ANESTHETIC IMPLICATIONS OF ACUTE METHYLENEDIOXYMETHAMPHETAMINE INTOXICATION IN A PATIENT WITH TRAUMATIC INTRACEREBRAL HEMORRHAGE

- Case Report-

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Abstract

The use of the street drug methylenedioxymethamphetamine (MDMA), commonly referred to as ecstasy, has become increasingly prevalent amongst teenagers and young adults in the United States and many other parts of the world. While most anesthesiologists are facile with the intricacies of managing patients intoxicated by alcohol, cocaine and narcotics the new “club” drugs present a challenge, especially under emergency conditions. MDMA, in particular, is the most commonly abused club drug and potentially one of the most dangerous in the perioperative period. We present a case report of traumatic subarachnoid hemorrhage in a patient with acute MDMA intoxication and a review of the anesthetic implications.

Case

A 19-year-old man with an unknown medical and surgical history presented to the Emergency Department after a motor vehicle collision in which he was the unrestrained driver. The patient presented initially with a Glasgow Coma Score (GCS) of 9 and was emergently intubated in the field. A passenger in the vehicle stated the patient was at a “rave” before the accident. He did not know whether the patient took any illicit substances but stated that there was “X” at the party.

The patient was of average height and weight. Initial vital signs upon arrival to the Emergency Department included heart rate 115 beats per minute, blood pressure 157/88 mmHg, respiratory rate 12 breaths per minute, and O₂ saturation 99% on FiO₂ 0.4 via mechanical ventilator. Rectal temperature was 38.2°C. He had numerous facial abrasions but no open lacerations or obvious fractures. Neurologic examination did not reveal any focal deficits and the patient was moving all four limbs spontaneously. His lungs were clear and his cardiovascular exam was remarkable only for tachycardia. Laboratory evaluation indicated sodium of 124 meq/L. Cerebral computed tomography revealed a left-sided intracerebral hematoma and blood in the fourth ventricle with slight midline shift.
The patient was transported to the operating room for emergent evacuation of the hematoma. A 20 gauge intra-arterial catheter was placed in his left radial artery prior to induction. Tachycardia persisted. Anesthesia was induced with propofol 140 mg, fentanyl 100 mcg and rocuronium 50 mg. The hemodynamic status remained stable during the induction period. A bladder temperature probe was placed and a temperature of 38.4°C was recorded. A forced air blanket set to ambient air (24°C) was applied and cold normal saline hydration with 1.5 liters and sodium chloride 3% (500 ml) was administered during the four hour case. The patient received an infusion of remifentanil (0.05-0.1 mcg/kg/hr) and propofol (75-125 mcg/kg/min) throughout the case as well as a low concentration of isoflurane (0.5%) in oxygen and air. Electrolyte sampling prior to closure showed a sodium of 133 meq/L. Temperature prior to transport to the ICU was 36.4°C, heart rate 87 beats per minute and blood pressure 138/89 mmHg. Sedation was continued for 24 hours and his trachea was extubated 2 days later.

Following surgery, he had right-sided weakness that improved over the next week. Three weeks after the event, neurological examination was normal. He was discharged home without neurologic sequelae.

**Discussion**

While alcohol, cocaine/amphetamine and opiate use occasionally complicate the perioperative period, the rise of designer and club drugs demands a new paradigm in anesthetic management. The club drug, ecstasy (methylenedioxymethamphetamine, MDMA) has effects that may confuse the diagnosis, especially in the head injured patient.

In the US, there were an estimated 19.7 million people (or about 8.1 percent) over the age 12 using illicit drugs in 2005. About 500,000 of these had taken MDMA at least once during the year prior to being surveyed. According to the Texas Commission on Alcohol and Drug Abuse people attending “raves”, where ecstasy is prevalent, range in age 13 to 40 years. MDMA is available at 70% of these gatherings according to one study. A 2001-2002 survey in Chicago showed that roughly 40% of 18-40 year olds had gone to a “rave” and roughly half of these participants had taken a club drug.

