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Ecstasy Intoxication: An Overlap Between Serotonin Syndrome and Neuroleptic Malignant Syndrome

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Summary: 3,4-Methylenedioxymethamphetamine (MDMA), also known as "ecstasy" is a popular recreational drug with potential for abuse. Although its neurotoxic effects have been established in animal studies, the acute and long-term effects of this serotonergic agent in humans are still unknown. We describe a 19-year-old woman with overlapping symptoms of neuroleptic malignant syndrome and serotonin syndrome after a single exposure to MDMA. We also review 15 other cases reported in the literature to draw attention to the serious neurotoxicity, including fatal outcomes, caused by the use of this increasingly popular, illicit drug. **Key Words:** 3,4-Methylenedioxymethamphetamine—Ecstasy—Serotonin—Neuroleptic malignant syndrome—Serotonin syndrome.

Ecstasy is the name commonly used for 3,4-methylenedioxymethamphetamine (MDMA), a ring-substituted amphetamine derivative. Although patented in 1914 as an appetite supressant, the drug did not become popular until the 1970s, when it was marketed as an adjunct to psychotherapy because of its effects in lowering the defensiveness of the patient, thus breaking the barriers between the patient and the therapist (1). Because of concerns for its abuse potential and reports of neurotoxicity in animal studies, it was declared illegal in the mid-1980s. Despite its well-established neurotoxicity in animals (2,3), the acute or chronic effects of this drug have not been well studied in humans. Its recreational use, especially on college campuses, and reports of cases associated with severe toxicity and death have increased awareness about the drug (4). We report here a patient with severe MDMA toxicity and review other cases described in the literature. The purpose of this report is to draw attention to the abuse potential and serious toxicity of this increasingly popular, illicit drug.

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CASE REPORT

A 19-year-old female college student was seen with an acute confusional state. After a day of skiing, she had taken one tablet of Ecstasy. Within 15 min of taking the drug, she became nauseated and vomited. She was disoriented and somnolent and had a bout of diarrhea on the way to the hospital. In the local emergency room, she was found to be tachycardic, drowsy, but responsive to pain, and her pupils were dilated. Urine toxicity screen was positive only for amphetamine. She had low sodium (120 mEq/L) and phosphorus (2.0 mg/dl); and lactate dehydrogenase (LD) was elevated to 1,060 IU/L, and creatinine phosphokinase (CK) to 3,960 U/L.

While being transferred to St. Mary's Hospital, Grand Junction, Colorado, she had a generalized seizure. On admission, she was found to have a blood pressure of 123/72 mm Hg, pulse 100–120/min, and respiration 20–24/min. Her temperature was 37.1°C initially, and then it increased to 38.5°C. She was somnolent and disoriented, and her dilated pupils reacted sluggishly to light. Her skin showed piloerection. Deep tendon reflexes were hyperactive in all extremities. No prominent rigidity was observed during the initial examination.

The white count was 13,100, hematocrit 34.9%, and blood chemistry showed a sodium of 124 mEq/L, aspartate aminotransferase (AST) 136 U/L (normal, 5–30), lactate dehydrogenase (LD) 1,273 IU/L (normal, 287–580), creatine kinase (CK) 6,357 U/L (normal, 35–230), phosphorus 1.6 mg/dL (normal, 2.7–4.7), and calcium 7.7 mg/dl (normal, 8.4–10.7). Cerebrospinal fluid (CSF) analysis and computed tomography (CT) scan were normal. Electroencephalogram (EEG) showed grade III, diffuse, dysrhythmia and very severe delta grade I slowing and disorganization of the background activity, suggesting severe and diffuse cortical dysfunction. The blood and urine screen was negative for all drugs except for MDMA. Urinalysis was positive for amphetamine and *N*-methylmethylene dioxyamphetamine (MDA), a metabolite of MDMA. Subsequent analysis of a sample of the substance she took confirmed that it contained MDMA.

The patient was diagnosed with possible neuroleptic malignant syndrome and rhabdomyolysis. She received gastric lavage with charcoal and sorbitol and was treated with intravenous (i.v.) fluids, bromocriptine ($\leq$30 mg/day), and i.v. dantrolene sodium (900 mg/day in three divided doses).

