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Methylenedioxymethamphetamine (MDMA, "Ecstasy")

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CASE

A 21-year-old male was brought to the emergency department (ED) after taking 30 "hits" of Ecstasy. Witnesses reported he had a seizure at home before the arrival of paramedics. In the ED, he was agitated with pulse 130 and blood pressure 150/98. Diazepam (5 mg IV) was given for agitation with poor results. He developed a temperature of 105°; his initial serum creatine phosphokinase (CK) was 1350 IU/L. The patient was endotracheally intubated; he was given activated charcoal via nasogastric tube and transferred to the intensive care unit. In the intensive care unit he developed disseminated intravascular coagulation (DIC) with an initial INR of 4.2. CK rose to 17,000 IU/L. Liver enzymes became abnormal with an aspartate aminotransferase (AST) of 286 IU/L and an alanine aminotransferase (ALT) of 149 IU/L. CK rose to 27,000 IU/L while INR rose to 6.5. Serum creatinine increased to 1.6 then 4.6 mg/dL; oliguria developed. Alkaline diuresis was initiated through the addition of sodium bicarbonate to his intravenous fluids. AST rose to 2000 IU/L and ALT to 5004 IU/L. Serum creatinine rose to as high as 9.1 mg/dL with BUN 54 mg/dL. Hemodialysis was initiated. At 25 days post-ingestion, he was extubated. However, he continued to require daily hemodialysis and demonstrated evidence of permanent neurologic sequelae.

INTRODUCTION

Ecstasy is the name given to 3,4-methylenedioxymethamphetamine (MDMA), an increasingly popular substance of abuse. Other common names for the drug are Adam, XTC, and "the love drug." Ecstasy is also related to the drug of abuse methylenedioxymethamphetamine (MDEA, "Eve") (1). Although structurally related to the stimulant methamphetamine (Fig. 1), MDMA possesses unique properties that are described as a combination of anxiolytic, stimulant, and hallucinogenic. The toxicity of MDMA is substantial, with a wide range of toxic manifestations appearing, even after a single "hit." Because of Ecstasy's growing use among adolescents and young adults, there is a need for pediatric emergency physicians to have a complete understanding of this drug, its profile of toxicity, and general principles of management.

EPIDEMIOLOGY

MDMA was first synthesized in 1914; however, clinical use did not begin until 1972. Initially, the drug was used therapeutically by psychologists as a facilitating agent for psychotherapy. It quickly became a recreational drug. In 1985, to combat Ecstasy's growing illicit use, the Drug Enforcement Administration placed it on the Schedule I list of controlled substances, making its possession illegal (2–5). Despite this proscription there has been an explosion in the use of Ecstasy over the last decade. Currently, it is a favorite "club drug" in both Europe and the United States. Rates of lifetime use among college students range from 2 to 39% (6, 7). The increase in MDMA's popularity is also reflected in the number of recent drug seizures by government agencies; the Drug Enforcement Administration confiscated approximately 216,000 MDMA tablets in the United States in the first 5 months of 1999, while the U.S. Customs Service seized 3,000,000 MDMA tablets over the same year (8). Production of MDMA tablets is centered in Europe, particularly Belgium and the Netherlands (8). Trafficking of MDMA is stimulated by an enormous profit margin – tablets that cost 2 to 25 cents to make are sold for as much as $40.

CHEMISTRY, STRUCTURAL RELATIONSHIPS

Ecstasy was one of the first so-called "designer drugs," modified from an illegal drug (methamphetamine) as a means of avoiding the legal prosecution resulting from possession of the banned agent (4, 9–13). Designer drugs did not become illegal until passage of the Controlled Substances Analogue Enforcement Act in 1986 (4, 10).

Like amphetamine, methamphetamine, catecholamines, and other stimulants, Ecstasy has the basic phenylethylamine structure that characterizes most sympathomimetic agents (Fig. 1) (10). The phenylethylamines possess a broad range of central nervous system (CNS) actions. For example, mescaline (3,4,5-trimethoxyphenylethylamine), derived from the psilocybin mushroom, is a phenylethylamine with primarily hallucinogenic activity; in contrast, amphetamine has only mild CNS stimulant actions (13). The wide spectrum of CNS effects produced by the phenylethylamines, as a result of minimal changes in their structure, is unlike that of any other class of drugs (13, 14). Of equal importance, the methyl group that is added to amphetamine to produce methamphetamine enhances the drug's lipophilicity, facilitating its entry into the brain and producing more rapid, potent, and long-acting effects (12 15). Being a methamphetamine derivative, Ecstasy similarly has a rapid-onset, potent action.

