3 cases of primary intracranial hemorrhage associated with “Molly”, a purified form of 3,4-methylenedioxymethamphetamine (MDMA)

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A B S T R A C T

3,4-Methylenedioxymethamphetamine (MDMA, or “Ecstasy” in tablet form) is a powerful sympathomimetic drug that is commonly perceived as safer than other stimulants such as methamphetamine or cocaine. “Molly” is a purified form of MDMA that is perceived by users as being even safer, as it is free of adulterants such as methamphetamine. Previously, all reports of intracranial hemorrhages in MDMA abusers were associated with coingestion of other sympathomimetic drugs, or with pre-existing cerebrovascular lesions. We describe a series of three young, otherwise healthy patients with various types of intracranial hemorrhages associated with “Molly” ingestion. All three patients underwent extensive workup including catheter angiography that did not demonstrate aneurysm, arteriovenous malformation, or vasculitis. We suggest that even the purified form of MDMA can cause serious intracranial hemorrhagic complications and should not be thought of as a safe recreational drug.

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1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA), also known as “ecstasy,” is a commonly used recreational drug that is usually taken as a tablet. Its primary effect is that of mood enhancement. The drug was first developed in 1914 as an appetite suppressant, but gained small scale popularity as an adjunct to psychotherapy in the 1970s. MDMA appeared to facilitate communication and increase self esteem, but it was designated a schedule 1 drug in 1985 because of reports of severe toxicity and high potential for abuse [1]. MDMA has been associated with deaths secondary to hyperthermia, convulsions, rhabdomyolysis, cardiac arrhythmias, and disseminated intravascular coagulation [2]. MDMA ingestion has also been associated with various forms of intracranial hemorrhage, including subarachnoid hemorrhage and intracerebral hemorrhage. To date, all reports of intracranial hemorrhages associated with MDMA ingestion have either been in patients who either coingested MDMA with other stimulant drugs such as cocaine or amphetamines [3–5]; or who had pre-existing vascular malformations or aneurysms [4–7] or vasculitis [8,9]. In this report, we describe three patients who developed MDMA induced intracranial hemorrhage in the absence of any cerebrovascular abnormalities on extensive neuroimaging, including catheter angiography.

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trauma. The prior evening, he had smoked marijuana laced with “molly” while working at a bar in South Beach. He had not taken any cocaine or other amphetamines. Upon arrival in the emergency department, he complained of a sharp frontal headache but no focal weakness or numbness. Levetiracetam 1g was administered intravenously in the emergency department and he suffered no further epileptic events.

On examination in the emergency department, his temperature was 36.7 °C orally, pulse 89 beats per minute (BPM), blood pressure 110/67 mm Hg, and saturating 99% on room air. The patient was awake but inattentive. He spoke fluently and was able to follow commands. Extraocular movements were full. There was no pronator drift. Strength was full in the arms and legs. His laboratory studies showed white blood cells (WBC) 9.5 10×3/uL, hemoglobin 12.2 g/dL, and platelet count of 288 10×3/uL. PT 13.7, PTT 27.2, INR 1.20. His urine toxicology was positive for amphetamines (which include MDMA in our laboratory’s assay) and cannabinoids. Other routine toxicology tests including urine toxicology tests for cocaine, opiates, and benzodiazepenes, and serum testing for alcohol, acetaminophen, and aspirin, were negative. Basic metabolic panel revealed sodium 141 mmol/L, potassium 4.1 mmol/L, chloride 110 mmol/L, bicarbonate 19 mmol/L, BUN 12 mg/dL, creatinine 0.79 mg/dL, glucose 121 mg/dL. CT imaging of the head without contrast demonstrated bilateral convexity subarachnoid hemorrhage (Fig. 1).

The patient was admitted for observation to the neurosurgical intensive care unit and continued on levetiracetam for seizure prophylaxis and analgesics for his headache. Strict blood pressure control was initiated; he was started on atorvastatin 10 mg daily and nimodipine 60 mg orally every 4 h for subarachnoid hemorrhage. On hospital day 2, MRI and MRA/MRV revealed no evidence of aneurysm, vascular malformation or venous sinus thrombosis. A diagnostic angiogram was performed, which showed no distal aneurysm, arteriovenous malformation, venous sinus thrombosis, or changes consistent with vasculitis.

