American Journal of Emergency Medicine
Volume 21 • Number 2 • March 2003

Multiple toxicity from 3,4-methylenedioxymethamphetamine ("ecstasy")

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Key words
Toxicity

3,4-methylenedioxymethamphetamine

ecstasy

case series

serum concentration

hyperpyrexia

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Manuscript received June 18, 2002.
Accepted June 18, 2002.
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0735-6757/03/2102-0007$30.00/0

There have been no published case series illustrating "ecstasy" (3,4-

methylenedioxymethamphetamine [MDMA]) toxicity in a group of patients who have ingested ecstasy in the same environment. We report a series of 7 patients who ingested ecstasy in a nightclub and presented with varying degrees of MDMA toxicity. Three patients presented with features of severe MDMA toxicity. One died within an hour of hospital admission, another died 4 days later, after developing fulminant hepatic failure, and the third recovered after 12 days in intensive care. MDMA was identified in the serum of all 7 patients. High serum MDMA concentrations correlated with severe clinical and biochemical features including coma, hyperpyrexia, cardiovascular compromise, acidosis, and hyperkalaemia. "Poisoned ecstasy" was widely reported by the media as being responsible for the adverse effects observed. This report highlights a relationship between serum concentrations and toxic effects of MDMA, and the ongoing need to educate the public about the dangers of this substance. (Am J Emerg Med 2003;21:121-124. Copyright 2003, Elsevier Science (USA). All rights reserved.)

3,4-Methylenedioxymethamphetamine (MDMA), commonly known as "ecstasy," is a synthetic amphetamine. MDMA stimulates the sympathetic nervous system, producing tachycardia, sweating, hypertension, dilated pupils, and an increase in muscle activity, with these effects commonly being seen within 1 hour of ingestion of MDMA. [1]Its popularity as a "rave drug" comes from the stimulant action and ability of MDMA to induce a feeling of euphoria and intimacy. [2]

Previous individual case reports [3][6]have illustrated the wide range of toxicity seen after ingestion of ecstasy tablets, typically containing MDMA. There have been no published series describing a group of patients who have ingested ecstasy in the same environment and who subsequently developed features of MDMA toxicity. We report clinical and toxicokinetic data for 7 patients treated at 2 London hospitals following ingestion of ecstasy in a local nightclub. All patients presented on the same day, between the hours of 6 and 8 am . Three of the patients were found collapsed in or around the nightclub and arrived in the emergency department (ED) by ambulance. Four patients self-presented. Serum MDMA concentrations were obtained for each patient through gas-chromatographic analysis. [7][8]Clinical and toxicokinetic data are summarized in Table 1.

Table 1. Clinical and Toxicokinetic Data for 7 Patients With MDMA Toxicity

Case	**Sex/age**	**No. of Tablets Ingested**	**Presentation**	**Clinical Course**	**Outcome**	**MDMA Plasma (mg/L)**
1	M 20	Not known	Found collapsed in reception area of club	Comatose, temp 43°C, pulse 130 bpm, BP 60/35 mm Hg, potassium 7.7 mmol/L, pH 7.12	EMD arrest, resistant VF, death 1 hour after admission	2.40
2	M 22	Not known	Fell through glass roof			

Comatose, temp 38.5°C, pulse 140 bpm, BP 80/40 mm Hg, potassium 6.8 mmol/L, pH 7.0.
Trauma screen negative
Hepatic failure, rhabdomyolysis, death 58 hours post admission
0.93

3
M 18
5, and 1 g of “speed” powder
Found collapsed in street outside club
Agitated, temp 41.6°C, pulse 170 bpm, BP 100/40 mm Hg, potassium 5.5 mmol/L, pH 7.24
ICU admission, residual cerebellar deficit
0.35

4
M 23
2
Self-presented
Alert, orientated, temp 37.6°C, dilated pupils, pulse 148 bpm, BP 110/60 mmHg
Discharged in healthy condition after 8 hours observation
0.25

5
M 18
4
Self-presented
Alert, oriented, anxious, temperature 37.2°C, pulse 90 bpm BP 150/75 mmHg
Discharged in healthy condition after 4 hours observation
0.23

6
F 18
2
Self-presented
Alert, oriented, temperature 37.4°C, pulse 100 bpm, BP 125/65 mmHg
Discharged in healthy condition after 6 hours observation
0.13

