Ecstasy (3,4-Methylenedioxymethamphetamine): History, Neurochemistry, and Toxicology

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Background: **3,4-Methylenedioxymethamphetamine (MDMA; ecstasy), a compound chemically related to stimulant and hallucinogenic drugs, has been found to induce a state of euphoria and increased self-awareness. MDMA has been increasingly used for recreational purposes, especially among college students and other young adults, and has been associated with multiple toxic effects.**

Methods: **Using MEDLINE, the medical literature was searched from 1986 using the key words "ecstasy," "MDMA," and "designer drugs." Articles dating before 1986 were accessed from cross-reference of the more recent articles. A case report is described.**

Results: **MDMA was developed in 1912 as an appetite suppressant but never became commercially successful. It resurfaced in the 1950s as a psychotherapeutic agent. In 1985 MDMA was classified as a schedule 1 drug by the Food and Drug Administration after reports of neurotoxicity in laboratory animals. It again resurfaced in the mid 1980s as a recreational drug used primarily among college students and other young adults. There are a number of case reports describing toxic effects from MDMA, including hyperthermia, rhabdomyolysis, coagulopathy, and acute renal failure. Little information is available regarding acute management or treatment of toxic ingestions.**

Conclusions: **MDMA ingestion has been associated with severe toxic effects. Although the literature describes numerous cases of toxic ingestion, there are no published recommendations or suggestions to guide physicians in the evaluation and treatment of such cases. By reviewing the history, neurochemistry, and toxicology of MDMA, as well as providing some guidance regarding management of toxic ingestion, we can arm the provider with valuable information for use in the acute setting. In addition, this information will assist providers in counseling young adults regarding the possible consequences of using this substance.**
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3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is a compound chemically related to stimulant and hallucinogenic drugs that has been noted to induce a state of euphoria and increased self-awareness. It has been increasingly used for recreational purposes, especially among college students and other young adults. Its recreational use has been associated with multiple toxic effects. We present the results of a literature review and describe a case of toxic ingestion.

Methods

Using MEDLINE, the medical literature was searched from 1986 using the key works "ecstasy," "MDMA," and "designer drugs." Articles dating before 1986 were accessed from cross-reference of the more recent articles.

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History of MDMA

The first preparation and description of MDMA was through a patent issued by the E. Merck Pharmaceutical firm in Darmstadt, Germany, in 1912. The drug was developed as an appetite suppressant but never became commercially successful. It resurfaced in the 1950s as a method of lowering inhibitions in patients undergoing psychoanalysis.[1] Patients using the drug found it gave them a sense of closeness with others around them. They believed it let down barriers or filters to free communication and aided in the introspective analysis of one's psyche. In 1983 a study performed on 29 volunteers (primarily academics and medical professionals), MDMA was found to be an adjunct to insight-oriented psychotherapy and to facilitate intimacy and communication between people involved in intimate relationships.[2,3]

Despite some of these reported benefits of MDMA, in July 1985 the Food and Drug Administration (FDA) placed the drug into the schedule 1 category, which greatly restricted its availability.[1] Since that time its use as an adjunct to psychoanalytical therapy has greatly diminished, but its illicit use has become more common, perhaps in response to all of the attention given to MDMA by the lay press during the hearings that led to its schedule 1 classification.

Recreational use of MDMA began to surface in the early to mid 1980s. Reports from Ireland and college campuses in the United States showed its use was growing noticeably. Cases of ingestion reported by the Irish Poison Information Center increased 130 percent from January 1991 to June 1992.[4] Recreational use by college students surveyed at a private southern university increased from 8 percent in 1986 to 24 percent in 1991.[5] In addition, reports of adolescent knowledge of MDMA in England showed a dramatic increase in awareness of MDMA in the past 5 years.[6]

Currently most MDMA use occurs during "raves"—large (sometimes numbering thousands of participants) dance parties held in abandoned warehouses or other similar structures. Apart from techno-pop music and "smart drinks" (drinks laced with amino acid mixtures), MDMA seems to be an integral component of the rave scene.

