

Death by "Ecstasy": The Serotonin Syndrome?

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"Ecstasy" or 3,4-methylenedioxymethamphetamine (MDMA) is a popular drug of abuse and is generally regarded as safe by the lay public. There are an increasing number of reports of MDMA-induced toxicity that exhibit features of the serotonin syndrome. We report a case of severe hyperthermia, altered mental status, and autonomic dysfunction after a single recreational ingestion of MDMA.

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INTRODUCTION

Serotonin syndrome, a condition in which there is central serotonin receptor hyperstimulation, has been described since the 1950s. Classic findings of severe serotonin syndrome include hyperthermia, mental status changes, autonomic instability, and altered muscle tone or rigidity.¹ A number of medications have been implicated in the induction of serotonin syndrome, including those that reduce metabolism (ie, monoamine oxidase inhibitors [MAOIs]), increase production (ie, L-tryptophan), or inhibit uptake of serotonin (ie, fluoxetine, clomipramine, meperidine, dextromethorphan, pentazocine, fenfluramine).^{2,3} MDMA has been shown in animal models to cause massive release of serotonin from presynaptic vesicles and inhibit its uptake.^{4,5} The following case illustrates that MDMA can induce a toxidrome consistent with severe serotonin syndrome.

CASE REPORT

A 20-year-old woman was brought to the emergency department by paramedics unresponsive and cyanotic with agonal respirations. She had ingested 2 tablets of MDMA for recreational purposes within the previous 4 hours according to her boyfriend. She had a negative past medical history, was taking no medications, and had not been previously treated with any antidepressant or other prescription medications.

History of previous use of MDMA or other illicit drugs was not available.

Vital signs were as follows: blood pressure 105/77 mm Hg, heart rate 160 beats/minute, and a rectal temperature of 41.7°C (107°F). Her skin was hot and dry without track marks, pupils were 5 mm and sluggishly reactive, neck was supple, and she was unresponsive to painful stimuli. No rigidity was noted. After suctioning of a large piece of chewing gum from her oropharynx, an orotracheal tube was inserted. No drugs were used to facilitate intubation. A postintubation arterial blood gas study revealed the following: pH 7.31, P_{aCO_2} 28 mm Hg, P_{aO_2} 150 mm Hg, and HCO_3^- 14 mEq/L on 100% O_2 . Shortly after intubation, the patient's blood pressure decreased to 77/33 mm Hg and a wide complex supraventricular tachycardia was noted on the monitor and confirmed by ECG. She was treated with crystalloid infusion, 6 mg, and 12 mg of intravenous adenosine, followed by 100 mg intravenous lidocaine without improvement. She subsequently had a grand mal seizure and was treated with 10 mg intravenous diazepam and 1 ampule intravenous 50% dextrose solution (D50) to correct a bedside glucose reading of 42 mg/dL (subsequently 70 mg/dL by the hospital laboratory). A critical potassium value of 7.2 mEq/L was treated with 1 ampule intravenous D50, 10 units of intravenous regular insulin, 1 ampule intravenous $NaHCO_3$, and 1 ampule intravenous CaCl. The potassium level 45 minutes later was 5.5 mEq/L. The patient's cardiac rhythm deteriorated to fine ventricular fibrillation versus asystole with no palpable pulse, and chest compressions were initiated. She was treated with lidocaine, magnesium sulfate, epinephrine, and defibrillation with return of a palpable femoral pulse. A lidocaine infusion was then begun. Shortly thereafter, the patient had another grand mal seizure lasting approximately 5 minutes. An additional bedside glucose level was 246 mg/dL. She was treated with diazepam and phenobarbital. At this time, approximately 30 minutes after arrival, evaporative cooling measures were initiated and vecuronium was administered. The patient also received 30 g activated charcoal per nasogastric tube. She remained hypotensive despite administration of 4 L normal saline solution, so a levaterenol drip was aggressively titrated upward to a maximum dose of 0.6 µg/kg per minute. She was admitted to the ICU with a rectal temperature of 39°C (102.2°F) 3 hours after presentation. Despite aggressive supportive management, she remained hypotensive and continued to have malignant dysrhythmias, and died 4½ hours after presentation.

Initial laboratory data revealed normal liver function, creatine phosphokinase 448 IU/L, WBC 7.9 K/mm³,

hemoglobin 12.2 g/dL, prothrombin time 12.9 seconds, and partial thromboplastin time 24.9 seconds. Results of an initial urine drug panel by enzyme-mediated immunoassay were positive for amphetamine, and negative for cocaine, benzodiazepine, barbiturate, opiate, and cannabinoid. Autopsy revealed an antemortem MDMA blood level of 2.3 mg/L with an MDMA metabolite methylenedioxymphetamine (MDA) blood level of .095 mg/L by gas chromatography-mass spectrometry. No other toxic substances were present except acetaminophen, barbiturate, and benzodiazepine used during treatment in the hospital.

