CASE REPORT

N-Methyl-3,4-methylendioxymethamphetamine (MDMA)-related coagulopathy and rhabdomyolysis: A case series and literature review

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Abstract
Coagulation changes, thrombosis, and hemorrhage have been described in patients following N-methyl-3,4-methylenedioxymethylamphetamine (MDMA) intoxication who subsequently developed serotonin syndrome and rhabdomyolysis. The clinical features and mechanism of this remain poorly described. We describe 5 sequential cases admitted to critical care due to severe recreational MDMA toxicity where coagulopathy occurred, and discuss key clinical issues. All patients presented with hyperpyrexia then developed subsequent rhabdomyolysis accompanied by a coagulopathy within 24 hours of presentation. This included a severe thrombocytopenia, prolonged coagulation times, grossly elevated D-dimer levels, and hypofibrinogenemia. Multiorgan dysfunction was seen in all patients, including stroke in one patient and major hemorrhage in another. In 2 cases, low-dose low-molecular-weight heparin was used early after presentation, with no significant bleeding complications. Blood products usage was high but variable between the patients with lower use in those who received low-molecular-weight heparin early. Other treatments included intravascular therapeutic cooling, renal replacement therapy with large filter pores and cyprohepatidine. Current evidence suggests that in this group, rhabdomyolysis with subsequent myosin release may be a profound activator of coagulation leading to disseminated intravascular coagulation. Myosin-activated coagulation seems a potential cause of MDMA-related coagulopathy in the setting of rhabdomyolysis and serotonin syndrome. Further studies are needed to validate this and explore the use of low-molecular-weight heparin to reduce the clinical effects of this coagulopathy.

KEYWORDS
3,4-methylenedioxymethylamphetamine, coagulopathy, critical care, rhabdomyolysis, serotonin syndrome
Essentials

- Bleeding and thrombosis are complications of N-methyl-3,4-methylenedioxymethylamphetamine (MDMA) use.
- We describe 5 cases of coagulopathy after MDMA use and rhabdomyolysis.
- Evidence suggests that myosin released from muscle damage may activate coagulation.
- Myosin may trigger disseminated intravascular coagulation in MDMA-induced rhabdomyolysis following serotonin syndrome.

1 | INTRODUCTION

3,4-methylenedioxymethylamphetamine (MDMA; “ecstasy”) has psychoactive properties causing euphoria and hyperenergetic sensations. It exerts its effects by inducing the cerebral release of dopamine, serotonin, and noradrenaline. Its use has been associated with the development of the serotonin syndrome, although the incidence is unclear.

Serotonin syndrome describes a clinically altered mental state and neuromuscular and autonomic hyperactivity as a result of serotonergic drugs. This can lead to malignant hyperthermia and muscle clonus. Additional factors contributing to hyperthermia include exertional heat stroke, environmental temperatures, concurrent drug and alcohol misuse, and dehydration. Serotonin syndrome can be associated with the development of multiorgan failure and rhabdomyolysis due to coagulopathy, which has been cited as disseminated intravascular coagulation (DIC). MDMA-related DIC is reported in a minority of users and is associated with hemorrhage and thrombosis.1-8

We describe 5 sequential cases admitted to critical care due to severe recreational MDMA toxicity where coagulopathy occurred, and discuss key clinical questions on potential mechanisms and management.

2 | CASE REPORTS

2.1 | Case 1

A 33-year old man presented following a collapse at a party after taking MDMA. His Glasgow Coma Scale (GCS) score was 3 on arrival at the emergency department, and he was intubated. His lactate level was 10 mmol/L at this time. He was pyrexial (40°C) and received therapeutic intravascular cooling (CoolGard system, Alsius Corporation, Irvine, CA, USA) in intensive care. Computed tomography (CT) of his brain showed cerebral edema, and subsequent imaging showed a cerebellar infarct after 6 days. On admission, he had a coagulopathy, with activated partial thromboplastin time ratio (APTTTr) 2.0, prothrombin time ratio (PTr) 1.4, fibrinogen 1.8 g/L, and platelets 264 × 10^9/L with no red cell fragmentation on peripheral blood smear.