The neurologic condition improved gradually, and she became oriented 4 days after the admission. She complained of diplopia, generalized weakness, and painful stiffness of her limbs. During the hospital course, which lasted 11 days, the liver and muscle enzymes remained elevated. The most remarkable increase was in CK, which increased to 71,760 U/L; alanine aminotransferase (ALT) increased to 413 IU/L, aspartate aminotransferase (AST) to 819 U/L, and γ-glutamyl transferase (GGT) to 86 IU/L. Although CK, AST, and LD gradually decreased, they were still abnormally high at discharge. Sodium normalized within a week, and the EEG also improved. Dantrolene and bromocriptine were gradually decreased and discontinued. She received physical therapy and had complete range of motion when discharged.

After discharge, she had residual blurring of vision, positional vertigo, postural

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tremors in her hands, and constant, intermittently throbbing headaches sometimes associated with nausea. She was evaluated at our Movement Disorders Clinic 10 days after the discharge and was noted to have bilateral mild postural tremor with a frequency of 8–9 Hz and a slight kinetic component. Her CBC and blood chemistry, including electrolytes, ALT, AST, CK, LD, and alkaline phosphatase (ALP) were normal. EEG was within normal variation except for occasional prominent slow activity in the occipital regions bilaterally, rarely accompanied by a sharp wave discharge.

Her medical history was significant only for a reactive depression that involved a suicide attempt a year ago and was treated by counseling. She denied any other drug abuse except for occasional marijuana.

DISCUSSION

The clinical effects of MDMA toxicity have been described with increasing frequency during the past decade (Table 1; 5–17). Previously reported cases, similar to our patient, have shown alterations in mental status, convulsions, hyperthermia, hypo- or hypertension, tachycardia, mydriasis, rigidity, coagulapathy, and rhabdomyolysis. A few patients also displayed signs of acute renal failure (ARF; 10,11), and at least one had inappropriate antidiuretic hormone secretion syndrome (SIADH) (15). Besides seven cases with hepatotoxicity already reported in the literature (11), five additional cases (including the case described here) with abnormal liver function tests were described (6,10,11). Some patients were found dead (5), and therefore, their clinical presentation was unknown.

A characteristic feature of the syndrome associated with MDMA exposure is the rapid onset of symptoms with a latency ranging between 15 min and 6 h after ingestion of the drug. The severity of symptoms and potential outcome do not seem to correlate with overdose; an ingestion of only few tablets resulted in either mild toxicity or caused severe symptoms and death. In one case of an MDMA overdose with 47 pills and plasma level of 7.72 mg/L, only hypertension and tachycardia were observed (11). Another patient who has taken 18 tablets and had a plasma MDMA level of 4.05 mg/L survived without complications (17). In contrast, several others with relatively low MDMA levels, ranging from 0.05 to 1.26 mg/L, died (5,8,9,11). This marked variability in response suggests individual, possibly genetically determined, patterns of metabolism. It is possible that some "slow metabolizers" are genetically predisposed to more serious MDMA toxicity.

Animal studies have shown that MDMA causes an acute release of 5-hydroxytryptamine (5-HT) from central serotoninergic nerve terminals within minutes after drug injection and is maximal in 1 to 3 h (18–20). Even a single dose can result in marked change in brain serotonin levels (20–22). McKenna and Peroutka (4) categorized the effects of MDMA as short term (< 24 h) and long term (>36 h). The short-term effects are presumably due to acute release of 5-HT and are associated with a decrease in 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), decrease in tryptamine hydroxylase (TPH) activity, and recovery of 5-HIAA lev-

