

A Case Series of Life-Threatening 3,4-methylenedioxyamphetamine (MDMA) Poisoning in an Electronic Dance Music Party in Hong Kong

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Abstract

Background: MDMA (3,4-methylenedioxymethamphetamine), which is also known as Ecstasy or Molly, is a commonly found abusive agent in Hong Kong. MDMA abuse is widely reported in electronic dance music (EDM) festivals all over the world. It brings about uncommon mortality and serious morbidity with recreational use, which are believed to be related to serotonin toxicity. Cyproheptadine has anti-histamine and 5-HT antagonist property which are reported to be an effective agent in managing serotonin syndrome of moderate severity. However, there is not much information concerning whether it is useful in life-threatening situations. **Case Presentation:** Four victims who collapsed while attending an EDM festival were sent to our Emergency Department (ED). They showed clinical symptoms compatible with life-threatening serotonin toxicity. One patient died 30 minutes after arrival to the ED. Aggressive attempts were made to resuscitate the other three; cyproheptadine was administered to them from 0.75 to 10 hours after arrival. They were all admitted to intensive care unit (ICU) for further management. Their urine showed a presence of MDMA. **Discussion:** Except for the one who died on arrival, the other three survived, who were later discharged. An early use of cyproheptadine (0.75 vs 3.5 vs 10 hours) results in better outcome as well as a shorter ICU stay (3 vs 10 vs 53 days) and total hospital stay (11 vs 37 vs 98 days).

Results: Supportive treatments as well as early use of cyproheptadine might have some beneficial effects in reducing the severity and hospital stay in patients presented with life-threatening serotonin syndrome related to MDMA.

Keywords: Cyproheptadine; MDMA; Poisoning; Serotonin Syndrome

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INTRODUCTION

MDMA, popularly known as “ecstasy” or “Molly”, is a synthetic compound of phenethylamine with stimulant and hallucinogenic properties. It is a common drug used for abuse in Electronic Dance Music (EDM) parties globally (1).

Earlier, mortalities and major adverse events due to recreational use of MDMA alone were uncommon and seldom reported (2). However, recently, there have been increasing number of mortalities and serious adverse events reported in patients abusing MDMA in rave parties or EDM festivals (3, 4). It has been postulated that life-threatening serotonin syndrome might contribute to mortalities and major adverse outcomes (5).

Management of life-threatening serotonin syndrome includes aggressive cooling of hyperthermia, intubation and muscle paralysis, intravenous fluid replacement, sedation

with intravenous benzodiazepine, and supportive treatment in intensive care unit (ICU).

Cyproheptadine hydrochloride is a histamine H1-receptor and serotonin antagonist, with antimuscarinic effects. It is primarily used for symptomatic control of urticaria, angioedema, rhinitis, and pruritic skin conditions. Cyproheptadine is also effective for the treatment of serotonin syndrome from mild to moderate severity. However, the effectiveness of using cyproheptadine in life-threatening serotonin syndrome remains unclear.

This article presents a case series of 4 patients suffering from life-threatening serotonin syndrome while attending an EDM festival, 1 of whom died on arrival to Emergency Department (ED), the others' urine showed the presence of MDMA and its metabolites. The 3 survivors were resuscitated with aggressive attempts and treated in ED and ICU. Cyproheptadine was given to them at intervals. Their clinical outcome and the lengths of ICU and total hospital

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stays were compared with the time to administrate cyproheptadine.

CASE PRESENTATION

In September 2017, 4 patients presented to the Emergency Department of Queen Elizabeth Hospital after attending an electronic dance music (EDM) rave party. They all had symptoms compatible with life-threatening serotonin toxicities, such as hyperthermia, with a temperature ranging from 41.2 °C to 42 °C, comatose, convulsions, marked tachycardia, dilated pupils, and an increased muscle tone. They were aggressively resuscitated in ED. However, one died upon arrival, despite aggressive resuscitation attempts. Others were admitted to ICU after resuscitation. Cyproheptadine was administrated to all of them at intervals

from 0.45 to 10 hours after arrival. Their urine solely showed the presence of MDMA and its metabolites. Their clinical data are summarized in Table 1.

Case 1:

A 21-year-old lady with dysthymia, but no history of substance abuse, was found collapsed during an EDM festival. Generalized tonic convulsion was witnessed for 5 minutes. She arrived at our ED at 15:30. She was febrile with a temperature of 42 °C. She was comatose and markedly dehydrated, with a heart rate of 140 beats/min. She was intubated for airway protection. Active external cooling was aided with a cooling blanket namely Criticool – an external cooling machine, which is marketed for Target Temperature Management, therapeutic hypothermia (TTM). The water

Table 1. Demographic and vital parameters of the four patients.

