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Case Report

The Use of Cyproheptadine and Dantrolene in Prolonged MDMA-Induced Hyperthermia

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Abstract

Introduction

MDMA (3,4 methylenedioxymethamphetamine), also known as "Ecstasy", "XTC" or "E", although perceived as a safe recreational drug can have severe adverse effects including delirium, hyperthermia, rhabdomyolysis and multi-organ failure.

Case Report

A 16 year old female presented with altered level of consciousness, tachycardia, tachypnea, and hyperthermia after taking two tablets of Ecstasy. She was intubated for airway protection and treated symptomatically with sedation and active cooling. The patient had a prolonged duration of hyperthermia for 7 days which led to the administration of 2 antidotes, cyproheptadine and dantrolene. Cyproheptadine had no effect on the patient's hemodynamic parameters or temperature after 24 hours. The next day, three doses of intravenous dantrolene 80mg (1mg/kg) were administered. Within 1 hour of the first dose, the patient defervesced and became more hemodynamically stable. The next 2 doses of dantrolene had less apparent effect. The patient was extubated uneventfully on day 7.

Conclusion

Our case does not support the use of cyproheptadine in MDMA-induced hyperthermia. The benefit of dantrolene in this case is unclear. It is unknown whether dantrolene would have had an effect at higher doses. Furtherer research is warranted to ascertain the benefit of dantrolene in treatment of hyperthermia induced by MDMA.

Introduction

MDMA (3,4 methylenedioxymethamphetamine), also known as “Ecstasy”, “XTC” or “E”, was originally developed as an appetite suppressant [1], but its potential for abuse was quickly recognized. It has become a popular drug of abuse at “raves” due to its euphoric effects as well as its ability to increase energy, wakefulness, sociability and sexual arousal [2]. In 2004, 4.1% of Canadians reported having used Ecstasy at least once in their lifetime [3]. Although perceived as a safe recreational drug, severe adverse effects such as, delirium, hyperthermia, rhabdomyolysis and multi-organ failure, have been reported [4]. MDMA comes in different formulations but is commonly sold as tablets. Tablets are usually manufactured with 30-150mg MDMA and may contain other amphetamine derivatives. One would expect that toxicity of MDMA is dose-related, however, individual variability is large and the same dose could induce almost no change in some individuals and serious health complications in others [4]. Fatalities have been reported with serum MDMA levels of 0.1-2.1mg/L, and on the contrary, subjects have survived with levels as high as 7.72 mg/L [5]. Moreover, severe toxic symptoms have been documented with ingestion of a single Ecstasy tablet and normal blood levels, whilst others may recover without complications from a MDMA overdose [6]. Death rate has been estimated to be between 0.002% and 0.053% in users 15-24 years of age [7]. Here, we report a case of MDMA toxicity with persistent hyperthermia despite cyproheptadine and dantrolene administration.

Case Report

A 16 year old healthy female on no regular medications took 2 tablets of Ecstasy at a “rave”. Within 2 hours, she became agitated, disoriented, and developed incomprehensible speech and Emergency Health Services were called. Upon arrival to hospital, she was delirious and febrile with a temperature of 42°C. She was markedly diaphoretic; heart rate (HR) was 184 beats/min and respirations 32 breaths/minute. She had diffusely increased muscle tone with spontaneous jerking and twitching of her limbs. Intravenous (IV) lorazepam had little effect and our patient was intubated for airway protection and to facilitate cooling with a cooling blanket. Cooling can cause shivering and sedation is often required to control shivering. Admission lab work showed an elevated white blood cell count (WBC) count $14.0 \times 10^9/L$ ($4.0-11.0 \times 10^9/L$), serum creatinine (SCr) $209 \mu\text{mol/L}$ ($60-115 \mu\text{mol/L}$), lactate 16.5 mmol/L ($0.5-2.2 \text{ mmol/L}$) and creatinine kinase (CK) 283 U/L ($40-275 \text{ U/L}$). Urine drug screen was positive for 3,4 methylenedioxymethamphetamine (MDMA) and methamphetamine (MAMP). After receiving charcoal 50g, our patient was transferred to the intensive care unit (ICU).

Over the subsequent 6 days, her hyperthermia proved refractory despite sedation (initially with midazolam and subsequently propofol) and active cooling. In addition, she developed rhabdomyolysis (peak CK of 72,500 U/L ($40-275 \text{ U/L}$) on day 2) and disseminated intravascular coagulation (DIC) with a platelet nadir of $47 \times 10^9/L$ ($150-400 \times 10^9/L$),

an INR of 1.3 (0.9-1.2) and a PTT of 47 (24-40 s).

By day 3, our patient’s laboratory parameters were normalizing and we tapered her sedation. However, she promptly became hypertensive (blood pressure [BP] 150/75 mmHg), tachycardic (HR 105 beats/min) and hyperthermic ($T_{\text{max}} 39.0^\circ\text{C}$) requiring resumption of the sedation and active cooling.