Case Report

A 19-year-old man came to the emergency department by ambulance. The paramedics reported that they were called to a party where the patient had collapsed. Witnesses detailed that the young man had been at the party (a rave) for more than 30 hours and had taken several doses of ecstasy during this time. It was unknown whether he had consumed any other illicit substances or alcohol. No other medical history was available.

He was a well-developed, well-nourished man who was incoherent and agitated. His rectal temperature was 102.2°F (39°C); his blood pressure 140/96 mmHg, pulse 128 beats per minute, and respirations 24 per minute. Pulse oximetry was 100 percent on room air. Findings of his physical examination were also remarkable for flushed skin color as well as diaphoresis, slightly dilated pupils (4 to 5 mm in both eyes), a supple neck, and sinus tachycardia. Other than his fever, there were no signs of an infectious process. His neurologic examination showed him to be awake but disoriented. His cranial nerves appeared intact, as did gross motor strength. Sensation to sharp prick appeared to be without deficit, deep tendon reflexes were brisk and symmetrical, and both toes were down-going on plantar stimulation.

Initial laboratory studies were remarkably normal except for a blood urea nitrogen of 68 mg/dL and creatinine of 1.3 mg/dL; his white blood cell count was 11,000/μL with 44 percent neutrophils, 12 percent band cells, and 28 percent lymphocytes. A urinalysis was normal except for an elevated specific gravity of 1.025. The patient's ethanol level was 110 mg/dL. A computed tomographic (CT) scan of the head showed no abnormalities. He had a normal opening pressure on a lumbar puncture, and no abnormalities were found with cerebrospinal fluid analysis. Initial urine toxicology screening was positive for amphetamines. Acetaminophen and salicylate levels were negative. Blood, urine, and cerebrospinal fluid were sent for culture.

The patient was admitted to the intensive care unit for close observation. He was rehydrated with intravenous fluids and received three doses of dantrolene (1 mg/kg) intravenously to help control his hyperthermia. Empiric antibiotics were considered but withheld because infection was not suspected. A toxicologic analysis of the urine showed MDMA. Seventy-two hours after admission his dehydration and hyperthermia had resolved, and his complete blood cell count became normal. The cultures of blood, urine, and cerebrospinal fluid were negative. He was subsequently discharged home with scheduled follow-up in the substance abuse center of his local university health center.

Preparation of MDMA

At least six methods of making MDMA are described in the scientific literature. Several recipes can be located easily on the World Wide Web. Some specialized equipment is required as well as some expertise in organic chemical synthesis. Most expert black-market manufacturers recommend 1 to 2 years of undergraduate chemistry experience, including organic and analytic chemistry courses that have laboratory components. Problems with impure or incorrect synthesis can result in some rather potent and toxic contaminants,

however, which could be the reason for toxic ingestions noted in the literature.

Pharmacology

In vivo and in vitro animal studies have shown that MDMA affects the serotonergic (and to a lesser extent dopaminergic) neurons of the brain. The compound seems to cause a calcium-independent flood of serotonergic neuron release into the synaptic cleft while inhibiting serotonin reuptake. This response results in the euphoria and stimulus effect of MDMA.