When MDMA was first used, it was noted to have an unusual property; it produced a feeling of calm coupled with an ease of communication (16). Therefore, it was thought to be a powerful tool in psychotherapy because it could facilitate conversation without producing psychosis, agitation, or visual disturbances (13, 16–18). The term "entactogen" was coined to describe this novel effect (4, 9, 14).

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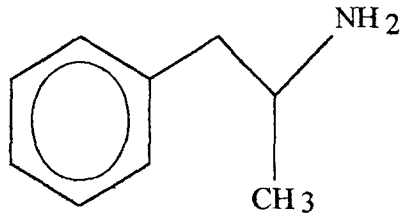

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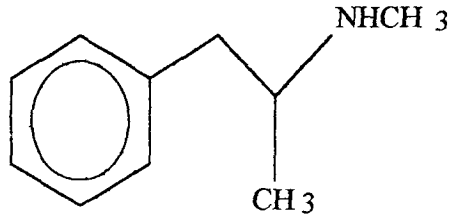

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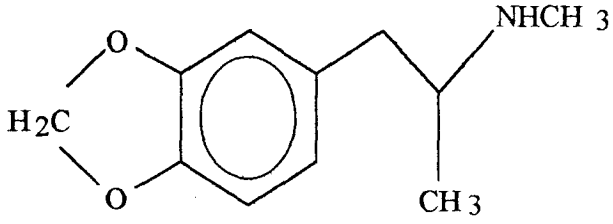

FIG 1. Methylenedioxymethamphetamine (MDMA, "Ecstasy").

PHARMACOLOGY

MDMA is well absorbed after ingestion with peak plasma concentrations occurring 2 to 3 hours after ingestion (9). Its volume of distribution is not firmly established but is thought be large (>5L/kg). An oral dose of 1.5 mg/kg produces a plasma concentration of approximately 300 μg/L (19). At steady state, spinal fluid concentrations are 80% that of plasma (12). As much as 75% of a dose of Ecstasy is eliminated via urinary excretion of unchanged drug. Because all amphetamines are weak bases with pKa values of 8.0 to 10.5, renal elimination is increased in an acid urine and markedly decreased with urinary alkalinization. Serum half-lives generally range from 7 to10 hours in acid urine to 16 to 31 hours in alkaline urine.

As an indirect sympathomimetic, MDMA has clinical effects resulting primarily from an ability to stimulate the release of endogenous catecholamines and decrease their reuptake into presynaptic vesicles. The release of both central and peripheral catecholamines, particularly epinephrine, norepinephrine, and dopamine is stimulated by MDMA. While amphetamines generally have little, if any, ability to directly stimulate adrenergic receptors (12), MDMA appears to act at adrenergic, serotonergic, and dopaminergic receptors (10, 13). The drug also stimulates and inhibits the reuptake of serotonin, which partially explains its mood-elevating effects.

MDMA shares the pharmacologic properties of other stimulants, producing effects on the cardiovascular system, smooth muscles, and the central nervous system. Cardiovascular effects include tachycardia and modestly elevated blood pressure. In the central nervous system chief effects are mood elevation, loss of fatigue, anorexia, and increased ability to concentrate (15).

CLINICAL EFFECTS, TOXICITY

A typical dose or "hit" of Ecstasy is 100 mg but ranges from 50 to 250 mg (1–4 mg/kg) (20, 21). The street price for Ecstasy is approximately $40 for a 100-mg dose (5). Unlike methamphetamine, which is typically synthesized in clandestine laboratories (18), MDMA is usually available as pharmaceutical-grade tablets that have been smuggled into the United States. When "basement-made" Ecstasy has been confiscated, it has been found to contain a range of other substances (22).

Ingestion of as little as 50 mg of Ecstasy produces the desired effect; users describe seemingly contradictory actions of CNS stimulation and talkativeness, simultaneously with a feeling of relaxation. Others describe the drug's ability to produce a lucid, peaceful, and uninhibited state, a feeling that "all is right in the world" (16). This sensation has given MDMA the nickname "the hug drug" [Boston Globe; March 18, 2000]. At low doses, users do not experience hallucinations, although they may appreciate alterations in color perception and texture, or magnification of "fantasy states"; these distinguish Ecstasy from classic hallucinogens such as lysergic acid diethylamide (LSD) (13, 14, 16). True hallucinations do not occur unless larger doses are ingested, at which point visual perceptions can become markedly distorted. A typical "high" lasts 3 to 5 hours (10, 19).

