**Case report**

Fatal multi-organ failure after suicidal overdose with MDMA, ‘Ecstasy’: case report and review of the literature

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A 53-year-old prisoner died of multiorgan failure after a suicidal overdose with 3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’). Twelve hours after ingestion of MDMA, the patient became severely hyperthermic (107.2 °F) with evidence of rhabdomyolysis. He subsequently developed acute respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC) and acute renal failure. At autopsy, plasma concentration of MDMA was 3.05 mg/L. This case shows that MDMA is still abused in our community and clinicians should know the symptoms of MDMA intoxication. In particular, MDMA should be considered when patients have symptoms or signs of increased sympathetic activity. The pathophysiology and treatment of MDMA-induced hyperthermia are discussed.

**Keywords:** MDMA; ‘ecstasy’; overdose; hyperthermia; multiorgan failure

**Introduction**

3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’), is a ring-substituted amphetamine patented in 1914 as an appetite suppressant, though it was never marketed as such. It reappeared in the early 1970s as an adjunct to psychotherapy, as psychiatrists claimed it enhanced therapeutic communication and patients’ self-awareness without psychotic or visual disturbances. Recreational use of MDMA was first reported in 1972 but did not gain popularity until the early eighties. Subsequently, animal experiments revealed MDMA-induced neurotoxicity, and several unintentional fatalities were reported following recreational use. Therefore, in 1985 the Drug Enforcement Administration (DEA) classified it as schedule I controlled substance, implying that the drug has a significant potential for abuse, no medical value and, even if administered under medical supervision, its safety could not be guaranteed. Although the use of MDMA has declined, the drug is still widely abused in the United States of America (USA) and many other countries such as the United Kingdom, Australia, Italy, Germany, Belgium, and Spain. Unfortunately, information on the clinical toxicology of MDMA is limited. As a ‘designer drug’, MDMA was not evaluated in controlled clinical trials, hence, there is no information on its efficacy and safety in humans. MDMA-induced toxicity in humans is predicted by extrapolation from animal observations and by comparison with adverse effects of its analogs such as 3,4-methylenedioxymphetamine (MDA). Furthermore, information from pharmaco-epidemiology studies on the effects of MDMA in humans is not adequate because it is based on subjective reporting. Consequently, our understanding of the clinical toxicology of MDMA is based on case reports. Several unusual manifestations of MDMA overdose such as MDMA-induced hepatotoxicity, inappropriate secretion of anti-diuretic hormone syndrome (ISADH), aplastic anemia have been reported. Here, we report a patient who died of multiple organ failure heralded by prominent respiratory failure and coagulopathy following suicidal overdose with MDMA. Pathophysiological aspects of MDMA intoxication are discussed.

**Case Report**

A 53-year-old psychiatrist with a history of gastritis and an unidentified platelet disorder was jailed for possession of marijuana and narcotics. Eight hours following imprisonment, he was found lying on the floor breathing heavily with his eyes wide open. A hand-written will dated the same day was found in...
his back pocket. He was rushed to a nearby health facility. He was semicomatose, diaphoretic, and trembling with 'decorticat posturing'. His temperature was 104.7°F (40.4°C), pulse 140 per min, blood pressure 146/67 mm Hg and respiratory rate 32 per min. Intravenous fluids were infused, active cooling initiated, a nasogastric tube inserted and activated charcoal was administered. He was treated with naloxone, diphenhydramine, methylprednisolone and furosemide. His blood pressure rose to 220/80 mm within 15 min of arrival and nitroprusside was given by infusion. He was intubated and transferred to Vanderbilt Hospital by Life Flight. Laboratory findings were as follows: arterial blood gases pH 7.21, pCO₂ 51 mm Hg and pO₂ 121 mm Hg; packed cell volume (PCV) 39%; platelets 366 x 10⁹/ccm; serum creatine 1.9 mg/dL; blood urea and nitrogen (BUN) 22 mg/dL; glucose 255 mg/dL; and creatine phosphokinase (CPK) 88 i.u./L.