Twenty-four hours later he developed compartment syndrome of all limbs with a creatine kinase (CK) of 554 490 IU/L (normal levels, <229 IU/L), severe thrombocytopenia (34 × 10^9/L [normal levels, 150-400 × 10^9/L]) and hypofibrinogenemia (0.6 g/L [normal levels, 2-4 g/L]). He underwent emergency bilateral evacuation and fasciotomies of all limb compartments with subsequent surgical debridement. During the admission, he required 80 units of packed red blood cells (PRBCs), 26 pools of fresh frozen plasma (FFP), 18 pools of cryoprecipitate, and 12 units of platelets principally around the time of surgery. He also required renal replacement therapy (RRT) due to acute kidney injury (AKI) with an EMIC2 filter to remove middle-sized proteins.

After 13 days, the patient had a cardiac arrest with successful cardiopulmonary resuscitation, with an underlying Mobitz type 2 heart block secondary to cardiac ischemia. A pacemaker was inserted. The patient required a tracheostomy for 3 months and had further physiotherapy at a rehabilitation center. His neurological impact was profound, requiring long-term physical and social support.

2.2 | Case 2

A 25-year old man presented with an altered mental state, pyrexia (39.8°C), and GCS of 3. He was found to have taken MDMA and ketamine by urinary testing. He was intubated in intensive care and given therapeutic intravascular cooling and cyproheptadine. He was commenced on RRT due to AKI, with CK of 256 390 IU/L. Within 24 hours of admission, his APTTr was 2.6, PTr 1.8, fibrinogen 1.5 g/L, and platelet counts were 6 × 10^9/L. There was an associated acute liver injury, and CT of his lower limbs showed generalized edema but no bleeding. He required 14 units of PRBCs, 10 pools of FFP, 12 pools of cryoprecipitate, and 9 units of platelets during his admission of 19 days in intensive care.

He had a slow ventilator wean, with electroencephalography (EEG) showing global encephalopathy. Following extubation, he had several seizures. Magnetic resonance imaging showed posterior reversible encephalopathy syndrome (PRES). He was commenced on antiepileptics, with imaging after 3 months showing complete resolution.

2.3 | Case 3

A 16-year old girl had an out-of-hospital cardiac arrest after taking MDMA at a party. After successful cardiopulmonary resuscitation, she was admitted to intensive care requiring inotropic support and RRT. She had a concurrent acute liver injury. Cerebral CT showed global cerebral edema. The patient showed features
of coagulopathy within 24 hours: APTTr 5.3, PTr 2.9, fibrinogen 0.4 g/L, and platelet counts were 39 × 10⁹/L. The peak CK level was 197 800 IU/L 24 hours after admission. There were no clinical features of bleeding.

The patient had a prolonged ventilator wean and subsequently developed dystonia and required percutaneous endoscopic gastrostomy feeding. She had significant motor disability following this episode and received further long-term rehabilitation after 61 days in intensive care.

### 2.4 | Case 4

A 19-year old woman presented with altered mental state and pyrexia (42°C) after taking MDMA. She was intubated and received therapeutic intravascular cooling and cyproheptadine. She received RRT for AKI and hyperkalemia and developed acute liver injury. A brain CT showed no significant changes, and abdominal CT showed ileus and periporal edema around the liver. She developed a coagulopathy within 24 hours of admission, with APTTr 1.6, PTr 1.7, fibrinogen 0.6 g/L, and platelet count 42 × 10⁹/L, and was immediately given dalteparin 5000 IU subcutaneously and cryoprecipitate (to correct hypofibrinogenemia). The peak CK level was 19 622 IU/L. There were no clinical features of bleeding or thrombosis. The patient was admitted to intensive care for 3 days and recovered with no long-term disability or organ damage.

### 2.5 | Case 5

A 19-year old man presented with a decreasing conscious state and hyperpyrexia (42°C) after taking MDMA at a party. His GCS was 6, so he was intubated, received therapeutic cooling, and given cyproheptadine. Cerebral CT was normal. Dalteparin 5000 IU was started on admission. He developed a coagulopathy on his second day, with APTTr 1.5, PTr 1.3, fibrinogen 1.5 g/L, and platelet count 58 × 10⁹/L. The peak CK level was 28 108 IU/L, and he required RRT for 4 days. There were no features of bleeding or thrombosis. The patient recovered after 6 days in intensive care and no long-term sequelae.

### 2.6 | Summary of cases

The clinical features, coagulation parameters, and CK levels of these patients are described in Tables 1 and 2. There were varying clinical outcomes following the development of rhabdomyolysis and coagulopathy after MDMA use. The most significantly abnormal coagulation parameters were recorded within the first 36 hours for all patients, with deterioration after admission. All patients developed multiorgan failure presumed to be contributed to by a thrombotic microangiopathy with renal, cardiac, and liver dysfunction shown serologically, and acute neurological involvement was shown by CT and/or EEG in 3 patients – 2 with ischemic events and 1 with PRES and seizures. There were no episodes of venous thromboembolism during follow-up. One patient developed acute hemorrhage into muscle compartments where rhabdomyolysis had occurred. Three patients had long-term complications from MDMA use, although there were no deaths despite 2 having cardiac arrests.