Even at low doses, Ecstasy can produce undesired effects (23). Common side effects include nausea, diaphoresis, anorexia, tremor, myoclonus, tics, paresthesias, nystagmus, hyperreflexia, hypertension, urinary retention, and ataxia (4, 14, 16, 21, 24). Bruxism (jaw clenching) is almost universal; it is not uncommon for Ecstasy users to suck pacifiers or lollipops to ameliorate this effect. Despite its reputation for heightening sexual stimulation, Ecstasy typically reduces libido and can produce sexual dysfunction (25). In one survey, difficulty achieving orgasm while under the influence of MDMA was reported by 70% of males and 35% of females (25). The stimulant effects of the drug may produce rapid heart rate or palpitations. Occasionally, marked hallucinations occur, resulting in severe agitation or traumatic injury (from reckless behavior or a motor vehicle crash) (20, 26). There is a dose-response relationship for these effects; they are uncommon after a 50-mg hit but relatively common after 150 mg is ingested (22).

Part of the acute toxicity of Ecstasy stems from its pattern of use. In the current drug scene, users take the drug before entering a "rave" or some other type of dance club (9, 23). While high rates of concomitant ethanol use have been reported (18), users, who may be below the drinking age, typically drink water or a "brain tonic" containing amino acids such as tryptophan. Repeated dosing of Ecstasy may occur during a rave; subjects have reported taking 6 to 8 doses over a 12- to 14-hour period (6, 9). In these often poorly ventilated areas, high ambient temperatures coupled with incessant dancing can produce dehydration, hyperthermia, or frank heat stroke (9, 23).

An acute single ingestion of greater than 200 mg can be considered an overdose. After Ecstasy overdose, the clinical picture resembles that of acute methamphetamine intoxication with the apppearance of agitation, delirium, paranoia, tachycardia, hypertension, hyperthermia, marked diaphoresis, vomiting, diarrhea, abdominal

cramps, seizures, hypoglycemia, cerebral hemorrhage, rhabdomyolysis, myoglobinuric renal failure, or DIC (9, 13, 23, 26–28). In a published pediatric case, MDMA overdose in a 13-month-old boy produced seizures, tachyarrhythmias, hypertension, and hyperpyrexia (29). The psychosis of acute MDMA intoxication is a classic toxic psychosis, associated with paranoia as well as auditory and visual hallucinations. Major toxicities of MDMA in overdose are summarized in Table 1. Death after as few as two hits of MDMA has been reported (1, 19, 20, 26). In rapidly fatal cases, plasma MDMA levels ranged from 360 to 1260 μg/L (20, 26).

Ecstasy overdose can have two unusual complications, hepatotoxicity and hyponatremia. Hepatotoxicity has been described after both acute single overdose and chronic use. Its etiology is unclear. In severe cases fulminant hepatic failure, requiring liver transplantation, can occur (12, 26). Hyponatremia only occurs after acute overdose. Like hepatotoxicity, its etiology is uncertain. The observed falls in serum sodium probably have multiple etiologies including water intoxication secondary to excess free water ingestion, severe dehydration and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (30). Serum sodium concentrations as low as 115 mEq/L have been reported.

The serotonin syndrome, consisting of temperature instability, autonomic disorders, and muscular hypertonicity has been described after Ecstasy use (19).

Drug interactions exist between MDMA and other drugs. Best characterized among these is the interaction between MDMA and monoamine oxidase inhibitor antidepressants (MAOI). Smilkstein et al. described a patient who was chronically taking an MAOI, who developed severe hypertension, diaphoresis, altered mental status and hypertonicity after ingesting MDMA. The clinical picture resembled a tyramine reaction (31).

The manifestations of MDMA overdose are typically short lived, with most victims having marked improvement within the first 6 to 24 hours of treatment. However, some sequelae, including sleep disturbances, tremor, and tachycardia may persist for several days (13.)

Tolerance to amphetamines builds rapidly after chronic use, leading to escalating patterns of abuse (12). This may also occur with regular use of Ecstasy. As with amphetamines, long-term use of Ecstasy has been associated with the appearance of a delusional psychosis that may persist long after the cessation of use (13, 23).

TABLE 1
Major toxicity associated with acute MDMA overdose

Cardiac	Psychiatric
Ventricular ectopy	Paranoia
Tachyarrhythmias	Delirium/Hallucinations
Myocardial ischemia/infarction	Psychosis
	Irritability/Anxiety
Respiratory	Aggression
Pulmonary hypertension	
Noncardiogenic pulmonary edema	
	Neuromuscular
Neurologic	Hypertonicity
Seizures	Rhabdomyolysis
Cerebral hemorrhage	Myoclonus
Urinary retention	
	Metabolic
Other	Metabolic acidosis
Serotonin syndrome	Hyponatremia
Hyperpyrexia	Hypoglycemia
Disseminated intravascular Coagulation (DIC)	
Myoglobinuria	
Renal failure	
Hepatitis	

Other neuropsychiatric complications have been reported following chronic Ecstasy abuse. These include panic disorder, aggression, flashbacks, and major depression (23). Non-neurologic sequelae of chronic Ecstasy abuse consist of vasculitis, pulmonary hypertension, and ischemic colitis (23).

