a) Red streaks and yellow confluent spots on the liver surface. (b, c) Histological findings of acute hepatitis (H&E).

found. Histological findings were diagnostic for acute hepatitis (Figure 3(b,c)). Femoral blood, urine, and hair were collected for further toxicological investigation.

2.2.2. Toxicological analysis

Toxicological analyses were performed on femoral blood and urine by following the same approach as Case 1. Results revealed the presence of both MDMA and MDA in blood and urine. Also in this case, no other psychotropic substances were retrieved in blood or urine when a target analysis on NPS was carried out by LC-HRAM. Ethanol testing was also negative. A lock of hair was used for segmental analysis by dividing the total length (14 cm) into three segments. All results are summarized in Table 2.

3. Discussion

MDMA presents two focal metabolic pathways: (a) subsequent reactions of O-demethylenation, giving the formation of MDA first and then 3,4,-dihydroxymethyamphetamines (HMMA and HMA), followed again by an additional O-demethylenation and then finally a methylation and/or conjugation; and (b) subsequent reactions of N-dealkylation, deamination and oxidation leading to the corresponding benzoic acid products finally

Table 2. Blood, urine, and hair toxicological results in Case 2.

			Hair (ng/mg)		
Substance	Blood (ng/ml)	Urine (ng/ml)	0–3 cm	3–7 cm	7–14 cm
MDMA	3700	168000	20.7	15.5	5.5
MDA	100	8200	0.6	0.5	0.4

conjugated with glycine. The O-demethylenation pathway is partially under the activity of the polymorphic enzyme CYP2D6. The existence of this polymorphism proposes that 'poor metabolizers' (with an abnormal, dysfunctional CYP2D6) phenotype might present an increased risk of acute toxicity compared with a 'normal metabolizer'. Moreover, as a worsening issue, MDMA itself inhibits the activity of CYP2D6 in the case of first assumption, thus, in cases of an extra dose, all subjects become 'poor metabolizers'. It should be highlighted that this cytochrome is associated with the metabolism of a variety of psychoactive drugs and even nicotine [7,8]. When considering MDMA, CYP2D6 pharmacogenetics seem to play a minor role on acute toxicity, but hypothetically MDMA-mediated CYP2D6 inhibition could boost the toxicity of concomitant assumed drugs [9–11]. The half-life of ecstasy is determined as 4–7 hours, but it depends greatly on the assumed dose, which means the greater quantity of the drug, the more time it needs to be broken down. The half-life of MDA (3,4-methylenedyoxyamphetamine), its psychoactive metabolite, is longer than MDMA, reaching peak plasma levels one tenth as compared to parent compound. MDMA can cause neurotoxicity, acting at the sites of the heart and the central nervous system, triggering the release of catecholamine (also 5-HT) and preventing their uptake. Neurotoxicity in animal models (rats, monkeys) is displayed by impairment of serotonergic neurons, but there is no clinical evidence so far that humans ever develop the typical symptoms, such as disorders of sleep, mood and appetite. Users of MDMA are reported to be at increased risk of seizure activity, mainly due to its acute systemic effects (e.g. hyponatraemia and hyperthermia). Liver failure is reported to arise as a possible secondary effect of hyperthermia, along with multi-organ failure, but some animal studies tend to point to a MDMA-mediated oxidative stress, caused by lipid peroxidation and reduced glutathione levels in the liver. Even modest oral doses of MDMA are reported to cause a rise in heart rate, blood pressure and myocardial oxygen consumption [12]. Both acute and chronic toxicities have been extensively reported among MDMA users [13]. Acute toxicity includes agitation, tachycardia, hypertension, hyperthermia, hyponatraemia, convulsions, cardiac arrhythmias, cerebral haemorrhage, hepatotoxicity, disseminated intravascular coagulation (DIC), rhabdomyolysis with hyperkalaemia and acute renal failure [14–17]. So far, it is recognized that repeated ingestions of ecstasy are associated to impaired cognitive performances and depression [18,19]. However, MDMA-related deaths are still debated since they can occur both due to the instauration of the processes of hyperthermia, rhabdomyolysis and disseminated intravascular coagulation [20], and to lethal cerebral oedema caused by hyponatraemia [13] with no real possibility of prediction. Hyponatraemia was firstly described by Maxwell et al. in 1993 [21] and it may arise in up to 40% of subjects exposed to ecstasy [22]. Although the pathophysiology of hyponatraemia is not completely described, it seems to result from a combination of factors: (a) increased body concentration of antidiuretic hormone (ADH), with a consequent syndrome of inappropriate anti-diuretic hormone release (SIADH) [23]; (b) increased water resorption, independent from ADH levels, due to the altered aquaporin 2 channels function in renal collecting ducts [24,25]; (c) extreme fluid intake due to MDMA-induced polydipsia [13,26,27]. Regarding polydipsia, it is also one of the most common symptoms of poorly controlled diabetes mellitus. The consumption of amphetamine in patients with diabetes has been related to an increased risk of incurring hyperglycaemic crises, associated with the direct action of amphetamines on insulin