There was significant blood product use in 3 patients due to active bleeding, with 1 requiring surgical intervention. The median use of PRBCs, platelets, FFP, and cryoprecipitate were 15 units, 7 units, 12 pools, and 8 pools, respectively, for all patients. Two patients without significant blood product transfusion

### TABLE 1  Clinical features of patients with MDMA intoxication

| Patient | Age (y) | Sex | Hyperpyrexia | Organ injury | Thrombotic complications | Bleeding |
|---------|---------|-----|--------------|-------------|--------------------------|---------|
| 1       | 33      | Male| Yes          | Cerebral Renal Cardiac Muscle | Cerebellar infarct Myocardial infarction with heart block | Muscle hemorrhage with compartment syndrome |
| 2       | 29      | Male| Yes          | Cerebral Lung Cardiac Muscle Renal | No | No |
| 3       | 16      | Female| Yes          | Cerebral Cardiac Liver Renal | Stroke | No |
| 4       | 19      | Female| Yes          | Cerebral Renal Liver Cardiac | No | No |
| 5       | 19      | Male| Yes          | Cerebral Renal Liver | No | No |

Abbreviation: MDMA, N-methyl-3,4-methylenedioxymethylamphetamine.
Table 2: Laboratory results of patients with MDMA intoxication

| Patient | Admission and peak APTT (0.8-1.2) | Admission and peak PT (0.8-1.2) | Admission and trough fibrinogen (1.7-3.9 g/L) | Admission and trough platelets (150-400 x 10^9/L) | D-dimer (<0.55 mg/L) | Peak creatine kinase (<229 U/L) |
|---------|----------------------------------|--------------------------------|-----------------------------------------------|-------------------------------------------------|----------------------|-------------------------------|
| 1       | 2.0, 2.1 (day 1)                 | 1.8, 1.8 (day 1)               | 1.8, 0.6 (day 1)                               | 264, 34 (day 1)                                  | 34.7                 | 554 490 (day 4)               |
| 2       | 1.3, 2.6 (day 1)                 | 1.2, 1.8 (day 1)               | 1.8, 0.6 (day 1)                               | 310, 6 (day 1)                                   | 256 390 (day 3)      |                               |
| 3       | 0.8, 1.6 (day 1)                 | 1.0, 1.7 (day 2)               | 2.1, 0.6 (day 2)                               | 355, 42 (day 3)                                  | 16.9                 | 19 622 (day 4)                |
| 4       | 1.3, 5.3 (day 1)                 | 1.3, 2.9 (day 1)               | 1.3, 0.4 (day 1)                               | 246, 39 (day 1)                                  | 198 700 (day 2)      |                               |
| 5       | 0.9, 1.5 (day 2)                 | 1.1, 1.6 (day 2)               | 2.1, 1.5 (day 2)                               | 37, 58 (day 3)                                   | 3.8                  | 28 108 (day 2)                |

Abbreviations: APTTr, activated partial thromboplastin time ratio; MDMA, N-methyl-3,4-methylenedioxymethylamphetamine; PTr, prothrombin time ratio.

received prophylactic low-molecular-weight heparin early in admission. Three patients were given cyproheptadine at the time of admission.

3 | DISCUSSION

We describe 5 patients who developed a profound coagulopathy and rhabdomyolysis within the 36 hours of taking MDMA. This was associated with multiorgan failure in all and thrombosis and/or hemorrhage in 3 patients. The development of concurrent coagulopathy and rhabdomyolysis following MDMA use has been described previously with the presence of DIC on postmortem studies (see Table S1).13

Rhabdomyolysis is a key feature in these cases. It is purported to occur due to sustained skeletal muscle activity from catecholamine release and hyperthermic injury as part of the serotonin syndrome with MDMA use. There has not been a clear, elucidated mechanism for this coagulopathy; although likely multifactorial, rhabdomyolysis and the intracellular contents of injured muscle could be key initiators in this process. The temporal nature of the DIC and rise in CK, and the absence of other causes of coagulopathy, are suggestive of this. We noted that hyperpyrexia was present on admission, following an early elevation of CK and coagulopathy, with the peak of CK in the subsequent days.