TABLE 1. *MDMA toxicity: a review of the reported cases*

Patient no.	Age/sex	Dose	Latency	Clinical findings	Lab. findings	Outcome	Ref
1	22/M	?	<6 h	? (found dead)	MDMA + in blood	Death	5
3	32/M	?	?	? (found dead) asthma attack?	1.1 mg/L MDMA, alcohol (−), theophylline (−)	Death	
4	18/F	150 mg	<2 h	Ventricular fibrillation	1 mg/L MDMA, 40 mg/dl ethanol	Death	
1	32/F	100 mg	<2 h	Agitation, BP 90/50, hallucination, mydriasis, DTR ↑, vertical nystagmus, hyperventilation, tachycardia, DIC, T: 41.6°C	MDMA + in blood and urine, CK 756, ALT 214, AST 1,820, LDH 1,320, ALP 145	Recovered	6
1	35/M	? (Regular user)	?	Convulsions, ventricular fibrillation	MDMA + in blood and urine	Death	7
1	16/F	1 tb (2nd time)	?	Convulsions, hallucinations, mydriasis, T: 40°C, BP: 80/50, tachycardia, DIC	0.424 mg/L MDMA, muscle biopsy: non-specific changes	Death	8
1	18/M	3 tb	?	Convulsion, T: 42°C, hypotensive, tachycardia, DIC, oliguria	1.26 mg/L MDMA in blood, CK: 9,000	Death	9
1	23/M	3 tb	<6 h	Convulsion, T: 40°C, BP: 120/60, tachycardia, ARF, mydriasis, DIC	0.2 mg/L MDMA, MDMA + in urine, ALT 289, AST 2,659, LD, 3,510, CK 5,849	Recovered	10
1	18/M	3 tb	?	Fixed dilated, T: 41.8°C, tachycardia, BP: 70/60, arrhythmia	0.36 mg/L MDMA	Death	11
2	17/M	2 tb	<3 h	Convulsion, comatose, hypertonic, tachycardia, hypertension, T: 41°C, DIC	MDMA + in blood	Death	
3	18/M	5 tb	<4 h	Comatose, rigid, gastric hemorrhage, T: 42.1°C	MDMA + in blood and urine	Death	
5	21/F	?	?	Convulsions, T: 41°C, tachycardia, DIC, BP: 170/100, ARF	0.11 mg/L MDMA, rhabdomyolysis	Death	
6	20/M	?	?	Convulsions, T: 40°C, hypertonic, DIC, tachycardia, ARF, BP: 81/40	1.16 mg/L MDMA, 0.06 mg/L MDA, 0.10 mg/L amph, rhabdomyolysis	Death	
2	1/M	1 tb	<30 min	Agitation, T: 38/5°C, convulsion, BP: 180/70, mydriasis	0.7 mg/L MDMA	Recovered	11
3	19/F	2 tb	<2 h	Vomiting, diarrhea, comatose, T: 39.7°C, tachycardia	0.97 mg/L MDMA, 0.05 mg/L MDA, thrombocytopenia, AST ↑	Recovered	
4	20/M	3 tb	?	Agitated, sweating, tachycardia, T: 40°C, BP: 210/70, DIC	0.24 mg/L MDMA, MDMA + in urine, 0.02 mg/L MDA, abnormal liver function tests,	Recovered	