Patient	1	2	3	4
Age(y) & Sex (F female M male)	21/F	22/M	29/M	27/M
Temperature on arrival (in degree Celsius °C)	41.2 °C	42 °C	41.9 °C	High
Pulse rate/minute (in beats per minute)	140	170	138	Wide Complex - >Ventricular Fibillation
Blood pressure (in mmHg)	112/48	150/113	64/25	Arrest
Endotracheal intubation (+ perform – not perform)	+	+	+	+
Succinylcholine Use (+ use - not use)	+	+	+	-
Seizure at scene (+ present - not present)-	+	+	+	+
Acidosis (pH value)	7.28	7.33	7.3	7.088
Na/K (mmol/L)	139/6.3	145/4.7	143/4.2	138/6.4
Creatinine (umol/L)	177	207	208	242
Creatine kinase (IU/L)	9900	16700	61600	585
Disseminated Intravascular Coagulopathy (DIC) (+ present - not present)	+	+	+	na
High sensitive Troponin I (hsTnI) (ng/L)	1047	478	271	538
Cooling (Method)	CritiCool	CritiCool	Ice packs	Ice packs
Time to cooling in ED (in minutes)	40	25	60	na
Temperature reduction (in °C)	(4.2°C)	(2°C)	(2.9 °C)	na
Intravenous Fluid PlasmaLyte (in L)	4.5	3.5	5	3.3
Urine Toxicology (Abusive Drugs detected)	MDMA MDA	MDMA MDA	MDMA MDA	na
Outcome	Survival	Survival	Survival	Death

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blanket covers 70% of body surface area and is an efficient way of external cooling for hyperthermia patients. A total 4.5l of intravenous fluid and 6mg of intravenous midazolam with titration were given in A&E. On arrival, her limbs' tone and ankle clonus were not documented before the administration of muscle relaxants and intubation. Electrocardiogram (ECG) showed sinus tachycardia with narrow QRS complexes. CT scan of the brain showed no acute hemorrhage. She was then admitted to the ICU.

The patient was later noted to have increased muscle tone in the ICU. Cyproheptadine was then administered for potential serotonin syndrome. It was given at about 10 hours after her ED arrival.

Case 2:

A 22-year-old gentleman, with good past medical health and no history of substance abuse, collapsed during the same EDM festival 6 hours after the arrival of Case 1. He showed witnessed generalized tonic convulsion for 5 minutes. Upon arrival, he was febrile with a temperature of 41.2 °C, and blood pressure of 150/113mmHg. His pupils were dilated and he was markedly diaphoretic. ECG showed sinus tachycardia with narrow QRS complexes. Heart rate was 170 beats/min. External cooling was aided with Criticool. Muscle tone and ankle clonus were not documented before giving muscle relaxant. He was admitted to the ICU for further management. CT scan of the brain showed no acute hemorrhage. He was then admitted to the ICU.

He was later noted to have increased muscle tone in ICU. Cyproheptadine was also administered about 3.5 hours after his ED arrival for potential serotonin syndrome.

Case 3:

A 29-year-old gentleman with an unremarkable past medical health was admitted to ED at midnight. He was found collapsed at the same EDM festival with convulsions. He was febrile with a temperature of 41.9 °C on his ED arrival with dilated pupils and profuse sweating. His blood pressure was 64/25mmHg. ECG showed sinus tachycardia with a heart rate of 138beats/min. He had increased muscle tone, but no ankle clonus. External cooling was aided by ice packs over axilla and groins. He was intubated. In the view of suspected serotonin syndrome, 8mg cyproheptadine syrup were administered through nasogastric tube at 45 minutes after arrival. The patient was then admitted to the ICU.

Case 4:

Another 27-year-old gentleman with an unremarkable

past medical health was admitted to ED at 21:30 after having been found collapsed with convulsions at the same EDM festival. Upon arrival to the ED, he suffered a cardiac arrest with ECG showing ventricular fibrillation. His body temperature was documented to be "High". He was immediately intubated and actively resuscitated according to the Advanced Cardiac Life Support (ACLS) guidelines. Unfortunately, he failed to respond to the resuscitation attempts. His urine showed the presence of MDMA in the forensic reports.

Urine for Toxicology Analysis:

Urine of all the admitted cases was sent to Hospital Authority Toxicology Reference Laboratory (HATRL) for a toxicology analysis.

A qualitative urine toxicology screening was performed using gas chromatography mass spectrometry (GC-MS) and liquid chromatography mass spectrometry (LC-MS/MS).

3,4-methylenedioxyamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA) which is a metabolite of MDMA, midazolam metabolite, lidocaine, and ranitidine were found in Case 1. MDMA, MDA, midazolam, temazepam, paracetamol, and propofol metabolite were found in Case 2, and MDMA, MDA, and midazolam metabolite were found in Case 3.