Muscle injury and inflammation have been associated with DIC and thrombosis in many other conditions and illnesses. These include heatstroke, trauma, inflammatory myositis, and statin-induced myopathy. The involvement of DIC in muscle-related conditions suggests muscle inflammation, and injury may therefore contribute to a coagulopathy. Inflammatory myopathies, such as polymyositis and dermatomyositis, are associated with muscle damage, particularly in periods of disease presentation and exacerbation. The risk of venous thromboembolism is significantly increased in these conditions, and its risk is highest around the time of diagnosis.9-10 DIC and rhabdomyolysis have been described in heatstroke and evidence of elevated CK levels shown in a murine model of exertional heart stroke suggestive of rhabdomyolysis.11-13

Following the demonstration of an association between rhabdomyolysis and muscle inflammation to coagulopathy and thrombosis, the question is then raised regarding the mechanism for this. Muscle tissue contains various intracellular proteins, in particular actin and myosin filaments. Deguchi et al14 performed exome genotyping in patients who had venous thromboembolism, showing an association with polymorphisms in the myosin gene cluster. Significantly elevated levels of serum myosin have been demonstrated in polymyositis and dermatomyositis for several days following rhabdomyolysis and after trauma.15-17 At present, elevated myosin levels have not yet been described in relation to MDMA use.

Deguchi et al17 evaluated the role of myosin in thrombosis in more detail. They showed that the presence of myosin increased thrombin generation in plasma independent of the presence of platelets. Factor Xa binds to the myosin heavy chain at the neck region, forming a stable tertiary complex in addition to factor V.18 Comparing thrombin generation in controls and trauma patients with the addition of antmyosin antibodies to both groups, thrombin generation was significantly reduced in trauma patients with higher baseline levels of myosin.17 This suggests that in trauma, and potentially in other conditions with muscle damage, there may another mechanism activating coagulation in addition to or alternatively to tissue factor.

In combination with an activation of hemostasis, there is evidence that hyperpyrexia alone can cause activation of the vascular endothelium. This has been suggested by increased circulating levels of von Willebrand factor, endothelin, and intercellular adhesion molecule 1 (ICAM-1).19 This would likely further increase the prothrombotic nature of patients with MDMA-related serotonin syndrome.

Treatment considerations in this setting can be considered as (i) reducing the development of hyperpyrexia and subsequent rhabdomyolysis, (ii) removing potential causative toxic proteins, or (iii) inhibiting coagulation. The first can be achieved by using active cooling methods to achieve therapeutic normothermia. This has been shown to reduce von Willebrand factor and ICAM-1 levels in hyperthermia.18 The administration of cyproheptadine, an antiserotonergic drug, antagonizes the effect of MDMA. It is important to avoid other serotonergic substances in critical care, such as fentanyl, which can exacerbate hyperthermia. The second can be achieved by enhancing middle molecule clearance using a large-pore membrane in continuous hemodiafiltration (up to 40 kDa). This filters molecules such as myoglobin and interleukins 1, 6, and
10 that can cause additional organ damage. The molecular mass of the myosin heavy chain is 220 kDa and would not be removed by filtration. The last consideration can be achieved by giving a low dose of anticoagulation early, before bleeding develops, to halt the progression of the consumptive coagulopathy. If this develops, major bleeding can become an issue such as demonstrated in 3 cases requiring significant blood product use to correct.

In summary, rhabdomyolysis in the setting of MDMA use is temporally related to coagulopathy with features of both thrombotic microangiopathy and hemorrhage with similarities to DIC. Muscle injury of varying etiologies is associated with a prothrombotic tendency, and myosin has been suggested as potential novel trigger for this. Therefore, myosin may be a contributing factor to coagulation activation of MDMA-related rhabdomyolysis and a potential target for early intervention.

4 | CONCLUSIONS

We suggest that patients presenting with features of serotonin syndrome from MDMA should have early and frequent monitoring for the development of rhabdomyolysis and DIC. Early use of a low dosage of an anticoagulant, such as heparin, and other supportive methods to reduce the development of hyperpyrexia and removal of potentially toxic molecules merit consideration. Further understanding of coagulation activation will help to prevent and treat this significant complication of MDMA use.

RELATIONSHIP DISCLOSURE
The authors declare nothing to report.

AUTHOR CONTRIBUTIONS
AD collected patient information, performed the relevant literature search, and wrote the article. BH, JM, and KB reviewed the article for submission and provided additional points for discussion.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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