Toxicology and Neurotoxicology

Concerns about MDMA have arisen as a result of studies showing both reversible and possible irreversible damage to serotonergic neurons.[7-15] These studies involved rats, rabbits, and nonhuman primates. Human studies of the effect of MDMA, which have been limited to indirect analysis through assays of cerebrospinal fluid obtained from patients, have shown conflicting results. Some studies have found a reduction in serotonin metabolites in the cerebrospinal fluid, suggesting a general depression or loss of serotonin from the brain.[16] Another study showed no such loss of the serotonin metabolites.[17] Because these studies were uncontrolled, the results are difficult to interpret. Ongoing controlled trials in Europe, as well as positron emission tomography (PET) scanning, could aid in further answering the question of neurotoxicity in humans.[18]

The lethal dose (LD_{50}) of MDMA has been studied in various animal models and by various routes of administration. Studies in rats have shown an LD_{50} of 49 mg/kg (parenterally) and 325 mg/kg orally.[1] Nonhuman primate studies have shown an LD_{50} of 22 mg/kg.[13] While no LD_{50} studies in humans have been done, serum levels assayed on patients with toxic MDMA ingestions have approached or in some cases exceeded the primate LD_{50} dose.

Case Reports of Adverse Reactions

Most case reports in the medical literature have come from England, where the rave scene has been popular for quite some time. Since the early 1990s, however, the phenomenon of raves has been transported to the United States, where they are gaining in popularity, especially in East Coast and West Coast cities. The most commonly seen reaction to severe or toxic ingestion of MDMA is a syndrome of altered mental status, tachycardia, tachypnea, profuse sweating, and hyperthermia. This constellation of symptoms closely resembles that caused by acute amphetamine overdose, which is not surprising given the chemical similarity of MDMA. Severe reported complications from MDMA ingestion include rhabdomyolysis, acute renal failure, cardiac collapse, malignant hyperthermia, disseminated intravascular coagulation, hepatic failure, hyponatremia, urinary retention, cerebral infarct, and cerebral hemorrhage (Table 1).[19-34] In addition, cases of profound psychosis and depression (once thought to be seen only in chronic users of MDMA) have been reported after minimal use.[35-42]

Table 1. Potential Complications of 3,4-Methylenedioxymethamphetamine (MDMA) Ingestion

Acute renal failure
Cardiovascular collapse
Cerebral edema
Cerebral infarction or bleeding
Depression
Disseminated intravascular coagulation (DIC)
Hepatic failure
Hyponatremia (severe)
Psychosis (chronic)
Respiratory failure
Rhabdomyolysis

Adapted from references 19-42.

It is not yet known exactly what pathophysiologic role MDMA plays in the variety of adverse events that have been observed. Academic experts who advocate judicious use of the drug report no such reactions. Some believe that the conditions at a rave (a hot, crowded environment, poor ventilation, excessive physical exertion, dehydration), as well as toxic dosages of and contaminants in the preparations ingested, might be the culprits, not necessarily the MDMA itself.[1,43,44] For these reasons MDMA continues for some to have a reputation as a safe recreational drug.

Treatment

Management of suspected MDMA overdose is the same as for any amphetamine overdose (Table 2). Attention to the ABCs (airway, breathing, circulation) should be the first priority. Assessment for ventricular dysrhythmias and hypertensive crisis should also be part of the initial assessment of these

Table 2. Treatment of Toxic Ingestion of 3,4-Methylenedioxymethamphetamine (MDMA).

1.	ABCs (airway, breathing, circulation)
2.	Complete history and physical examination (emphasis on neurologic findings)
3.	Cardiac monitoring and pulse oximetry
4.	Oral charcoal and sorbitol, if ingestion occurred within 30 to 60 min
5.	Consider serum chemistries, liver function studies, complete blood cell count, urine toxicology screening, serum ethanol level, creatine kinase measurements, and arterial blood gas determinations
6.	Monitor temperature and treat hyperthermia with a cooling blanket (dantrolene is controversial)
7.	Insert Foley catheter to prevent urinary retention
8.	Consider α-blocker to treat hypertension
9.	Consider β-blocker to treat tachycardia
10.	Intravenous fluids or dopamine to treat hypotension
11.	Correct metabolic acidosis, if present
12.	Intensive care unit monitoring with close observation of blood chemistries, hepatic transaminases, creatinine kinase, and urine output

patients. American Cardiac Life Support protocols should be initiated in the event of life-threatening dysrhythmias. Gastrointestinal decontamination using charcoal is also indicated. Initial studies should include a complete blood cell count, blood chemistry analysis, liver function tests, cardiac enzyme measurements (especially in the event of chest pain or dysrhythmias), creatine kinase measurements, and urine toxicology screening. Intravenous access is imperative. Other studies to consider are an electrocardiogram for chest pain, a chest radiograph for chest complaints, and a CT scan of the brain for persistent mental status change.