Serum MDMA and MDA quantitation were analyzed by liquid-chromatography tandem mass spectrometry (LC-MS) with supported liquid extraction (SLE) extraction. The result was summarized in Table 2.

Outcomes:

All the three survived patients were discharged. One of them required a prolonged ICU and hospital stay (53 and 98 days, respectively). Otherwise, they had no major clinical sequelae. We compared their lengths of ICU and hospital stays against the time of initiation of cyproheptadine from their ED arrival, which seemed to be correlated.

Patient 3 was administered with cyproheptadine 45 minutes after his ED arrival. He showed the best outcome and the shortest lengths of ICU and total hospital stays (3 days in ICU and 8 days hospitalization). Patient 2 received cyproheptadine at 3.5 hours from his ED arrival. His length of stay in ICU was 11 days and needed 26 days of hospitalization. Patient 1 showed the worst outcome among the three patients. She had cyproheptadine administration at 10 hours after her ED arrival. She stayed in ICU for 53 days and was discharged from the hospital after 98 days (Figures 1 & 2).

Table 2. Urine toxicology screening result and serum MDMA and MDA concentration of the patients.

Case	Urine toxicology screening	Serum MDMA ng/mL	Serum MDA ng/mL
1	MDMA, MDA, midazolam metabolite, lidocaine, and ranitidine	835	19.4
2	MDMA, MDA, midazolam, temazepam, paracetamol, and propofol metabolite	308	11.2
3	MDMA, MDA, and midazolam metabolite	282	17.9

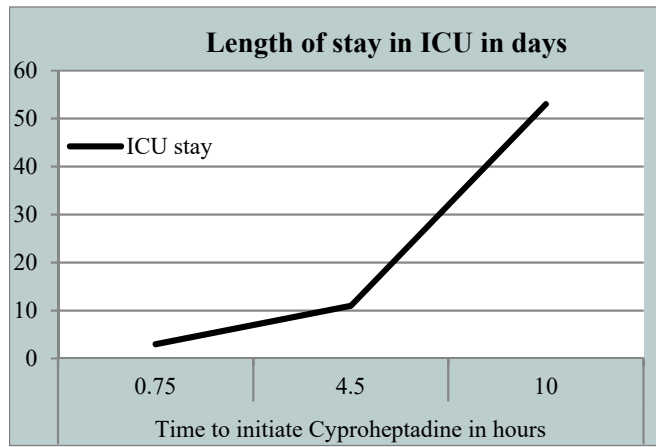


Figure 1. Relationship between Time to initiate Cyproheptadine and Length of ICU stay

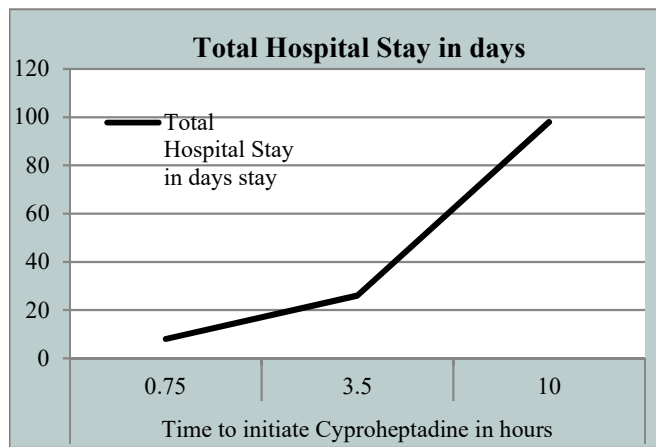


Figure 2. Relationship between Time to initiate Cyproheptadine and Length of Total hospital stay

DISCUSSION

MDMA was first introduced by Merck in 1914, as an appetite suppressant for animals and was later used in psychotherapy (1). Since the late 1970's, it is primarily used as a recreational street drug to achieve euphoric effects, particularly at urban dance parties. It is a popular recreational drug to abuse, and has been increasingly found at rave parties and electronic music festivals. The users of MDMA report experiencing a relaxed, euphoric state that is characterized by increased empathy, openness, communication, and tranquility.

Despite the high prevalence of the use of methamphetamine and its derivative MDMA, relatively few serious adverse events have been reported (2). However, in the recent years, sporadic reports were found describing mortalities and morbidities resulting from MDMA abuse at rave parties and EDMs (3,4). Serotonin syndrome was postulated to be one of the factors accounting for death and serious adverse effects due to recreational MDMA abuse (5). Serotonin syndrome results from over-activation of both the

central and peripheral serotonin receptors caused by high level of serotonin. Several different pharmacological mechanisms may be attributed to these elevated levels, namely inhibition of the metabolism of serotonin by monoamine oxidase inhibitors, prevention of the reuptake of serotonin in nerve terminals (serotonin reuptake inhibitors SSRI), and increased serotonin release (MDMA). The exact role of different serotonin receptors is not completely clear, but evidence suggests that severe life-threatening clinical effects, such as rigidity and hyperthermia, are mediated by the 5-HT_{2A} receptors (6).