Ecstasy is a hallucinogenic amphetamine analog known amongst recreational drug users as XTC, X, E and Adam. The drug is classified as a club drug along with GHB (gamma hydroxybutyrate), ketamine and flunitrazepam because of its use predominantly at dance parties (“raves”) and dance clubs. MDMA was patented in 1914 by Merck Pharmaceuticals as an appetite suppressant. Given its purported entactogenic effects (i.e., feelings of enhanced communication with and closeness to others), it was promoted as a psychotherapy adjunct in the 1970’s. Despite this potential clinical use, abuse of MDMA prompted the Drug Enforcement Administration (DEA) to issue a schedule 1 drug classification in 1985. Since that time, MDMA abuse in the US has steadily climbed.

MDMA is most often abused orally as a small pill or capsule. As it is produced illegally, the purity of street MDMA is highly variable, with numerous compounds commonly mixed into the final product. Indeed, the concentration of MDMA itself may vary and accidental overdoses are likely. Any acute MDMA intoxication should be approached as polysubstance intoxication.

MDMA closely resembles the hallucinogen mescaline and the stimulant amphetamine. These structural relationships are predictive of its effects. MDMA increases the release and decreases the reuptake of serotonin and dopamine and may also have direct agonist properties at serotonergic and dopaminergic receptors as well as monoamine oxidase (MAO) inhibitor effects. In vitro studies suggest an indirect agonist effect on norepinephrine release. Effects may be felt within 20 minutes of ingestion and can last up to 8 hours.

Effects include heightened alertness, “closeness” to others, increased emotional lability, decreased aggression and increased sexual arousal. Hypertension, tachycardia and hyperpyrexia are common. Mydriasis, bruxism, sweating and agitation with later lethargy, fatigue, anorexia and depressed mood follow.

The drug is metabolized principally through the cytochrome P450 (CYP450) 2D6 enzyme. Phase II metabolism of MDMA is poorly understood. One metabolite has been shown to be a 2D6 inhibitor in vitro. 2D6 inhibitors (e.g., cocaine, methadone, haloperidol, fluoxetine, paroxetine) block the main...
metabolic pathway of MDMA and may substantially increase the effects. Benzodiazepines are metabolized principally by the 3A4 enzyme and likely have limited metabolic interaction with MDMA. Pro-serotonergic drugs (e.g., fluoxetine, amphetamines, St. John’s wort, tramadol, lithium,) may increase the severity of MDMA’s pro-serotonin effects.

Hyperthermia is the most common adverse effect and a leading cause of MDMA-related mortality. The mechanism relates most likely to serotonergic effects in the hypothalamic thermoregulatory center compounded by sustained muscle hyperactivity from long periods of dancing in a warm environment (e.g., club), increased metabolic rate and rigidity. In genetically susceptible pigs, MDMA has been identified as a trigger of malignant hyperthermia (MH). Hyperpyrexia leading to rhabdomyolysis, disseminated intravascular coagulation (DIC) and multi-organ failure is the most dreaded consequence. Increased temperature increases cerebral blood flow and intracranial pressure and could worsen head trauma. Also, hyperthermia is not uncommon after head injury which will thus compound the differential diagnosis.

Sympathetic stimulation from MDMA intoxication increases myocardial oxygen demand and causes tachycardia, vasoconstriction, hypertension and occasionally acute myocardial infarction and dilated cardiomyopathy if prolonged. Cerebral autoregulation may fail, allowing dangerous increases in cerebral blood flow. Significant hypotension and low cardiac output may be encountered after the initial hyperdynamic state due to catecholamine depletion or autonomic dysregulation.

Electrolyte disturbances in MDMA abusers are particularly dangerous. Hyponatremia which often results from excessive water intake from increased physical activity (i.e., dancing at parties where MDMA is present) has been associated with MDMA-related seizures, stupor and incontinence. Increases in plasma ADH levels can be induced by MDMA use which may compound the increased intake of water by users. The occurrence of severe hyponatremia is an unusual complication in young patients with mild head injuries. One retrospective review of patients in a Thai hospital demonstrated that of over one thousand mild head injuries reviewed, only three patients demonstrated severe hyponatremia. All three of these patients were found to have recently ingested MDMA.