Treatment is then aimed at symptomatic management. Oxygen and intravenous fluids for hypotension; benzodiazepines or butyrophenones for agitation or seizures; dopamine or norepinephrine for hypotension unresponsive to fluid challenges; phentolamine or nitroprusside for hypertension; lidocaine for ventricular dysrhythmias; nitroglycerin for myocardial ischemic pain; aggressive cooling and possibly paralysis for hyperthermia (use of dantrolene is controversial[45-47]); fluids, mannitol, or bicarbonate for rhabdomyolysis; and correction of electrolyte abnormalities are all essential management principles in the care of these patients. Use of β-blockers is contraindicated because this might result in unopposed α-adrenergic stimulation.

These patients should be admitted to the intensive care unit for constant cardiac monitoring. A Foley catheter should be inserted to monitor urine output. Neurologic monitoring should be instituted along with frequent measurements of temperature, blood pressure, heart rate, and respirations. Platelet count, blood chemistry determinations, liver function tests, and creatine kinase measurements should be done regularly to assess for the development of disseminated intravascular coagulation, metabolic derangements, hepatotoxicity, and rhabdomyolysis. Once the patient becomes medically stable, particular attention should be paid to evaluation of mood disorder, psychosis, and other psychiatric findings before discharge.

Recreational Use in Popular Culture

Information concerning the use and synthesis of MDMA is available through the Internet. Many sites on the World Wide Web discuss dosage methods for safe usage. These instructions are supported by literature from academics who have spent time studying the effects of and analyzing MDMA.[1,2,43] Their recommended dosage is 2 mg/kg as an initial dose with a booster dose after 2 to 4 hours of 0.5 to 1 mg/kg. It is also recommended that the user stay well-hydrated and refrain from vigorous physical activity to reduce the risk of serious hyperthermia and dehydration. Another important safety tip is having a trip guide to protect the user from risky behavior.[48] The current street price of MDMA is $10 to $30 per dose. The drug can be ingested orally, injected, smoked, or snorted. The onset of action is directly related to the route of administration, and for an oral dose, onset usually occurs in 30 to 45 minutes.

Psychologic effects of MDMA include enactogenesis (touching within) or a sensation that all is right with the world; empathogenesis, which is a feeling of emotional closeness to others coupled with a breakdown of personal communication barriers; and enhancement of the senses of touch, taste, vision, smell, and proprioception. These effects last approximately 4 to 6 hours, but a noticeable decrease in effect occurs within 2 to 3 hours.

Known side effects of MDMA include trismus and bruxism for which gum chewing is recommended. The drug is contraindicated in persons taking monoamine oxidase inhibitors because it can cause malignant hyperthermic reactions.

MDMA should also be avoided by persons who have a history of hypertension or cardiac, peripheral vascular, or renal disease because of its propensity to increase blood pressure.

Final Comment

Ecstasy, or MDMA, is a substance that has become popular with a subset of today's young adults. It has been associated with numerous fatal outcomes when used in improper situations or to excess. Because of the illicit nature of its production, impurities and toxic by-products are an additional hazard. The family physician should be aware that this drug, as well as many other so-called designer drugs, are being used in the community. The clinician should also be prepared to deal with the consequences of MDMA ingestion in patients who have a constellation of symptoms described in the patient above. Further research is needed (and currently underway) to define better the pharmacologic effects of MDMA and determine whether it might be of therapeutic benefit to the medical and psychiatric communities.

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