On hospital day 2, the patient complained only of a minor right frontal non-radiating headache. His electroencephalogram demonstrated rare intermittent right hemispheric slowing, but no seizure activity. After counseling on avoidance of illicit drug use, he was discharged home on hospital day 3 and had complete resolution of symptoms in the neurosurgical clinic upon followup one month later.

3. Case 2

A 25 year old male had ingested a Molly along with alcohol on the night prior to presentation. He developed a one minute witnessed generalized tonic clonic seizure with a residual left sided hemiparesis and prolonged postictal state. In the emergency department, CT scan revealed a large 6.3 cm right frontal intracerebral hemorrhage with intraventricular extension, right to left shift of 9.9 mm, and early hydrocephalus (Fig. 2).

He required intubation for airway protection and was transferred to our hospital for further management. On examination, he was moving the right side of the body purposefully but was densely hemiparetic on the left. His pupils were equal and reactive at 3 mm. His temperature was 36.5 °C, pulse 117 BPM, BP 150/84 mm Hg, saturating 100% on room air. Laboratory evaluation revealed wbc 11.7 10×3/uL, hemoglobin 17.4 g/dL, hematocrit 54.1% platelets 156 10×3/uL. PT 10.4, PTT 26.7, INR 0.97. Basic metabolic panel showed sodium 135 mmol/L, potassium 3.3 mmol/L, chloride 98 mmol/L, bicarbonate 22 mmol/L, BUN 13 mg/dL, creatinine 1.30 mg/dL, glucose 120 mg/dL. EKG was normal sinus rhythm without ST-T changes. His urine toxicology was positive for cannabinoids and amphetamines. Urine toxicology testing for opiates, benzodiazepenes, and cocaine, and serum tests for alcohol, were negative.

An external ventricular drain was placed, and mannitol was administered. It was felt that the patient’s neurologic condition allowed catheter angiography prior to surgical decompression. Catheter angiography including views with cross compression of the left ICA showed no cerebrovascular abnormality, other than shift of the anterior cerebral arteries to the left (Fig. 3).

Immediately following catheter angiography, a right sided decompressive craniectomy and evacuation of the hematoma were performed. No evidence of vascular malformation was found at the time of surgery, and surgical pathology showed hematoma, with no evidence of tumor or vascular malformation. Postoperative MRI with
and without gadolinium showed no evidence of gadolinium enhancing tumor, and a follow up catheter angiogram obtained two weeks later showed no cerebrovascular abnormality (Fig. 4). The patient underwent cranioplasty one month later, and remains neurologically intact.

4. Case 3

A 23 year old man with no significant past medical history other than marijuana smoking presented to the ER with 4 days of nausea and vomiting with meals and increasingly severe headache. He had ingested “Molly” one day before the symptoms started. The headache was described as a holocephalic pressure that woke him up each morning. The headaches lasted up to several hours and decreased throughout the day, did not radiate, and were associated with nausea, vomiting, and photophobia but not phonophobia. Ibuprofen provided some relief.

On admission, his temperature was 36.4 °C, pulse 93 BPM, blood pressure 139/97 mm Hg, oxygen saturation 98% on room air. His examination was non-focal. Laboratory values included PT 12.6, INR 1.10, aPTT 26.1, WBC 17.0 10×3/μL, hemoglobin 16.5 g/dL, hematocrit 49.2%, platelets 309 10×3/μL. Basic metabolic panel included sodium 138 mmol/L, potassium 4.8 mmol/L, chloride 99 mmol/L, total co2 28 mmol/L, blood urea nitrogen 11 mg/dL, creatinine 1.04 mg/dL, creatine phosphokinase 43. Blood glucose was 117 mg/dL.

Urine drug screen was positive for cannabinoids but not amphetamines, consistent with his reported use of Molly five days previously. The screen was negative for cocaine, opiates, and benzodiazepines. CT of the head revealed subarachnoid blood along the right hemispheric convexity (Fig. 5). CT angiography and follow up catheter angiography showed no evidence of vasculitis, aneurysm, arteriovenous malformation, or venous sinus thrombosis.