He arrived at the Vanderbilt emergency department approximately 12 h after the police arrest. Vital signs were rectal temperature of 107.2°F (41.8°C), pulse 158 per min, blood pressure 120/52 mm Hg and respiratory rate 36 per min. He was still diaphoretic and responded only to deep pain. Ocular gyri was noted, pupils were 3–4 mm diameter and non-reactive to light. Except for the sinus tachycardia, there were no other abnormalities on the electrocardiogram. Intravenous fluids and active cooling were instituted. Physical examination revealed a right side pulmonary thrombosis for which a right intercostal tube was inserted and chest X-ray check showed the right lung completely re-inflated. Laboratory analysis revealed a moderate metabolic acidosis: blood pH 7.31, lactic acid 7.0 meq/L, anion gap of 17 and osmolar gap 8 mosmol/L. Signs of coagulopathy were evident with an increased prothrombin time (PTT) of 16 s, international normalized ratio (INR) of 1.7 and the bleeding time was 20 min. The CPK had risen to 647 i.u./L. Serum glutamylpyruvate transferase (SGPT) activity was 114 i.u./L and lactate dehydrogenase (LDH) 549 i.u./L. Other laboratory results were: white cell count 25 x 10⁹/ccm and a normal cortisol blood level of 42 i.u./L at 5.30 a.m. Urine pH 5, specific gravity 1.019, bacteria 2+, WBC+, RBC and hemoglobin+, no sugar and ketones. Head CT-scan was normal and lumbar puncture was withheld because of the evolving coagulopathy. He was treated with fentanyl, sodium bicarbonate, furosemide, ranitidine, antibiotics, acetaminophen (rectally) and Thiamine 100 mg, and thereafter, was transferred to the Intensive Care Unit (ICU) where dantrolene by infusion was commenced and assisted ventilation instituted. Correlatertal information revealed that he was a physician practicing psychiatry and addiction medicine. He was divorced with five children and had once been admitted to a rehabilitation unit for promethazine abuse. At the time of arrest he was in possession of several vials of unidentified drugs.

In the subsequent 3 h in the ICU, his temperature decreased to 99.9°F (37.7°C), pulse 120 per min and blood pressure 107/70 mm Hg. Respiratory rate with ventilatory settings on SMV was 14 per min, tidal volume of 1000 ml, FIO₂ of 100%. PEEP of 5 mm Hg. The lungs were clear on auscultation and there were normal bowel sounds. Pupils were equal, round and reactive to light.

Arterial blood gases were pH 7.31, pCO₂ 26 mm Hg, and pO₂ 459 mm Hg. Urinary output was 30 ml in 2 h and bleeding at the intercostal tube site was noted. Analytical screening revealed serum acetaminophen concentration of 9.1 mg/ml. salicylate less than 0.5 mg/dL, alcohol less than 10 mg/dL and a positive urine qualitative test for amphetamines but no cannabinoids, cocaine, morphine, heroine, pentobarbital, or phencyclidine.

During the following 3 days, his condition deteriorated. Oxygen requirements increased. CPK rose to 39 705 i.u./L, urinary output at 30–40 ml an hour with forced diuresis, and haematological parameters continued to worsen. By the fourth day in ICU laboratory values were as follows: creatinine 8.3 mg/dL, BUN 69 mg/dL, CPK 44 900 i.u./L, SGOT 4620 i.u./L, serum glutamylpyruvate transferase (SGPT) 1230 i.u./L, alkaline phosphatase 73 i.u./L, LDH 5090 i.u./L with a negative Hepatitis B surface antigen. PTT 100s. INR 73, fibrin split titre 1:32 (normal 1:4), platelets 53 x 10⁹/cu.mm, PCV 24%, Hb 8.5 g/dL, sodium 150 meq/L, potassium 5.6 meq/L, chloride 104 meq/L, bicarbonate 24 mmol/L, phosphate 9.4 meq/L, glucose of 114 mg/dL, blood pH 7.23, pCO₂ 45 mm Hg, pO₂ 84 mm Hg, and lactic acid 13.5 meq/L.