On day 4, her clinical picture remained unchanged. We administered cyproheptadine 12 mg orally, followed by 4 mg every 6 hours for an ongoing fever that still ranged up to 38.3°C . No effect on hemodynamics or temperature was apparent after 24 hours of therapy.

On day 5, her fever persisted up to 38.8°C . We decided to treat her with dantrolene 80mg (1mg/kg) IV. Within 1 hour, her heart rate dropped from 96 to 76 beats/min. She became afebrile and we stopped active cooling. However, within 4 hours hyperthermia recurred and cooling was re-initiated. Two subsequent doses of dantrolene 80mg were given over the next 24 hrs with less apparent effect. Hyperthermia recurred within 4 hours of each dose (Figure 1).

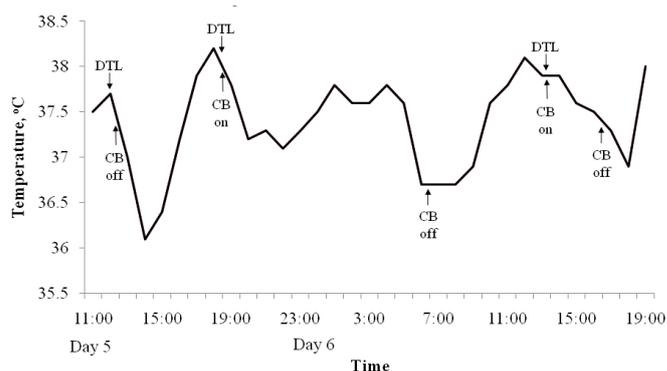


Figure 1. Temperature of a 16 year old female patient with MDMA toxicity, by time after dantrolene administration. CB=cooling blanket; DTL=Dantrolene.

On day 6, our patient’s hemodynamics and temperature continued to improve with maximum temperatures trending down to 38.2°C . On day 7, we were able to discontinue cooling and she was extubated uneventfully after 24 hours of normothermia.

Cultures and usual daily investigations failed to disclose any infectious source of fever. Chest x-ray (CXR) was clear on admission and day 2. On day 3, a modest right basal infiltrate was noted. Sputum was clear, but sputum cultures demonstrated light growth *Staphylococcus aureus*. Blood and urine cultures remained negative. Ceftriaxone was initiated for possible early ventilator-associated pneumonia. There had been no preceding history of respiratory illness or being unwell. The right basal infiltrate did not progress.

Discussion

MDMA is structurally similar to amphetamine and the hallu-

cinogen mescaline. It not only enhances presynaptic release of catecholamines (norepinephrine, serotonin, dopamine) but also inhibits reuptake of serotonin (5-HT) primarily [2]. As a result, the toxic profile of MDMA resembles a mixture of sympathomimetic and serotonergic toxicities. The onset of desired effects is approximately one hour after oral ingestion of MDMA and lasts for about 4-6 hours [4]. Delayed effects, such difficulty concentration, anxiety and fatigue, may last up to 2 days after MDMA use [2]. MDMA is broken down primarily by cytochrome P450 2D6 with a half-life about 8 hours [2].

paminergic blockade. The mainstay of treatment in neuroleptic malignant syndrome is the removal of psychotropic agents [10].

The clinical manifestations of serotonin syndrome can be summarized as a triad of mental status changes, autonomic instability and neuromuscular abnormalities (clonus, tremor, hyperreflexia). Severe muscle rigidity and hypertonicity may result in life threatening hyperthermia with a temperature > 41.1°C [11]. Other than removal of causative agents, cyproheptadine, a 5-HT_{2A} antagonist, is the recommended

	MDMA Toxicity	Neuroleptic Malignant Syndrome	Serotonin Syndrome	Malignant Hyperthermia
Etiology	Centrally dopaminergic and serotonergic effect	Centrally dopaminergic blockade	Centrally serotonergic effect	Peripheral calcium release
Hyperthermia	Up to 42.9°C	>41.1°C	>41.1°C	Up to 46.0°C
Muscular tone	Hyperreflexia, rigidity	Lead-pipe rigidity in all muscles	Hyperreflexia, clonus, mainly in lower extremities	Hyporeflexia, generalized rigidity
Autonomic instability	Present	Present	Present	Present
Treatment / Antidote	Supportive care ± dantrolene	Removal of agent(s)	Cyproheptadine	Dantrolene

Table 1. Similarities and differences between various hyperthermic syndromes [4,11-13].