regulation [28,29]. Augmented mortality and morbidity were hence observed in young adults with type 1 diabetes who use MDMA [30].

In Case 1, death was ascribed to cerebral oedema provoked by MDMA-induced hyponatraemia in a diabetic patient. In this case, both hyperglycaemia (305 mg/dL) and hyponatraemia (118 mmol/L) were present at the moment of the collapse. Post-mortem biochemistry values on BHB (4.8 mg/dl) and acetone (6 mg/dl) allowed ruling out a fatal case of diabetic ketoacidosis (DKA) [31]. On the basis of the integration of all available data, the pathophysiological hypothesis, was: (1) first instauration of hyperglycaemia, with probably at least the contributory factors of MDMA acute toxicity and diabetes; (2) the instauration of the mechanism of glycosuria and polydipsia; (3) excessive perspiration due to strenuous physical activity (dancing over several hours). All factors contributed to sodium losses in sweat, leading to a lowering of the total body sodium content [32]. Symptoms initially described were in line with the reported symptoms of hyponatraemia: muscle cramping, seizures, collapse, coma. Usually the analysis of MDMA-mediated hyponatraemia requires a history of MDMA consumption and low serum sodium levels, around 115–125 mmol/L (<135 mmol/L) [13]. In the presented case, no evidence of previous MDMA consumption was present as hair displayed negative for MDMA/MDA; blood and VH showed comparable results for both MDMA and its metabolite (i.e. [MDMA] ≫. . . [MDA]). These data suggest a rapid instauration of the MDMA-induced physiopathological state, which led to the rapid death of the young woman, preventing further conversion of MDMA to MDA. The pre-existing comorbidity (i.e. diabetes) may have also played a role in the fast MDMA-related toxicity [33,34] above all because the victim was naïve for MDMA. Lethal and non-lethal diabetic ketoacidosis (DKA) in association with ecstasy consumption has already been reported in the literature [14,20,23,35] as well as a case of documented endogenous hyperinsulinemia and persistent hypoglycaemia associated with MDMA intoxication [36]. In all cases, MDMA consumption was considered the triggering factor for the instauration of acute diabetic complications, as can be assumed in this case, where no history of amphetamines/ecstasy consumption was documented.

In Case 2, death was determined by fulminant liver failure due to MDMA consumption followed by disseminated intravascular coagulation (DIC). Hepatotoxicity after MDMA exposure was described for the first time in 1992 [34]. The severity may vary from asymptomatic liver injury with altered liver function tests, to acute hepatic failure as diagnosed by histology (e.g. histological changes may vary from a mild to moderate lobular hepatitis to features of massive hepatic parenchymal collapse with areas of nodular regeneration [37,38]). The extent of the liver injury seems not to be related to the dose of MDMA ingested, impurities in the tablets, body variables, co-morbidities, or concomitant consumption of other substances. The prognostic factors that may predict the outcome of this condition are still unknown and hypotheses presented so far include mechanisms involving impaired metabolism such as a deficiency in CYP2D6 liver enzyme [39], immune responses and suggestion of specific human leukocyte antigen (HLA) phenotypes, hyperthermia, glutathione depletion, systemic hypotension and hypoxia [40,41]. It is known that patients with hepatic failure may present the entire spectrum of factor deficiencies and may even develop DIC [42]. DIC is a widespread hypercoagulable state that can lead to both microvascular and macrovascular clotting and compromise blood flow, ultimately resulting in multiple organ dysfunction syndrome (MODS) and death. In our case, fulminant liver failure followed by DIC occurred in a chronic MDMA 'heavy