7
M 17
1
Self-presented
Alert, oriented, temperature 37.0°C, pulse 80 bpm, BP 115/65 mmHg
Discharged in healthy condition after 2 hours observation
< 0.1

Case presentations

Case 1

A 20-year-old man was found collapsed in a nightclub. On arrival in the ED he had a Glasgow Coma Scale (GCS) score of 3/15 and was receiving ventilation via a bag and mask. Initial examination revealed a pulse rate of 130 beats per minute (bpm) blood pressure of 60/35 mm Hg, rectal temperature of 43.0°C, blood glucose of 10.2 mmol/L, and widespread muscle

fasciculations of the chest and lower limbs. Arterial blood gas analysis revealed a pH of 7.14, base excess of _12.5 mmol/L, and potassium of 7.7 mmol/L. An electrocardiogram (ECG) showed a sinus tachycardia with prolongation of the QRS complex (230 milliseconds) and tall T waves. The patient was paralyzed with atracurium and artificially ventilated.

Cooled intravenous fluid (1 L of normal saline) was administered and topical ice packs were applied to the patient. Hyperkalemia was treated with bolus infusions of calcium gluconate (30 mL of a 10% solution in total) and an insulin-dextrose infusion (15 units of soluble insulin and 50 mL of 50% dextrose). Cardiac arrest (pulseless electrical activity) with unsuccessful resuscitation occurred 1 hour after admission of the patient. A serum sample obtained on the patient's arrival in the ED revealed an MDMA concentration of 2.4 mg/L.

Case 2

A 22-year-old man was found collapsed after falling 15 feet through a glass roof into a stairwell. His GCS score was 4/15 at the scene, and his capillary blood glucose was < 1.0 mmol/L. A bolus of 50 mL of 50% dextrose was administered intravenously. On arrival in the ED, the patient had a GCS score of 8/15, pulse rate of 140 bpm, blood pressure of 80/40 mm Hg, and rectal temperature of 38.5°C. The patient was paralyzed and sedated with atracurium and thiopentone.

Arterial blood gas analysis showed a pH of 7.0, base excess of _12.3 mmol/L, and potassium concentration > 8.0 mmol/L. Initial biochemistry and hematology revealed a potassium concentration of 6.8 mmol/L, creatinine of 264 _mol/L aspartate aminotransferase (AST) of 1,196 IU/L, creatine kinase of 88,000 IU/L, international normalized ratio (INR) of 1.29. An ECG showed a sinus tachycardia with prolongation of the QRS complex (217 milliseconds), and tall T waves. The patient's urine color was noted to be red. The patient received an intravenous bolus of calcium chloride (10 mL of a 10% solution) and cooled intravenous normal saline (1 L). Hyperkalemia was treated with an intravenous bolus of insulin and dextrose (10 U of soluble insulin and 50 mL of a 50% dextrose solution).

Trauma-series plain films were unremarkable. A secondary survey revealed an occipital scalp laceration and extensive abrasions. Computed tomographic (CT) scans (contrast enhanced) of the head and abdomen were normal. In the intensive care unit (ICU), noradrenaline (1.0 _g/kg/minute) and adrenaline (1.0 _g/kg/minute) were required to maintain adequate systemic perfusion. Metabolic acidosis persisted (pH 7.11-7.20) despite an 8.4% sodium bicarbonate infusion at a rate of 100 to 125 mL/hour. The patient's central temperature remained elevated (38.0-38.8°C) for 18 hours after admission. Continuous hemofiltration (bicarbonate filtration, 6 L/hour) was begun 20 hours after admission.

The patient's hepatic and renal function deteriorated during the first 24 hours after admission; his INR was > 15, activated partial thromboplastin time (APTT) 75 seconds, AST 4,890 iU/L, and creatinine 339 _mol/L. His creatine kinase peaked at 215,000 iU/L. Myoglobinuria was present. The serum lactate was 4.85 mmol/L. Intravenous infusion of N-acetyl-cysteine was begun (150 mg/kg over 24 hours) according to the regional acute liver failure protocol. The patient was transferred to the liver unit of the hospital and listed for urgent liver transplantation.

Over the following 24 hours, the patient's respiratory, cardiovascular, renal, and hepatic function continued to deteriorate despite full inotropic support and continuous hemofiltration. The patient died 58 hours after admission. Serum obtained at presentation contained MDMA (0.93 mg/L).