Because of oliguria, anarsaca, rhabdomyolysis and renal failure, hemodialysis was instituted. Spontaneous bleeding at puncture sites, bloody bronchial secretions and ecchymoses of mucus membranes, lips and conjunctiva, occurred. He received multiple transfusions of packed cells, platelets and plasma. A Swan-Ganz catheter was placed due to increasing respiratory distress. Pulmonary capillary wedge pressure was 28 mm Hg, pulmonary arterial (PA) pressure 54/27 mm Hg and central venous pressure (CVP) 20 mm Hg. The lungs were congested and bilateral infiltrates were seen on chest X-ray. Arterial blood gases were pH 7.25, pCO₂ 44 mm Hg and pO₂ 94 mm Hg. After hemodialysis, the pulmonary wedge pressure decreased to approximately 18 mm Hg. However, it was difficult to remove fluid during dialysis secondary to the ensuing hypotension. Norepinephrine infusion of 10 μg/kg/min was required to maintain his blood pressure.

In the evening of the fifth day in ICU, the balloon of the endotracheal tube ruptured, precipitating
Pathophysiology

Diagnosis of MDMA overdose will depend on the clinician’s appreciation of its abuse in the community and his knowledge of the symptomatology. The prominent symptoms of MDMA intoxication (anxiety, agitation, anorexia, tremors, muscle rigidity, mydriasis, diaphoresis, hyperthermia, hypertension, and tachycardia) are due to excessive sympathetic stimulation. Of these, hyperthermia is the most life-threatening. Hyperthermia may be responsible for the fatal complications following MDMA intoxication, i.e., rhabdomyolysis, renal failure, ARDS, DIC, and acidosis.\(^{3,4}\)

Although the mechanism of MDMA-induced hyperthermia is unknown, anecdotal evidence indicates that it is augmented by high environmental temperatures, dehydration and excessive physical exertion.\(^{5,6}\) There does not appear to be a dose response relationship between clinical signs and serum concentration of MDMA. Ingestion of 150 mg of MDMA, with a plasma concentration of 0.424 mg/L, resulted in severe hyperthermia and death, whereas another patient who ingested 42 tablets to a plasma concentration of 7.72 mg/L was asymptomatic.\(^{7}\) Hyperthermia is triggered by an increase in brain serotonin levels induced by MDMA. It was demonstrated in animal studies that MDMA induces release of brain catecholamines, serotonin and, to lesser extent, dopamine, with a concomitant inhibition of their reuptake and metabolism.\(^{8,9}\)

Serotonin stimulates the thermal control regions in the anterior hypothalamus/pre-optic area (AH/POA), possibly by increasing the temperature set point.\(^{10,11}\) which stimulates the sympathetic center and increases sympathetic discharge. Catecholamines are released and these stimulate alfa or beta adrenergic receptors (depending on the particular tissue’s receptor reserve), which increases mitochondrial metabolism and heat generation. Also, muscular contractions and peripheral vasodilatation contribute to body temperature elevation.

Increased peripheral catecholamines stimulate release of calcium from the sarcoplasmic reticulum\(^{12}\) and cause sustained muscular contraction. This increased locomotor activity increases metabolic and oxygen demand with consequent anaerobic respiration. As a result, there is increased production of carbon dioxide, lactic acid, energy and heat, which accentuate the hyperthermia and metabolic acidosis.\(^{13}\) Severe acidosis damages cell membranes, releasing more calcium, potassium, CPK and myoglobin from the muscle cells. Changes in membrane permeability may result in hyperkalemia (causing cardiac arrhythmias) and release of prothromboplastin (DIC), while reduced vascular integrity and platelet destruction may lead to petechiae and ecchymoses. Muscular hyperactivity
and release of myoglobin contribute to acute renal failure.\textsuperscript{74}