consumer', as shown by the presence of MDMA and MDA throughout the length of the analysed hair (14 cm). It is conceivable that MDMA concentrations at the proximal segment of hair might had been affected by sweat external contamination (20.7≫. . . 15.5≫. . . 5.5 ng/mg) and not be strictly related to an increased drug consumption in the last period, but this would not affect the following considerations. Indeed, two MDMA-induced toxicity scenarios are possible in this case. One hypothetical explanation may be found in MDMA metabolism relying on CYP2D6 enzyme. As previously discussed, the production of an enzyme–metabolite complex renders all consumers, regardless of genotype, suddenly 'poor metabolizers' in the case of consecutive doses. Circumstantial data report the ingestion of one single tablet of MDMA; however, the high blood MDMA levels (3700 ng/ml) strongly discourage this version. It is, however, conceivable that repeated doses of MDMA were taken during the night. In fact, typically, after oral ingestion of a usual recreational dose of MDMA (75–150 mg), blood levels in the range of 100–250 ng/mL are reached and desired effects begin within 1 h and last 4–6 h [6]. The second hypothesis is based on evidence in animal studies [43]: liver failure might be attributed to the MDMA-induced oxidative inactivation of key mitochondrial enzymes, which most likely contributes to mitochondrial dysfunction and subsequent leads to liver damage. In addition, reactive metabolites, developing after MDMA extensive metabolization i.e. quinones, could be responsible for induced hepatotoxicity, by inhibiting the mitochondrial respiratory chain [43]. In all cases, MDMA-provoked toxicity seems to be not really correlated with blood concentrations, but mostly relying on the instauration of irreversible cell and tissue damage.

In fact, overlapping MDMA blood concentrations between asymptomatic and severe symptomatic users are often described, suggesting that adverse reactions are likely to relate mainly to the circumstances of drug assumption. In addition, there may also be an idiosyncratic component. A case of MDMA overdose has been reported, with a described blood level of 4.3 μg/ml, with no more than mild sinus tachycardia and a degree of somnolence. Another documented overdose resulted in a plasma MDMA concentration of 7.72 μg/ml, the highest documented in a surviving patient, with symptoms consisting of just a 'hangover', tachycardia, and hypertension. These data support the hypothesis that the MDMA-mediated toxicity is mostly attributable to progressive or all-at-once degeneration of cell functions due to oxidatively stress, ultimately independent of its concentration. Finally, experiments on mice aimed at investigating the ambient conditions on the toxicity and lethality provoked by MDMA, showed that toxicity and lethality of MDMA was potentiated by high ambient temperatures, mainly acting on the mechanism of hepatotoxicity, plasma ammonia, and brain glutamate function [44]. Crowded night-life parties and dancing settings, both high ambient temperature scenarios, are the situations in which MDMA is prevalently consumed for its entactogenic properties and where most MDMA-related deaths occur in healthy young adults.

However, further studies are needed to clarify the MDMA-mediated toxic mechanism in humans and whether high ambient temperature scenarios could influence MDMA lethality.

4. Conclusions

The current misconception that MDMA is a safe recreational drug with only mild toxicity is erroneous. MDMA may display a wide range of acute toxicity affecting the brain, heart, liver and kidneys.

MDMA exposure is associated with sudden death both in subjects affected by pre-existing diseases (Case 1), and healthy individuals (Case 2). The finding of high ecstasy blood concentrations is not enough to explain fatalities since MDMA-related deaths can be caused by multiple physio-pathological aetiologies. The identification of the exact mechanism of death in individual cases requires, more than ever, the integration of all circumstantial, clinical, biochemical, toxicological, autopsy and histology data [45].

Disclosure statement

No potential conflict of interest was reported by the authors.

Consent for publication

Written informed consent for publication could not be obtained from the deceased individual's next-of-kin despite all reasonable attempts. Every effort has been made to protect the identity of the individual.

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