Case 3

An 18-year-old man was found collapsed outside a nightclub. Friends reported that he had ingested 5 ecstasy tablets and a gram of powder they identified as “speed.” He was vomiting and

agitated on arrival in the ED. His pulse rate was 170 bpm, with a blood pressure of 105/40 mm Hg, rectal temperature of 41.6°C, and blood glucose of 6.1 mmol/L. Arterial blood gas analysis revealed a pH of 7.24, base excess of _9.5 mmol/L, and potassium of 5.5 mmol/L. An ECG showed a sinus tachycardia with a QRS complex of normal duration.

The patient was immediately paralyzed with atracurium, sedated with thiopentone, and mechanically ventilated. Cold ice packs were applied topically and cool intravenous fluid was administered (1 L of normal saline over 15 minutes). Dantrolene in a dose of 80 mg was given intravenously and the patient was transferred to the intensive care unit (ICU).

Over the following 24 hours, noradrenaline (1.0 _g/kg/min) was required to maintain the patient's systemic perfusion. There was evidence of rhabdomyolysis and renal impairment at 24 hours after admission, with a creatinine of 225 _mol/L, and creatine kinase of 51,300 iU/L, and a urine dipstick test positive for blood, suggesting myoglobinuria. Transient hepatic dysfunction (INR = 2.34, alanine aminotransferase [ALT] = 2,700 iU/L) was treated with intravenous N-acetylcysteine (150 mg/kg over 24 hours), and resolved over 72 hours. Artificial ventilation was required for 10 days. The patient's central temperature remained elevated (38.0-39.0°C) for 7 days. The contribution of MDMA to this hyperpyrexia was unclear, since the patient developed pneumonia and a urinary tract infection (*Escherichia coli*). He was discharged to the ward on day 12 and left the hospital 32 days after admission, with a mildly ataxic gait and dysphonia secondary to right vocal-cord damage. A magnetic resonance imaging (MRI) scan of the patient's brain revealed mild cerebellar asymmetry that was thought to be a normal variant.

A serum sample obtained 2.5 hours after presentation contained MDMA (0.33 mg/L) and amphetamine (0.12 mg/L). The powder identified by the patient's friends as “speed” was found to contain MDMA.

Cases 4 through 7

Four patients who had attended the night club which the other patients reported here had also attended, presented themselves to an ED approximately 6 hours after ingesting ecstasy tablets. Serum MDMA concentrations were obtained from samples taken at the time of the patients' presentations.

A 23-year-old man who had ingested two tablets of ecstasy had a pulse rate of 148 bpm and was pyrexial (37.6°C). His serum MDMA concentration was 0.25 mg/L. His pulse rate and temperature normalized spontaneously over the following 8 hours. An 18-year-old man who had ingested 4 tablets of ecstasy was anxious but showed no clinical signs of MDMA toxicity. His serum MDMA concentration was 0.23 mg/L. An 18-year-old woman who had ingested 2 tablets of ecstasy had a serum MDMA concentration of 0.13 mg/L. She presented with a pulse rate of 100 bpm, but no other clinical signs of MDMA toxicity. The fourth patient, a 17-year-old man who had ingested 1 ecstasy tablet, was clinically well and had a serum MDMA concentration of < 0.10 mg/L.

No other drugs of abuse (benzodiazepines, opiates, cannabis, barbiturates, cocaine) were detected (gas chromatography and immunoassay techniques) in the serum of any of the patients in our series. An ecstasy tablet supplied by a patient, which was obtained at the scene, was analyzed and found to contain MDMA. No other contaminants were identified upon gas chromatographic analysis.

Discussion

As many as 11% of high school students in the United States have taken ecstasy. [9]The number of deaths related to ecstasy is small when compared to the frequency of its use. The death rate

among 420,000 ecstasy users in the United Kingdom in 1996 was estimated at 0.2 to 5.3 per 10,000 users, a rate much lower than the death rate among heroin users, which has been quoted to be as high as 81.5 per 10,000. [10]However, ecstasy-related deaths are unpredictable. Deaths have followed single tablet ingestions, and there has been a report of survival following ingestion of 42 ecstasy tablets. [3]The 7 patients described here illustrate the range of acute toxicity that may occur after MDMA ingestion.

