Multisystem Organ Failure and Death Resulting From Ingestion of "Molly" (3,4-Methylenedioxymethamphetamine)

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Background

"Molly" (short for *molecule*) is an illicit drug that has garnered recent popularity among young adults because of its euphoric effects and the belief that it is a safer form of the substance 3,4-methylenedioxymethamphetamine (MDMA), also known as *Ecstasy*. First used in 1914 as an appetite suppressant, MDMA was used as an adjunct to psychotherapy in the 1970s.[1] The widespread availability and abuse of the substance as Ecstasy in the 1980s ultimately caught the attention of the US Drug Enforcement Agency, which classified it as a Schedule I drug.[1,2] Multiple adverse effects have been associated with MDMA use, including hyperthermia, seizures, rhabdomyolysis, cardiac arrhythmias, intracerebral hemorrhage, acute kidney injury, disseminated intravascular coagulation, and death.[2–5] Given the multiple toxicities associated with MDMA in the form of Ecstasy, its popularity declined over the years. Over the past decade, a new form of Ecstasy has been branded and termed *Molly*.[6] Touted as "pure MDMA," Molly is believed by users to lack adulterants and thus have limited potential for adverse effects.[2] Despite the perceived safety, recent reports suggest that adverse effects similar to those experienced by Ecstasy users, including death, have been associated with the use of Molly.[2,4,7] We report a case of multisystem organ failure and death associated with the apparent ingestion of Molly.

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Case Study

A 21-year-old man was brought to the emergency department by emergency medical services (EMS) in respiratory distress. EMS found the patient unresponsive, obtunded, and pale, with agonal respirations and an oxygen saturation of 65%. Naloxone, 0.2 mg intravenously (IV), was administered with no response. The patient was intubated on arrival to the emergency department, given his unimproved oxygen saturation of 50% to 60% on bag-valve mask ventilation. Physical examination showed that the patient was diaphoretic with dry mucous membranes, and the pupils measured 3 to 4 mm and were reactive to light. The vital signs were remarkable, with a blood pressure of 61/29 mm Hg; heart rate, 210 beats/min; respiratory rate, 26 breaths/min; and temperature, 43°C rectally. Electrocardiogram (ECG) showed wide complex tachycardia. Because of the patient's decompensated state, synchronized cardioversion was performed with a 150-J shock, with no effect. The poison control department was consulted and recommended cooling the patient with concomitant administration of sedatives, sodium bicarbonate, and IV fluids. Cooling was performed by covering the patient with a cooling blanket and applying ice packs to the groin and axillae. Sodium bicarbonate, 100 mEq, and 1 L of normal saline solution were administered by bolus because of the patient's laboratory results, which were suggestive of severe acidosis (venous pH, 6.99; lactate level, 22.4 mmol/L) and early rhabdomyolysis combined with acute renal failure (creatinine kinase level, 899 units/L; serum creatinine level, 2.30 mg/dL; potassium level, 6.1 mmol/dL). After intervention, the patient's blood pressure and temperature improved to 96/46 mm Hg and 40.3°C, respectively. Urine drug screening was performed and returned positive findings for cannabinoids and opiates. At that time, family members arrived and reported that the patient had taken Molly earlier that night.

Although still abnormal, the patient's vital signs continued to improve over the next hour (heart rate, 146 beats/min; blood pressure, 121/36 mm Hg; temperature, 38.1°C) and a subsequent ECG showed narrowing of the previously wide complex tachycardia. However, the patient continued to have

severe metabolic acidosis (pH, 7.10; P_{CO_2}, 52.1 mm Hg; bicarbonate level, 16.3 mmol/L) despite administration of 150 mEq of sodium bicarbonate and continued administration of normal saline solution. A short time later, without any significant change in heart rate or blood pressure, the patient was noted to have 500 mL of dark, blood-tinged gastric contents drain from his orogastric tube (OGT). Cooling was stopped (temperature, 36.8°C). Disseminated intravascular coagulation (DIC) laboratory findings showed severe coagulopathy (hemoglobin level, 15.5 g/dL; prothrombin time >150 seconds; international normalized ratio [INR] >13.2; partial thromboplastin time >150 seconds; thrombin time >150 seconds; fibrinogen level, 59 mg/dL; 25 DIC platelets per nanoliter), and computed tomography imaging of the head showed a large, right-sided hematoma. The patient quickly underwent decompensation and went into asystolic cardiac arrest. After 2 rounds of cardiopulmonary resuscitation and 1 mg of epinephrine IV, the patient achieved return of spontaneous circulation (ROSC) and was transferred to the intensive care unit (ICU).