Other effects attributed to acute MDMA intoxication include hepatotoxicity with hepatonecrosis and fulminant liver failure, pneumothorax and pneumomediastinum, acute renal failure from rhabdomyolysis and creatine phosphokinase elevations lasting up to 4 days after hospitalization. Cerebrovascular events like subarachnoid hemorrhage, cerebral infarct and venous sinus thrombosis are relatively uncommon.

Most toxicology screens will not detect MDMA and its metabolites and a history is vital although often not available. A directed physical exam is also critical, with particular attention directed to vital signs (with suspicion heightened if patient is hyperthermic) and cardiopulmonary findings. Initial studies that may help the anesthesiologist’s approach are mostly nonspecific tests such as the electrocardiogram and electrolytes.

Succinylcholine should be used cautiously given the risk of compounding the malignant hyperthermia-like effects of the drug, raising intracranial pressure or potentially worsening hyperkalemia, if present. Also, the bruxism often associated with ecstasy may make intubation more challenging in spite of patient habitus. If the patient is conscious and capable of protecting his or her airway, anxiolysis with midazolam or diazepam may be useful and also raises seizure threshold.

Management of hyperthermia, cardiovascular instability, electrolyte derangements and renal and hepatic dysfunction are imperative. Wide swings in hemodynamic parameters are to be avoided given these patients’ higher risk of cardiomyopathy and coronary or cerebral vasospastic events. An intra-arterial blood pressure monitor, placed prior to induction, is advised.

Propofol and thiopental are appropriate induction agents as ketamine may induce catecholamine release from potentially exhausted stores. Etomidate tends to have stable hemodynamic effects but may increase seizure activity, which may be attenuated by pre-induction benzodiazepines. Paralysis with a non-depolarizing agent immediately slows heat production and help lower body temperature. Also, unlike succinylcholine, non-depolarizers are not associated with malignant hyperthermia. For this reason,
rocuronium may be ideally situated to both initiate a rapid sequence induction and maintain paralysis. Severe hypertension and raised intracranial pressure may occur during direct laryngoscopy and commonly used methods to blunt this response (e.g., intravenous lidocaine, opioids) are correct.

Maintenance of anesthesia for head trauma is generally with volatile anesthetics. However, volatile gases are known triggers of malignant hyperthermia and are best used conservatively if a patient has ingested MDMA. A narcotic infusion with remifentanil, which is metabolized by blood and tissue esterases, serves the dual role of blunting sympathetic output and lowering the amount of gaseous anesthetic necessary for surgery. Other narcotics, such as fentanyl, are also suitable. Serial sodium measurements and appropriate correction are important.

Potential intraoperative pitfalls are many. Intraoperative hypertension and tachycardia should be treated with labetalol, with its alpha and beta blocking effects. Pure beta blockade worsens hypertension by tipping the balance of catecholamine action to alpha-1 receptors. Intraoperative hypotension requires rapid infusion of crystalloid or the use of direct alpha-1 agonists. Avoiding indirect agonists such as ephedrine prevents the theoretical catastrophe generated when an already exhausted sympathetic nervous system is prompted to release catecholamines.

Hyperthermia must be treated promptly to avoid rhabdomyolysis and DIC. Basic measures include cold fluids, active cooling with ice packs and avoidance of warming blankets. Given the presumed central mechanism of MDMA-induced hyperthermia, dantrolene use is controversial as the drug inhibits the release of calcium from sarcoplasmic reticulum. Dantrolene may help exertional heat stroke which may be similar to MDMA-induced hyperthermia. Hall and Henry noted that during hyperthermia, the calcium levels required for excitation-contraction coupling are reduced such that hyperthermia alone can cause contraction and subsequent heat production and increased metabolic demand. They suggested that dantrolene, which raises the calcium requirements for excitation-contraction coupling, may be of some benefit even if it does not directly counteract central causes of hyperthermia.

In summary, patients acutely intoxicated by ecstasy may be hyperthermic, hyperdynamic and have many other dangerous complications. Neurological sequelae, in particular, present a challenge in terms of evaluation and treatment of the patient. We present a case of traumatic intracranial hemorrhage possibly worsened by concurrent ecstasy abuse. A conservative approach to such patients using thorough preoperative assessment, a gentle anesthetic induction and appropriate monitoring is crucial to a good outcome.

References