Hyperpyrexia has been documented in cases of severe MDMA toxicity. [3][6][11][12]This may arise from a number of mechanisms. MDMA-induced hyperpyrexia is often seen when the drug is used in a "rave" environment. [3]Its stimulant action increases muscle activity, and users will often dance at a sustained high level, leading to excessive heat production. In rats, MDMA increases temperature by a central serotonergic mechanism. [13]This effect is greater at higher ambient temperatures. [14]The environmental temperature in the nightclub during the episodes of rave reported here was unknown, but it is likely to have been high. Ambulance staff reported that the nightclub location was underground and was poorly ventilated. The ambient temperature that night in central London between the hours of 10 pm and 8 am ranged from 13.2° to 17.8°C (55.8-64°F). [15]

Evidence of the effectiveness of dantrolene when used to treat MDMA-induced hyperpyrexia remains inconclusive. [16][19]Dantrolene prevents calcium release in the sarcoplasmic reticulum and consequently reduces the heat produced by muscular activity. [20]However MDMA also acts on the central nervous system (CNS) to produce hyperpyrexia. There is no evidence that dantrolene has an antipyretic effect via the CNS. [21]

Hepatotoxicity has been described following ingestion of MDMA. [3][11][22]An autoimmune-mediated hepatitis-like injury [11]is one postulated mechanism for this. Amphetamine-related hepatotoxicity is often seen in patients who have been hyperpyrexial for a prolonged period. [11][23]Hepatotoxicity occurs in patients suffering from heat stroke. [24][25]The use of N-acetylcysteine to treat MDMA-induced hepatotoxicity has not been assessed. It may be beneficial as a free-radical scavenger in patients with fulminant hepatic failure. [26]

Renal failure has been documented following ingestion of MDMA. [27]Nontraumatic rhabdomyolysis with myoglobinuria can lead to renal tubular obstruction. Disseminated intravascular coagulation results in fibrin-platelet complex deposition within renal tubules. MDMA may also have a direct nephrotoxic effect. Interstitial nephritis following amphetamine use has been described. [28]

Serum MDMA concentrations in the 7 patients in our series correlated with the observed degree of MDMA toxicity (see Table 1). A concentration of > 0.6 mg/L has been associated with fatalities. [29]The 2 patients in our study who died had serum MDMA concentrations of 0.93 mg/L and 2.4 mg/L, respectively. The patient who required prolonged intensive care had an MDMA concentration of 0.35 mg/L in a sample obtained 2.5 hours after admission. The amphetamine concentration (0.12 mg/L) detected in his serum is associated with recreational use. [29]One patient, with a serum MDMA concentration of 0.25 mg/L, had signs of moderate MDMA toxicity. The other 3 patients had serum MDMA concentrations ranging from < 0.10 mg/L to 0.23 mg/L. They exhibited either very mild or no clinical signs of MDMA toxicity.

Although there is a correlation between serum MDMA concentrations and the degree of toxicity as indicated in our series, there have been reports of wide variation in the effects seen at different MDMA concentrations. A fatality was reported with a serum MDMA concentration of 0.42 mg/L, [30]whereas a concentration of 6.5 mg/L was associated with severe toxicity (hyperthermia, hypotension and coma) in a patient who survived. [31]Measurements of serum MDMA concentrations are not routinely indicated in the management of acute MDMA poisoning, which should be guided by clinical features. [1]

There was no clear correlation between the amount of ecstasy ingested and the resulting serum MDMA concentration in the 4 patients in whom we obtained an accurate history of the amount of MDMA ingested.

Despite widespread media reports of contaminated ecstasy causing the adverse effects in this series of patients, no contaminants were identified (by gas chromatographic analysis) in the tablets obtained from the scene. Amphetamine was detected in 1 patient's serum. However there were no other drugs of abuse detected in any patient's serum. News headlines on the day after the incident included “Poisoned ‘E’ leaves one dead, 3 critical.” One newspaper [32]quoted a police source as saying “We think the E tablets were sold by the same dealers. They have obviously been ‘cut’ with a pollutant, possibly something containing strychnine, like rat poison.” Reports such as these reinforce the mistaken belief among ecstasy users that MDMA is a safe drug that does not have severe adverse effects.

The cases presented here illustrate the range of toxic effects of MDMA, and the relationship between serum MDMA concentrations and toxicity. Environmental conditions (a high ambient temperature, underground club, and poor ventilation) may have increased the MDMA toxicity observed in these patients. The cases described also illustrate the public perception that MDMA is a safe drug and that the occurrence of fatalities must be due to a contaminant rather than to the inherent toxicity of MDMA itself.

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