The patient was admitted to the neurocritical care unit for observation and developed no new symptoms. He was discharged home two days later.

5. Discussion

Intracranial hemorrhages of various types are a known complication of amphetamine abuse [5], and usually, but not always, are associated with cerebrovascular abnormalities such as arteriovenous malformation or aneurysm [5,12]. It is thought that severe transient elevations in blood pressure cause hemorrhages in this context [13]. Methamphetamine can also cause vasculitis, another potential cause of intracerebral or subarachnoid hemorrhage [9,14,15]. A third potential cause of cerebrovascular complications after amphetamine abuse is provided by preclinical models suggesting that administration of amphetamine leads to an initial transient increase in cerebral blood flow, followed
by a prolonged decrease of cerebral blood flow over thirty minutes. In vivo two-photon imaging of cerebral blood vessels revealed sustained vasoconstriction of pial arteries [16].

MDMA, whether ingested as a pill (“Ecstasy”) or ingested orally or smoked in purified form as “Molly,” is widely perceived as being safer than other amphetamines. Despite this perception of relative safety, MDMA has been associated with many serious nonneurologic complications, such as tachycardia, arrhythmias, severe hypertension, serotonin syndrome, and metabolic acidosis. The likelihood of toxicity in individual patients may be related to differences in expression of the metabolic enzymes CYP2D6 and COMT, which are deficient in 5–9% of the population [17]. As discussed above, intracranial hemorrhage has been reported as a complication of MDMA abuse, but all previously reported cases have been in patients who either coincided other sympathomimetic drugs [3–5], who had other cerebrovascular abnormalities such as aneurysm, arteriovenous malformation, or vasculitis [4–7] or vasculitis [8,9]. The likelihood of toxicity is likely to be related to the dose of MDMA ingested, as well. “Ecstasy” tablets sold to drug abusers generally contain 80–150 mg of MDMA, and data from animal studies suggests that a toxic dose to humans is probably 140–190 mg in a 70 kg adult [18]. It is possible that inadvertent overdosage is more likely with the use of the powdered “Molly” form of MDMA, as compared with the relatively fixed dose provided in the form of an Ecstasy tablet.

Our patient population is unique in that all three patients ingested a purified form of MDMA (Molly) which is perceived among users as safer than typical “Ecstasy” tablets, due to the absence of possible toxic adulterants. In addition, all three of our patients underwent extensive workup including catheter angiography, and, in one patient, surgical exploration which did not reveal any cerebrovascular abnormalities. Similar to prior studies of intracranial hemorrhage among methamphetamine abusers [12], the frontal lobes were affected in all three of the patients in our series, and two of the three patients presented with seizures. Fortunately, there were no fatalities or serious permanent neurologic sequelae in our patient population.

We recognize some limitations in our report. First, our routine urine toxicology screens, were insufficiently specific to rule out the possibility that our patients had unknowingly ingested amphetamines other than MDMA, or were not giving accurate histories. However, each of our three patients was a habitual recreational drug user and felt confident that the “Mollies” were unadulterated with other amphetamines. Second, each of our patients had used other drugs of abuse (marijuana in two patients, alcohol in one patient), which makes it difficult to definitively establish that “Molly” caused the intracranial hemorrhages. However, we suggest that neither marijuana nor acute alcohol intoxication is usually associated with spontaneous intracranial hemorrhage. Third, it is possible that MDMA may have induced a form of vasculitis not apparent on catheter angiography; however, no evidence of vasculitis was found on histopathology obtained from the one patient who required surgical evacuation of his hematoma.

6. Conclusion

We report 3 patients who developed intracranial hemorrhage following “Molly” ingestion, in the absence of structural cerebrovascular lesions or vasculitis. MDMA has been perceived to be a safer recreational drug than other stimulants such as methamphetamine and cocaine, and “Molly” has been perceived as a particularly safe form of MDMA. This case series demonstrates that MDMA, and in particular the purified form, can cause potentially life threatening intracranial hemorrhage even in the absence of pre-existing vascular malformations.

Conflict of interest

I have no conflict of interest to declare.

References