Pathophysiology and Treatment of Molly Intoxication

Neurotransmitter release is at the root of MDMA toxicity. Ingestion of MDMA results in the blockage of serotonin, norepinephrine, and dopamine reuptake, as well as transporter-mediated release of these agents.[1,4] The combined effects of increased concentrations of these neurotransmitters in the central nervous system lead to the multitude of clinical signs of MDMA ingestion and toxicity, including mood changes, hyperthermia, tachycardia, seizures, rhabdomyolysis, renal failure, and liver damage.[2–4,8,9] MDMA also has the unique effect of causing the release of vasopressin, the body's natural antidiuretic hormone. This release of vasopressin is believed to be the mechanism behind the sometimes-severe hyponatremia seen in patients after taking MDMA.[4] Unfortunately, currently, there is no reversal agent for MDMA toxicity. This means that treatment relies solely on providing supportive care and targeting the patient's individual symptoms.

Hyperthermia is one of the most common symptoms seen in MDMA toxicity, with some patients having temperatures up to 43°C.[1,3,10] The effect may partly be a result of the drug's association with the "rave" scene, where prolonged periods of strenuous activity combined with dehydration provide the perfect pairing for hyperthermia.[5,10] However, the majority of the effect is due to increased levels of neurotransmitters. Dopamine and 5-hydroxytryptamine are released and act on the hypothalamus to increase body temperature.[5,10] Increased norepinephrine and serotonin levels can cause increased muscle activity and serotonin syndrome–like effects.[3] The resultant severe hyperthermia increases levels of cytokines and endotoxins within the body, which leads to increased inflammation, tissue breakdown, and multisystem organ failure.[5,10] Treatment entails the use of any method to rapidly return the patient to normothermia. Although dopamine binds to D_2 receptors within the hypothalamus, haloperidol and other D_2 receptor antagonists have shown no benefit in the reversal of MDMA-induced hyperthermia.[10] Dantrolene, commonly used to treat serotonin syndrome, has been suggested for reversal of MDMA-induced hyperthermia. Reports of dantrolene use show variable results.[5,8–10] Instead, treatment relies heavily on the use of ice packs and other external cooling methods to quickly decrease the patient's core temperature.[5,9,10] This comes with its own risks, however, because external cooling may result in an increased core temperature via increased peripheral vasoconstriction.[5] The patient's temperature should be monitored frequently and treatments adjusted as needed because both the duration and severity of hyperthermia have been considered important factors in predicting patient outcomes.[3,5]

Like hyperthermia, the development of tachycardia and seizures may be multifactorial. Tachycardia results from the increased levels of circulating neurotransmitters that bind to their respective receptors and elicit the response of an increased heart rate. However, tachyarrhythmias may also develop due to oxidative stress on the heart, brought about by the actions of several MDMA toxic metabolites.[4] There are currently no recommended preventative or treatment strategies for this effect, unless a life-threatening arrhythmia such as supraventricular tachycardia or torsades de pointes develops in the patient. In these cases, treatment with advanced cardiac life support strategies should be implemented.

Seizures may develop from the increased neurotransmitters' direct effects within the brain, from severe hyperthermia (febrile seizure), or due to the vasopressin-induced hyponatremia seen in some patients.[4,8] It has been suggested that seizure may be a precipitating factor in the development of rhabdomyolysis and, ultimately, renal dysfunction or failure.[4] There is no literature to support seizure prophylaxis with pharmacologic agents in these patients. Instead, symptomatic treatment with benzodiazepines has been the treatment modality used in these cases.[3]

Severe hyponatremia has been described as "one of the most serious medical complications of ecstasy abuse."[8] Manifestations of hyponatremia can range from asymptomatic, decreased serum sodium levels to cerebral edema, seizures, coma, and even death.[4,8] This effect is likely due to the previously described increased release of vasopressin

seen after MDMA ingestion. An aggravating factor in the development of hyponatremia in these patients is the induction of dry mouth and sensation of thirst by both MDMA and the physical setting in which this drug is often consumed.[4,8] This leads to the patient's desire to take in an excessive amount of water, resulting in dilutional hyponatremia. It has been suggested that treatment of symptomatic hyponatremia in these patients should consist of administration of 3% hypertonic saline solution to rapidly increase the serum sodium levels.[8] Caution should be taken when patients' sodium levels are rapidly corrected because correction at a rate greater than 10 to 12 mmol/L in 24 hours may result in central pontine myelinolysis. MDMA-induced hyponatremia has been reported to spontaneously correct with fluid restriction or no therapy at all.[8] However, in most of these cases, the specific cause of the patients' symptoms will not be known on initial presentation, and fluid resuscitation will ensue. Fluid restriction in these patients may also exacerbate nephrotoxicity, which could have detrimental effects. Frequent monitoring of the patient's mental status should occur, as well as targeted treatment of any symptoms that develop in the patient as a result of hyponatremia.