DISCUSSION

Diagnostic criteria for serotonin syndrome recommended by Sternbach and commonly recognized include the recent addition or increase in dosage of an agent that increases central serotonin neurotransmission, with at least 3 of the following signs or symptoms: mental status or behavioral changes (confusion, agitation, hypomania, coma), alteration in muscle tone or neuromuscular activity (incoordination, shivering, tremor, hyperreflexia, myoclonus, rigidity), autonomic instability (diaphoresis, tachycardia, hypertension, hypotension), hyperpyrexia, and diarrhea.^{1,2} Complications resulting from hyperthermia associated with severe serotonin syndrome include disseminated intravascular coagulation (DIC), rhabdomyolysis, cardiac dysrhythmias, renal failure, seizures, coma, and death.^{1,2}

Serotonin syndrome is believed to be caused by an increase in serotonergic tone at receptors in the central nervous system. It occurs after use of serotomimetic agents alone, in combination, or sequentially.^{2,3} It has been most commonly reported with an MAOI given concurrently with L-tryptophan, fluoxetine, meperidine, dextromethorphan, or a tricyclic antidepressant.^{2,3} It has also been reported with an MAOI in combination with MDMA.⁶

An extensive review of drugs and drug combinations reportedly leading to serotonin syndrome was recently reported.³

MDMA, a so-called "designer" amphetamine, has become an increasingly popular drug of abuse over the last 2 decades. Undergraduate students at Stanford University were randomly and anonymously polled regarding whether they had ever taken MDMA. Of a total of 369 subjects interviewed, 143 (39%) reported that they had used the drug at least once. Frequency of use ranged from 1 to 38 times, with a median of 4.⁷ An increased incidence of MDMA use from 16% in 1986 to 24% in 1990 was found among undergraduate students at Tulane University.⁸

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MDMA was introduced as an "underground" (unapproved by the Food and Drug Administration) adjunct to psychotherapy in the late 1970s and early 1980s. It was assigned schedule I status by the Drug Enforcement Agency in 1985 because of increasing nonmedical use of the drug for its psychoactive properties and concern over animal data suggesting serotonergic neurotoxicity by structurally similar amphetamine and methamphetamine compounds. MDMA has about one tenth the central nervous system stimulant effect of amphetamine.⁹ An oral dose of 1.5 mg/kg in adult patients produced an average maximum plasma MDMA concentration of .3 mg/L at 2.3 hours.¹⁰ Time to onset of drug effect is less than 30 minutes, with peak effects occurring at 1 to 1.5 hours, and duration of psychic effects lasting 3 to 4 hours.¹¹ Initial anxiety, nausea, tachycardia, and elevated blood pressure are followed by relaxation, euphoria, and feelings of enhanced emotional insight. Tolerance to the psychoactive properties of MDMA develops rapidly with loss of the ability to evolve the desired response with repeated doses within several hours; instead, sympathomimetic effects predominate resulting in anxiety, dysphoria, and paranoia.

Unlike amphetamine, MDMA is a potent releaser of serotonin from presynaptic vesicles and also inhibits its uptake.^{4,5} Extensive animal studies have shown it to cause a biphasic reduction in central serotonin levels. Acutely, serotonin levels fall 3 to 6 hours after drug administration with return to near-normal levels within 24 hours. Levels then

decrease again by 1 week. Acute depletion is considered to be secondary to enhanced release from nerve terminals, whereas long-term depletion occurs because of neurotoxic degeneration of serotonergic nerve terminals. Neurotoxicity is thought to be a cumulative, dose-related phenomenon.⁴ In contrast, similar changes in levels or turnover of dopamine or norepinephrine in response to acute treatment with MDMA have not been observed.⁴

There have been multiple case reports in the medical literature of MDMA-induced morbidity and mortality that fit the diagnostic criteria for serotonin syndrome. This is being increasingly recognized in the medical literature (Table). In addition, the National Poisons Information Service in London summarized severe complications and fatalities associated with MDMA use, many of which fit the diagnostic criteria for severe serotonin syndrome.¹² The mechanism is unclear, but it is suggested that a direct effect of the drug on thermoregulatory mechanisms could be potentiated by sustained physical activity, a high ambient temperature, and inadequate fluid replacement often encountered at "rave" parties.¹² Most cases of toxicity appear to be idiosyncratic and are not associated with massive overdose. Since MDMA has only about one tenth the stimulant effect of amphetamine on the central nervous system, excessive sympathetic stimulation by MDMA seems unlikely in these cases. Barrett¹³ reports a case of a patient who reportedly ingested 40 tablets of MDMA, and despite grossly toxic MDMA levels, developed no signifi-

Table 1.
Case reports of MDMA-induced morbidity and mortality.