MDMA-induced vasoconstriction or vasodilatation may lead to hypertension or hypotension, respectively. Hypertension may cause a cerebrovascular accident or seizures.\textsuperscript{75} Hepatotoxicity, inappropriate secretion of anti-diuretic hormone (ISADH) and aplastic anemia may occur through an as yet unexplained mechanism. Of note, no patients with MDMA-induced ISADH developed hyperthermia.\textsuperscript{45,46} Since anti-diuretic hormone (ADH or arginine vasopressin) is a potent endogenous antipyretic peptide through its action on the V1 central receptors in the ventral septal area and amygdala nucleus (animal studies),\textsuperscript{76} this suggests that ISADH during MDMA-induced hyperthermia is due to over-secretion of ADH beyond the amount required for normal endogenous antipyresis.

**Toxic metabolites**
The role of metabolites in MDMA-induced toxicity is still not clear. Three major metabolites, 3,4-dihydroxymethamphetamine (DHMA), 6-hydroxy-3,4-methylenedioxyamphetamine (6-OHMDMA) and MDA are potentially neurotoxic.\textsuperscript{62,74,75} Other metabolites such as amphetamine and methamphetamine, although active, are produced in small quantities. Current evidence shows that MDMA is metabolized to MDA by cytochrome P450 enzyme CY2D6.\textsuperscript{75,76} This same enzyme is responsible for debrisoquine metabolism (4-hydroxylation), and exhibits polymorphic activity resulting in fast and poor metabolizers.\textsuperscript{77-79} About 5–9% of Caucasians are poor metabolizers of debrisoquine, due to a low activity of this enzyme.\textsuperscript{78,79} As such, it was suggested that poor metabolizers may be at a higher risk of parent drug induced toxicity while extensive metabolizers risk metabolites-induced toxicity.\textsuperscript{77}

However, because the parent compound and metabolites have similar symptomatology during acute toxicity, they increase activity of central catecholamines, it has been difficult to incriminate a particular compound for toxicity in either group.\textsuperscript{69}

**Management of MDMA overdose**
Immediate treatment of hyperthermia and hypertension is required. Hyperthermia must be controlled by passive and active cooling, and dantrolene may be considered for muscular control because it inhibits calcium release from the sarcoplastic reticulum.\textsuperscript{61,62} Agitation and convulsions should be managed with usual agents, and hypertension can be controlled with drugs of short half-life. Acidosis and electrolyte imbalances should be corrected. Arterial blood gases, full blood counts, toxicology screen, liver enzymes, renal function tests, creatine phosphokinase and coagulation markers should be obtained and repeated at appropriate intervals. The use of serotonin antagonists to treat MDMA toxicity is still at an experimental stage.\textsuperscript{81}

Although a high prevalence of MDMA abuse occurs in the USA,\textsuperscript{2,19,21,23,75,85} and the earliest reports of MDMA abuse were from this country,\textsuperscript{14-17,19} the rate of MDMA intoxication remains low. There are only four reports of MDMA intoxication in the American literature in the past 5 years, 1990–1996,\textsuperscript{44,49,93} while nine comprehensive reports of MDMA intoxication were published in the same period in the British literature.\textsuperscript{27,30,44,45} Furthermore, a Medline search for case reports on the clinical toxicology of MDMA over the past decade (1986–1996) found 16 reports from the USA versus 48 from the United Kingdom (Figure 1). Such a discrepancy may indicate a higher incidence of MDMA intoxication or better reporting in the UK than USA. The use of MDMA at rave parties in the UK may predispose to MDMA-induced hyperthermia,\textsuperscript{40} while lack of sensitive MDMA assays in some medical centers in the USA may make the diagnosis and reporting of MDMA-induced hyperemia difficult.

**Figure 1** Annual reports of MDMA toxicity in the United Kingdom and USA from 1986 to 1996

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MDMA and hyperthermia
A Yudo and D Seeger

125

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