Serotonin syndrome could only be diagnosed clinically – through physical examination and patient's history of using the serotonergic agent. It is a diagnosis of exclusion (7). No single diagnostic test can confirm this syndrome. The gold standard for serotonin syndrome is a diagnosis by a medical toxicologist (8). The symptoms vary from mild to life-threatening. Serotonin toxicity is characterized by the presence of a triad of clinical features: (1) neuromuscular excitation, for instance, tremor and clonus, hyper-reflexia and muscle rigidity; (2) autonomic stimulation, for example hypertension, tachycardia, hyperthermia, dilated pupils, and diaphoresis; and (3) changes in mental state, such as disorientation, restlessness, and coma.

Recent research demonstrated that environmental conditions are more critical in determining the severity of MDMA-induced serotonin syndrome than the ingested dosage and serum concentration (9). Experiment in rats showed that ambient temperature has a significant effect on MDMA neurotoxicity, core temperature, and thermoregulation (10). This might explain why severe serotonin toxicity occurs even with a recreational dose of MDMA.

Management of serotonin syndrome includes discontinuing all the serotonergic agents, providing supportive care via stabilizing vital signs, providing adequate oxygenation and intravenous fluids, sedation with intravenous benzodiazepines, and administering the serotonin antagonists. With treatment, serotonin syndrome usually resolves within 24 hours. For life-threatening serotonin syndrome, management should be more aggressive. This generally includes active cooling of hyperthermia, intubation and muscle paralysis, intravenous fluid replacement, sedation with intravenous benzodiazepine, and supportive treatment in ICU (11). The 5-HT antagonists, like cyproheptadine, were demonstrated to have promising results in treating moderately severe serotonin syndrome in some case reports (12). However, cyproheptadine is only available in oral form, which includes 4 mg tablets or 2 mg/5 mL syrup. An initial dose of 12 mg is recommended as an antidote, which should be followed by 2 mg every two hours until a clinical response is seen (13).

However, definitive evidence of effectiveness of an early use of cyproheptadine is lacking. A small study used PET scan to assess 5-HT₂ blockade in two volunteers who took 12 and 18 mg of cyproheptadine, respectively, for six days on a daily basis. At 12 mg/day, there was 85% blockade and at 18 mg/day there was over 95% blockade of 5-HT₂ receptors in the prefrontal cortex (14).

Koichi Nisijima et al. demonstrated that rats pretreated with potent serotonin antagonist are completely prevented from the development of serotonin syndrome in an experimental model. In this experiment, rats were induced to develop serotonin syndrome with a high dose of MAOI and 5-hydroxy-L-tryptophan. Rats pretreated with potent 5-HT_{2A} antagonists or high dose cyproheptadine did not develop serotonin syndrome. They neither showed signs of mortality nor developed hyperthermia, even though they were given high doses of MAOI and 5-hydroxy-L-tryptophan (15).

A human case series reported a rapid reversal of mydriasis within one hour for patients with moderate serotonin syndrome secondary to psychiatric medications (16). In another case report, hyperthermia induced by MDMA failed to be reversed with the administration of cyproheptadine, whose usefulness was in doubt. However, the cyproheptadine was given with an inadequate dose, 4 days after the admission. The dosage and delayed administration might have contributed to the poor responsiveness (17).

All our cases showed clinical signs and symptoms that are compatible with life-threatening serotonin syndrome. They showed comparable vital signs on arrival, time to achieve cooling, blood parameters, and ways of resuscitation. The length of stay in ICU and hospital seems to correlate with the time to start cyproheptadine treatment. Thus, we postulate that an early use of cyproheptadine might be beneficial for patients with MDMA-related life-threatening serotonin syndrome. Our case series supports the early use of cyproheptadine in MDMA-induced serotonin syndrome related to MDMA toxicity.

CONCLUSION

In conclusion, we presented a case series of 3 patients with recreational abuse of MDMA in an electronic dance party, who developed life-threatening serotonin syndrome. It is the first case series in Hong Kong. In this case series, it seems that an early administration of cyproheptadine in patients presented with life-threatening serotonin syndrome may reduce the severity of the serotonin syndrome, which in turn can improve the outcomes. Thus, besides aggressive supportive management with active cooling, intravenous fluid, intubation and muscle paralysis, and benzodiazepine and ICU care, an early administration of cyproheptadine may have certain beneficial effects in terms of hastening the severity serotonin syndrome and shortening the length of ICU and hospital stay. Furthermore, it should also be considered as part of the treatment modality in patients with life-threatening serotonin syndrome.

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