Author/Journal	Age/Sex	Amount Ingested	Drug Level (mg/L)	Clinical Course
Brown C et al (<i>JAMA</i> 1987;258:780-781)	32/F *	100-150 mg	6.5-7.0	Hyperthermia, autonomic instability, tonic arm movements, rhabdomyolysis, coagulopathy, toxic hepatitis
Chadwick IS et al (<i>J Royal Soc Med</i> 1991;84:371)	16/F	1 tablet	.42	Hyperthermia, autonomic instability, seizure, DIC, death
Singarajah C et al (<i>Anaesthesia</i> 1992;47:686-687)	24/M	200 mg	*	Hyperthermia, autonomic instability, status epilepticus, rhabdomyolysis, organic brain syndrome
Campkin NTA et al (<i>J Royal Soc Med</i> 1992;85:61)	18/M	3 tablets	1.26	Hyperthermia, autonomic instability, seizure, DIC, rhabdomyolysis, death
Screaton GR et al (<i>Lancet</i> 1992;339:677-678)	19/M	*	Present	Hyperthermia, rigidity/DIC, rhabdomyolysis, death
Screaton GR et al (<i>Lancet</i> 1992;339:677-678)	19/M	*	*	Hyperthermia, rigidity/DIC, rhabdomyolysis, compartment syndrome lower extremities
Screaton GR et al (<i>Lancet</i> 1992;339:677-678)	19/M	3 tablets	*	Hyperthermia, rigidity, rhabdomyolysis, coagulopathy
Bedford Russel AR et al (<i>Arch Dis Child</i> 1992;67:1114-1115)	13 mo/M	1 tablet	.7	Hyperthermia/seizure, writhing, jerking movements
Logan AS et al (<i>Anaesthesia</i> 1993;48:1017-1018)	23/M	4 tablets	Present	Hyperthermia, autonomic instability, DIC
Nimmo SM et al (<i>Anaesthesia</i> 1993;48:892-895)	19/F	*	Present	Hyperthermia, autonomic instability, seizure
Roberts L et al (<i>J Acad Emerg Med</i> 1993;11:53-54)	20/M	18 tablets	4.05	Hyperthermia, autonomic instability, seizure

DIC, Disseminated intravascular coagulation.

*Not reported.

cant complications.¹³ The only reported exception is a case report of a patient who ingested 18 tablets of MDMA and presented with hyperthermia, seizures, and autonomic instability. His blood MDMA level was 4.05 mg/L, within the range reported in the other cases¹⁴ (Table).

Alternatively, the drug may have a low "therapeutic" to toxic ratio, although apparent widespread use of MDMA with relatively few cases of severe toxicity speaks against this. The 1995 annual report of the American Association of Poison Control Centers reported 2 deaths from MDMA among almost 13,000 amphetamine exposures, 27 of which resulted in death.¹⁵ Blood levels associated with toxicity reported in the medical literature range from .2 to 7.0 mg/L; however, the exact amount of drug ingested and the time the blood sample was tested after ingestion is not available in the individual cases. Our case fulfills the criteria for severe serotonin syndrome: altered mental status/coma, autonomic instability (tachycardia, hypotension), and hyperpyrexia in conjunction with taking MDMA, a known serotomimetic agent.

The differential diagnosis of serotonin syndrome includes neuroleptic malignant syndrome, MAOI overdose, tyramine reaction, cocaine, amphetamine or other sympathomimetic drugs, or strychnine ingestion. Neuroleptic malignant syndrome has similar clinical findings, but the patient has a history of taking a neuroleptic agent that antagonizes dopamine receptors, and "lead pipe" muscle rigidity may be seen.² Other causes such as infection or metabolic disturbances (ie, thyroid storm, pheochromocytoma) should also be excluded.

Optimal treatment of serotonin syndrome remains unclear and is largely anecdotal. Typically, therapy consists of withdrawing the offending agent and providing general supportive care. Rapid cooling measures should be instituted early. In animal studies, blockade of serotonin 1A receptors with nonspecific serotonergic antagonists such as methysergide, chlorpromazine, and cyproheptadine has effectively blocked the syndrome, whereas serotonin 2 receptor antagonists did not.¹ It has been suggested that β -blockers, specifically propranolol, can inhibit the serotonin syndrome through serotonin receptor blockade.¹ In addition, dantrolene has been used effectively for hyperthermia with presumed MDMA-induced serotonin syndrome.¹³

Acute toxicity after MDMA ingestion resulted in clinical features consistent with severe serotonin syndrome in our patient. Aggressive supportive management including rapid cooling measures is the mainstay of treatment. Further research efforts directed at pharmacologic intervention by serotonin receptor blockade may lead to improved outcome in these cases.

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