Hepatotoxicity and fulminant hepatic failure have been reported in a number of published MDMA cases, with the reported incidence having grown over time.[1,3–5,8,9] One study even suggested that MDMA was the number 2 drug indicated in drug-induced hepatotoxicity, at 31% of all cases.[8] Despite the high incidence, the mechanism behind the development of hepatotoxicity after ingestion of MDMA has not been fully elucidated. One report suggests that the direct effects of toxic metabolites, MDMA itself, or contaminants within the drug could be the cause.[9] Some hepatotoxic effects may be related to the co-ingestion of alcohol or a history of alcohol and drug abuse. However, these factors were eliminated as possible causes in one case series, bringing into question the true underlying cause.[9] Immediate treatment of hepatotoxicity in these cases consists of supportive care. Unfortunately, not all patients respond to supportive care, and hepatotoxicity may develop into fulminant hepatic failure. This can perpetuate the patient's multisystem organ failure because acute kidney injury may develop due to hepatorenal syndrome.[8] In patients who survive immediate intoxication and have persistent hepatic failure, liver transplantation may be an option.[8]

As previously mentioned, there are a variety of factors that may lead to a patient's development of nephrotoxicity. Given the drug's association with extreme dancing and alcohol consumption, volume depletion due to dehydration is a likely contributor to the nephrotoxic effects seen in patients. Yet, nontraumatic rhabdomyolysis is believed to be the number 1 cause of MDMA-induced nephrotoxicity.[8] Seizures are believed to be the precipitating factor in the development of rhabdomyolysis.[8] Animal models have shown the development of proximal tubule injury after the administration of MDMA and its metabolites, suggesting that direct toxic effects of these compounds at least partially contribute to nephrotoxicity.[8] Similar to hepatotoxicity, treatment of nephrotoxicity consists of supportive care with aggressive fluid resuscitation. In some patients the administration of dialysis has been required to prevent the development of severe, life-threatening electrolyte abnormalities.[3,4]

The development of DIC is among the effects considered to be due to the aforementioned toxicities. Hyperthermia is likely the causative factor of this severe and often fatal syndrome.[3] The severe bleeding in this syndrome is uncontrolled with the administration of pressure to the site of bleeding. Given the syndrome's underlying cause, dysregulation of the coagulation cascade, treatment consists of the administration of blood products and clotting factors to restore the body's depleted levels. Repletion with blood products and coagulation factors should occur as soon as symptoms are recognized, with regular coagulation monitoring recommended, so that prompt administration of blood products can be performed if coagulopathy is not reversed.

Case Outcome

On ICU arrival, the patient was found to be bleeding through his IV sites, with continued bleeding noted in his OGT. Despite the administration of 52 units of cryoprecipitate, 4 units of packed red blood cells, 11 units of fresh frozen plasma, and 4 units of platelets over the subsequent 17 hours, the patient contained to have coagulopathy, with an INR of 2.3, fibrinogen level of 99 mg/dL, and DIC platelets of 55 per nanoliter. Laboratory values collected throughout the day continued to show severe metabolic acidosis. Despite continuous infusions of sodium bicarbonate, the maximum arterial pH achieved was 7.15. Resuscitation with blood products and 7 L of normal saline solution was insufficient to maintain the patient's blood pressure. Norepinephrine, epinephrine, and vasopressin were initiated and titrated up to a maximum of 30 mcg/min, 12 mcg/min, and 0.04 units/min, respectively. In the afternoon a pulseless electrical activity cardiac arrest occurred. ROSC was achieved, but laboratory values collected shortly after this event showed a worsening of the patient's acidosis and renal dysfunction (arterial pH, 6.94; serum creatinine level, 4.0 mg/dL; creatine kinase level, 75,461 units/L).

Laboratory values collected the following day showed evolvement of the patient's multisystem organ failure; liver function tests returned with elevated aspartate transaminase, alanine transaminase, and total bilirubin levels. Continued administration of blood products totaling 8 units of cryoprecipitate, 2 units of packed red blood cells, 6 units of fresh frozen plasma, and 5 units of platelets was insufficient to fully reverse the patient's persistent coagulopathy. The patient's renal function and acidosis continued to worsen despite attempts at treatment (serum creatinine level, 6.0 mg/dL; lactate level, 20.4 mmol/L; arterial pH, 7.11), and the administration of 15 g of calcium gluconate IV was unsuccessful at raising the patient's critically low calcium level (5.8 mg/dL; ionized calcium level, 0.62 mmol/L). The addition of phenylephrine was required to maintain an adequate blood pressure, despite 30 mcg/min of norepinephrine, 100 mcg/min of epinephrine, and 0.04 units/min of vasopressin. Continued attempts to reverse the patient's multisystem organ failure were futile, and the patient died less than 72 hours after presenting to the hospital.

Conclusions

Currently, there is no antidote for MDMA, or Molly. Without government regulation, given its classification as a Schedule I drug, there is no control over the purity or dose of MDMA in each Molly dosage form. Thus, treatment for patients presenting with Molly toxicity relies on symptomatic supportive care. Hyperthermic patients need to attain normothermia as soon as possible. Seizing patients should receive the necessary medications to control their seizures. Hyponatremia must be corrected in a timely manner. Patients with renal dysfunction should be well hydrated and, if necessary, undergo dialysis. Any other supportive measures to control complications that arise should be undertaken until either the patient has recovered or treatment is deemed futile. The glorification of Molly by current celebrities, combined with a recent report by the Drug Abuse Warning Network, suggests that MDMA use is on the rise.[11] Understanding the potential signs of MDMA toxicity and how to best manage patients with these symptoms is important now more than ever.

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