3	18/M	5 tb	<4 h	Comatose, rigid, gastric hemorrhage, T: 42.1°C	MDMA in blood and urine	Death	
5	21/F	?	?	Convulsions, T: 41°C, tachycardia, DIC, BP: 170/100, ARF	0.11 mg/L MDMA, rhabdomyolysis	Death	
6	20/M	?	?	Convulsions, T: 40°C, hypertonic, DIC, tachycardia, ARF, BP: 81/40	1.16 mg/L MDMA, 0.06 mg/L MDA, 0.10 mg/L amph, rhabdomyolysis	Death	
2	1/M	1 tb	<30 min	Agitation, T: 38/5°C, convulsion, BP: 180/70, mydriasis	0.7 mg/L MDMA	Recovered	11
3	19/F	2 tb	<2 h	Vomiting, diarrhea, comatose, T: 39.7°C, tachycardia	0.97 mg/L MDMA, 0.05 mg/L MDA, thrombocytopenia, AST ↑	Recovered	
4	20/M	3 tb	?	Agitated, sweating, tachycardia, T: 40°C, BP: 210/70, DIC	0.24 mg/L MDMA, MDMA ' in urine, 0.02 mg/L MDA, abnormal liver function tests, rhabdomyolysis	Recovered	
5	25/F	2.5 tb	<5 h	Severe headache, subarachnoid hemorrhage	0.21 mg/L MDMA	Recovered	11
1	19/M	? (1st time)	?	Confusion, mydriasis, tachycardia, T: 43.3°C, rigidity, DIC	MDMA in blood and urine, myoglobinuria, CK 44,500	Death	12
2	19/M	? (1st time)	?	Comatose, T: 41°C, tachycardia, rigidity, DIC	CK 29,700	Partial recovery	
3	19/M	3 tb (Regular user)	?	T: 41°C, tachycardia, rigidity, mild DIC	CK 3,950	Recovered	
1	21/F	?	?	FP hematoma	0.07 mg/L amph	Partial recovery	13
1	23/M	4 tb	?	Agitation, mydriasis, tachycardia, T: 42°C, rigidity, BP: 167/?, DIC	CK 7,540	Recovered	14
1	24/F	1 tb	<6 h	Convulsion, sweating, mydriasis, T: 38°C, tachycardia, IADHS	0.05 mg/L MDMA, 0.006 mg/L amph, CK 45,000	Recovered	15
1	20/M	?	?	Convulsion, sweating, rigidity, mydriasis, tachycardia, T: 42°C, BP: 140/60	?	Recovered	16
1	20/M	18 tb	<40 min	Convulsions, T: 38.6°C, vomiting, trismus, rigidity	4.05 mg/L MDMA, 1.2 g/L ethanol	Recovered	17
This case	19/F	1 tb	<15 min	Confusion, agitation, convulsion, diarrhea, mydriasis, tachycardia, DTR ↑, T: 38.5°C	MDMA ' in blood and urine, MDA and amph in urine, CK 71,760, LD 1,273, ALT 413, AST 819, GGT 86	Recovered	

Amph, amphetamine; ARF, acute renal failure; BP, blood pressure; DIC, disseminated intravascular coagulation; FP, frontoparietal; T, temperature; tb, tablet; CK, creatine kinase; ALK, alkaline phosphatase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; IADHS, inappropriate antidiuretic hormone syndrome.

els in 24 h. The long-term effects are manifested by persistent slow decrease in 5-HT and 5-HIAA after initial recovery, persistently depressed TPH activity, and decrease in 5-HT terminal density. The biochemical changes appear to be species specific: primates are affected more severely and permanently than are rats or mice (23,24), and the long-term effects are dose dependent (18,25,26).

The histopathologic studies show that the neurotoxicity of MDMA is restricted to 5-HT nerve terminals arising from the dorsal raphe nucleus (27,28). The effects of MDMA on dopamine (DA) have been variable and are probably indirectly related to serotonin release (19,20,22,29,30). No long-term deficits in DA or its metabolites after MDMA administration have been reported so far.

The syndrome caused by MDMA produces clinical features that overlap between neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) (31). NMS results from exposure to neuroleptic drugs that block dopamine receptors or deplete dopamine. Some studies also suggest that the serotonin system is affected in NMS, as evidenced by a decrease in CSF 5-HIAA levels in patients with NMS (32–34). SS can occur after the use of serotomimetic agents alone or in combination with monoamine inhibitors (MAO-I). The increased bioavailability of 5-HT can inhibit dopaminergic neurons. The clinical characteristics of our case and some of the other cases resemble both NMS (mental status changes, hyperthermia, rigidity, elevated CK, and autonomic dysfunctions; 35,36) and SS (mental status changes, restlessness, hyperthermia, diaphoresis, hyperreflexia, diarrhea, myoclonus; 37,38). Because there is a considerable overlap between these two syndromes, the patients are sometimes first diagnosed with NMS and later considered to have SS or vice versa (38–40), and NMS has been reported occasionally with serotomimetic drugs (41,42). One of the main differences between the two syndromes seems to be the onset of symptoms after the drug administration, which is within hours in SS and in 3–9 days in NMS (38,43). Other features favoring SS are mild extrapyramidal symptoms (38,39), hyperreflexia, and myoclonic movements (39). Because MDMA seems to have a more pronounced effect on the serotoninergic than on the dopaminergic system, the syndrome related to the use of MDMA is more likely SS than NMS. The clinical manifestations (rapid onset of symptoms, hyperreflexia, diarrhea, and mild rigidity despite a high CK level) support this conclusion.

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