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CASE REPORT

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# MDMA induced hyperthermia: report of a fatality and review of current therapy

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**Abstract** Ingestion of 3,4-methylene dioxymethamphetamine (MDMA), commonly known as "Ecstasy", can produce toxicity that is characterised by hyperthermia, coagulopathy, rhabdomyolysis and renal failure. We report a fatality associated with MDMA ingestion and briefly review the current literature on MDMA-induced hyperthermia.

**Key words** 3,4-Methylenedioxymethamphetamine · Ecstasy · Hyperthermia

## Case history

A 17-year-old male was brought to the emergency room after being thrown out of a nightclub. He had reportedly ingested 10 tablets of Ecstasy and an unknown amount of alcohol. He was delirious and combative, requiring restraint, and was profusely diaphoretic. His axillary temperature was noted to be 41 °C, his heart rate was 178/min and his blood pressure was 120/70. His pupils were dilated with minimal response to light. Profound muscular rigidity was noted and noxious stimuli produced a withdrawal response.

Initial management included intravenous saline, general cooling measures with ice packs and soaked sheets, and 1 mg/kg body wt. of dantrolene was given i.v. His level of consciousness progressively declined and respiratory distress developed, requiring immediate intubation and mechanical ventilation with 100% oxygen. Intermittent second-degree atrioventricular block developed, which was transiently responsive to atropine, after which a temporary pacing wire was introduced and the ventricle paced at 100 beats per minute. The patient was transferred to the ICU and hemodynamic monitoring was instituted. Initial laboratory data included $K^+$ 4.5 mmol/l, bicarbonate 18 mmol/l, urea 4.4 mmol/l, creatinine 143 mic.mol/l and CPK 259 IU/l. Prothrombin time was normal with a platelet count of $404 \times 10^9$/l. Arterial blood gases on ambient air revealed pH 7.36, $PCO_2$ 33 mmHg, $PO_2$ 78. *Blood alcohol level was 78 mg/dl. Initial CVP was 17, pulmonary artery pressure 38/22 and PCWP was 21. Cardiac index was estimated at 1.82 l/m² and systemic vascular resistance index at 1086 dyne/m².*

Dantrolene was continued in doses of 1 mg/kg repeated as rapidly as possible, but his axillary temperature increased to 42 °C despite a dose of 5 mg/kg body weight (a total of 380 mg of dantrolene). Urine flow could not be established and the patient remained anuric. Evidence of progressive cardiogenic shock was seen with hypotension, pulmonary edema, and declining cardiac output with increasing systemic vascular resistance, which remained resistant to inotropic support. Clinical and laboratory evidence of coagulopathydeveloped with prothrombin and kaolin-cephalin time elevations > 300 s, which was unresponsive to infusions of fresh frozen plasma. Rapidly progressive metabolic acidosis (pH 7.06) developed with hyperkalaemia ($K^+$ 7.3) that persisted despite repeated doses of sodium bicarbonate, dextrose and insulin. The patient died 6 h after initial presentation.

At autopsy, there was evidence of gross pulmonary edema. The pericardial space was free of blood. There was no evidence of intracranial hemorrhage. Histology of the myocardium revealed a macrophage infiltrate and formation of contraction bands in the muscle sarcoplasma, features that are consistent with *amphetamine abuse* [1, 2]. The blood MDMA level was 0.23 mg/dl and the hepatic content was 1.2 mg/kg of liver tissue. *Apart from ethanol, no other toxins were identified in the body fluids.*

## Discussion

MDMA ingestion has been associated with a range of adverse effects that include psychosis, sudden cardiac death, seizures, tachycardia, hepatitis, subarachnoid hemorrhage, and acute renal failure. In a subset of patients, the drug produces an acute syndrome characterized by hyperthermia, coagulopathy, rhabdomyolysis and acute renal failure [3–6]. When fulminant, as in our reported case, death has been the usual outcome [3–5]. Hyperthermia from any cause can lead to rhabdomyolysis, coagulopathy, and multiple organ failure, and its control is of paramount importance in the management of MDMA toxicity. It is an unpredictable complication of MDMA ingestion and is usually associated with vigorous muscular activity such as dancing. MDMA does not have a dose-related effect in humans. A single tablet of "ecstasy", with an MDMA content of 50–150 mg, has resulted in severe hyperthermia and death while the alleged ingestion of 42 tablets, with a resultant plasma MDMA level of 7.72 mg/l, was asymptomatic in one reported case [5]. What predisposes certain individuals to develop hyperthermia following MDMA ingestion is not known. A pre-existing metabolic myopathy or genetic predisposition similar to that seen in patients with

malignant hyperthermia remains a possibility. Survivors of MDMA toxicity need to be evaluated for this if our understanding of this phenomenon is to be increased.

A review of reported cases of MDMA ingestion suggests that peak temperature and the duration of hyperthermia are important factors in predicting survival in patients with MDMA toxicity [3–7]. Treatment of hyperthermia consists of general cooling measures such as applying ice packs, infusion of cold fluids i.v., peritoneal lavage with cool dialysate, etc. Other measures include inhibition of thermogenesis from muscular activity, and the use of dantrolene has been reported in at least six cases (including this case) in the literature [4, 7–10]. The role of dantrolene in malignant hyperthermia induced by anaesthetic agents is well established. In this case there is excessive release of $Ca^{++}$ from the sarcoplasmic reticulum, and dantrolene interferes with this $Ca^{++}$ release. Its role in the treatment of MDMA-induced hyperthermia is less certain. Of the six reported cases of its use, three patients survived. Of note is the observation that all three fatalities were characterized by a peak body temperature of 42 °C or more. Two of the survivors had temperatures of 40.2 °C and the other patient is the only documented survivor of an MDMA induced peak temperature of 42 °C. Since dantrolene has no known central effects, a neuromuscular blockade with a non-depolarizing agent should be just as efficacious, if not more, and would also have the advantages of ease of administration and lower cost. Although the data are too limited to draw meaningful conclusions from, there is no evidence that neuromuscular blockade influenced survival when dantrolene was ineffective. *Neuromuscular blocking agents were not administered to our patient.*

If survival is to be improved in MDMA toxicity, it is important to identify patients with a potentially fatal outcome as early as possible. This group of patients may be identified by a failure of hyperthermia to subside with cooling measures and the administration of dantrolene (or a neuromuscular blocking agent). In addition to more aggressive supportive care, other therapeutic measures need to be considered in these cases.

MDMA-induced hyperthermia results from augmentation of central serotonin function by stimulation of neuronal serotonin release. MDMA toxicity bears a striking resemblance to the serotonin syndrome, features of which include hyperthermia, coagulopathy, tachycardia, rhabdomyolysis and acute renal failure [11]. In animals, the non-selective serotonin antagonists methysergide and cyproheptadine have been shown to block this syndrome [12]. Furthermore, Schmidt et al. demonstrated that in rats given low doses of MDMA, the hyperthermia and neurotoxicity produced by the drug were antagonized by the selective 5-$HT_2$ receptor blocker MDL 11,939 [13]. This suggests that 5-$HT_2$ receptors are involved in both the neurotoxicity and hyperthermia produced by the drug, which also provides a possible therapeutic option in humans. No data on the use of selective serotonin antagonists (such as ketanserin) or non-selective antagonists in humans with MDMA-induced hyperthermia are available to date. However, the use of these drugs should be seriously considered, particularly in the patient with severe and prolonged hyperthermia that is unresponsive to other therapeutic interventions.

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