Several complications of MDMA can occur, including: hyperpyrexia, acute renal and hepatic failure, hyponatremia, seizures and sudden death [2,4]. Severe hyperpyrexia in MDMA toxicity can initiate a cascade of adverse effects, such as muscle rigidity, rhabdomyolysis, myoglobinuria, and DIC, that constitute the hyperpyrexia syndrome [2,8]. Mechanisms involved in hyperthermia induced by MDMA include constriction of blood vessels via sympathetic stimulation, including adrenergic receptor stimulation, resulting in decreased peripheral blood flow and heat dissipation via the skin, and dysregulation of central thermoregulation via effects on dopamine and serotonin. (9) Acute hyperthermia from MDMA intoxication has been linked to serotonin syndrome (SS). Moreover, the similarities between MDMA-induced hyperthermia, malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS) have also been noted [2]. (Table 1) MDMA-induced hyperthermia can be modulated by a constellation of prolonged physical exertion, hot environment, crowded conditions, reduced fluid intake, as well as increased muscle tone [4,9]. Treatment of MDMA overdose is mainly supportive care. Active cooling measures are utilized in the management of hyperthermia [2].

NMS is a life-threatening complication of antipsychotic medications [10]. Although its clinical presentation overlaps with MDMA-induced hyperthermia, the etiology differs mechanistically as NMS is thought to be associated with do-

therapy for serotonin syndrome. There is a variety of cyproheptadine dosing regimens available. A review recommended an initial dose of 12mg, then 2mg every 2 hours should symptoms persisted. Maintenance therapy of cyproheptadine can be given at 8mg every 6 hours. Adults may require up to 32mg of the antidote [11]. Despite similarities in pathophysiology, cyproheptadine has not been well studied in MDMA-induced hyperthermia and the use of this antidote is controversial. Cyproheptadine was tried first in our patient without any effect; however, it is important to note that the patient received a lower maintenance dose.

MH is an autosomal dominant disorder in which defective calcium ion channels are found in the sarcoplasmic reticulum of skeletal muscles [12]. It is often associated with the use of inhalation anesthetics and depolarizing neuromuscular blocker succinylcholine. Upon triggering, calcium is released uncontrollably and that leads to significant elevation in norepinephrine, generalized muscle rigidity, and production of heat [13]. Clinically important findings that are similar to MDMA toxicity include: muscle rigidity, tachycardia, lactic acidosis, hyperthermia. Progression of symptoms is rapid and dramatic; body temperature can increase by 1-2°C every 5 minutes. Rhabdomyolysis leading to CK elevation and myoglobinuria are also diagnostic criteria of this syndrome [12]. Dantrolene is a muscle relaxant that acts di-

rectly on calcium channels to inhibit calcium ion release, and therefore, an effective antidote for this syndrome. The recommended dose is 1-3mg/kg IV, repeated every 15 minutes as needed to a maximum of 10mg/kg/day [13].

It has been hypothesized that, in individuals with MDMA-induced hyperthermia, there may be an underlying metabolic myopathy which disrupts calcium homeostasis. The use of dantrolene inhibits calcium ion release and limits muscle injury due to rhabdomyolysis, thus preventing cascade of downstream events such as increase in metabolic rate, generation of ATP, and inflammatory markers [14]. Numerous case reports on treating MDMA overdose in hyperthermic patients with dantrolene have been published with conflicting results. A recent systematic review found that survival was higher in dantrolene users (21/26 cases; 80.8%) versus non-users (25/45 cases; 55.6%). When stratifying patients who had temperatures $\geq 42^{\circ}\text{C}$ and $40\text{-}41.9^{\circ}\text{C}$, survival rates were found to be even greater in dantrolene users (8/13 cases for $\geq 42^{\circ}\text{C}$ and 10/10 cases for $40\text{-}41.9^{\circ}\text{C}$) compared to non-users (0/4 cases for $\geq 42^{\circ}\text{C}$ and 15/27 cases for $40\text{-}41.9^{\circ}\text{C}$) [8]. Although this appears encouraging, the results of this review should be taken with caution as publication bias is a major limitation. In our patient, the first dose of dantrolene had a pronounced effect. She defervesced within one hour of dantrolene administration and the cooling blanket was turned off; she also became more hemodynamically stable. Unfortunately, the benefit did not persist with repeated dosing and a higher dose (i.e. 2-3mg/kg) was not tried.

Our case was particularly interesting because of the prolonged duration of fever which caused us to consider alternative possible causes for the fever and allowed us to trial two reported antidote strategies. Our case does not support the use of cyproheptadine in MDMA-induced hyperthermia as it did not provide any benefit in temperature lowering. However, the benefit of dantrolene in this case is unclear. A benefit was observed at first dose of dantrolene but not with subsequent doses. It is unknown whether dantrolene would have had an effect at higher doses. Furtherer research is warranted to ascertain the benefit of dantrolene in treatment of hyperthermia related to MDMA toxicity.

Conflict of Interest

The authors report no known or suspected competing interests.

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