MDMA has been found in several animal models to be a potent neurotoxin, with seemingly lethal effects on CNS serotonergic neurons (6, 32, 33). A marked decrease in CNS serotonin activity occurs as soon as 1 week after repeated exposure to MDMA (33, 34). The neuropathologic lesion has been referred to as a "distal axotomy" (6, 35). When as little as 2.5 mg/kg twice daily is given for 4 days, there is a 44% depletion of serotonin (32); doses of 5 mg/kg produce 83 to 95% reductions in serotonergic density within the cerebral cortex (6). While subsequent sprouting of serotonergic neurons, resulting in neuronal recovery, has been reported, reinnervation patterns remain abnormal for as long as 7 years after MDMA use is terminated.

While an MDMA abstinence syndrome (withdrawal) has not been clearly described, like other amphetamines, the drug has the potential to produce malaise, fatigue, depression, insomnia, and suicidal ideation in the hours to days after use is terminated (23).

DIAGNOSIS

Because Ecstasy is an amphetamine derivative, it can be identified by many commercial tests for drugs of abuse through the presence of a positive amphetamine screen (9, 30). However, false-negative screens may also occur, depending on the specific test and method. The diagnosis of Ecstasy ingestion is otherwise made on clinical grounds with particular attention to the syndrome of stimulant use, ie, tachycardia, agitation, tremor, mydriasis, and diaphoresis. Ecstasy ingestion can simulate LSD ingestion. Ingestion of an anticholinergic agent can also produce a similar picture, with the notable exception of hot, dry skin with anticholinergics *versus* diaphoresis after Ecstasy (although in Ecstasy-induced heat stroke sweating may be absent). Because other street drugs are referred to as Ecstasy, including ephedrine, Ma-Huang (herbal ecstasy), caffeine, and gammahydroxybutyrate (GHB), clinical and laboratory assessment should be thorough to correctly diagnose MDMA ingestion.

MANAGEMENT

Basic measures, including measurement of all vital signs should be initiated. In patients with significant MDMA intoxication, vascular access should be established to provide hydration and in anticipation of more serious effects. Cardiac arrhythmias can be treated according to current protocols; underlying etiologies eg, metabolic acidosis, should be corrected. Hyperthermia should be treated aggressively; if it does not respond to cooling blankets, acetaminophen, and benzodiazepines, the patient should be paralyzed and intubated to reduce muscular thermogenesis (9 36 4). Physical restraint may be necessary for agitated patients although it should be replaced by chemical restraint as quickly as possible. Agitation should be initially treated by administration of a benzodiazepine although with severe agitation or frank psychosis, major tranquilizers, eg, haloperidol may be necessary. Hypertension often responds to sedating agents alone. However, if hypertension persists after victims are calmed, blood pressure should be controlled with the use of nitroprusside or a calcium channel blocker. Use of β-blocking agents is relatively contraindicated since the blockade of β- but not α-receptors can worsen vasospasm, exacerbating hypertension (12). Gastrointestinal decontamination is rarely needed since pa-

tients typically present several hours postingestion, at a point when Ecstasy absorption is complete. Activated charcoal should be administered if the ingestion is recent or if there is concern about drug coingestants. Laboratory assessment should include measurement of serum electrolytes, acid-base status, hepatic and renal function tests, serum CK, a toxic screen, and urinalysis.

Urine acidification was once recommended therapy for amphetamine overdose and does effectively enhance urinary elimination of amphetamine-like drugs. However, this procedure carries the risk of metabolic acidosis and myoglobin precipitation in the renal tubules; it is therefore contraindicated (31). Urinary alkalinization, often undertaken to prevent myoglobin precipitation, markedly reduces the rate of Ecstasy elimination and can prolong the drug's effects. Alkalinization should therefore be performed cautiously and only when clearly needed. Given the relative absence of data demonstrating significant benefit from sodium bicarbonate in the treatment of myoglobinuria, it cannot be strongly recommended.

SUMMARY

Ecstasy (MDMA) is an amphetamine derivative of growing popularity. The drug produces a range of toxicities when taken either in standard doses or overdose. In overdose it has major toxicity, producing several different life-threatening manifestations. Hepatotoxicity and hyponatremia are common but poorly understood consequences of MDMA overdose. The drug can produce long-term, if not permanent, neurologic sequelae by destruction of serotonergic neurons. Chronic Ecstasy use can result in psychosis, depression, and suicidal ideation. In the ED setting, it is essential for physicians to recognize and treat appropriately those who present with intoxication from this drug.

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