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CLINICAL REVIEW

Methamphetamine and MDMA: 'Safe' drugs of abuse

Méthamphétamine et MDMA: Abus de drogues "récréatives"

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Methamphetamine and MDMA have been called safe drugs of abuse. Worldwide there is an increased consumption of these drugs, which has become a focus of research in South Africa. As the number of methamphetamine users has increased in many African countries, it is essential that emergency care practitioners are able to diagnose and manage intoxication with methamphetamine, MDMA, and other derivatives. The most common presentations include restlessness, agitation, hypertension, tachycardia, and headache while hyperthermia, hyponatraemia, and rhabdomyolysis are among the most common serious complications. Most deaths are secondary to hyperthermia complicated by multiple organ failure. A number of laboratory analyses should be obtained if locally available. We provide a review of the current recommended general and specific management approaches. Benzodiazepines are the first line therapy for hyperthermia, agitation, critical hypertension, and seizures. Patients with serious complications are best managed in an intensive care unit if available. Emergency centres should create protocols and/or further train staff in the recognition and management of intoxication with these 'not so safe' drugs.

La méthamphétamine et le MDMA ont été qualifiées de drogues « récréatives ». Partout dans le monde, la consommation de ces drogues est en augmentation, ce qui a attiré l'attention des chercheurs en Afrique du Sud. Du fait que le nombre d'usagers de méthamphétamine a augmenté dans plusieurs pays d'Afrique, il est primordial que les médecins des services d'urgence soient capables de diagnostiquer et de prendre en charge une intoxication à la métamphétamine, au MDMA et autres dérivés. Les symptômes les plus fréquents sont la nervosité, l'agitation, l'hypertension, la tachycardie et les maux de tête, l'hyperthermie, l'hyponatrémie et la rhabdomyolise étant les complications sérieuses les plus fréquentes. La plupart des décès font suite à une hyperthermie qui se complique par une défaillance multiviscérale. Il conviendra de procéder à des analyses de laboratoire, si elles sont localement disponibles. Nous fournissons un compte-rendu des modes de prise en charge généraux et spécifiques actuellement préconisés. Les benzodiazépines constituent le traitement de première intention pour l'hyperthermie, l'agitation, l'hypertension sévère et les crises. Les patients présentant des sérieuses complications devraient être pris en charge dans une unité de soins intensifs, le cas échéant. Les services d'urgence devraient développer des protocoles et/ou former leur personnel à la reconnaissance et la prise en charge de l'intoxication par ces drogues qui ne sont pas aussi « récréatives » qu'elles le paraissent.

African relevance

- The prevalence of methamphetamine use is increasing in Africa.
- Patients with methamphetamine or MDMA intoxication often present to an emergency centre and thus emergency health practitioners should be comfortable with appropriate management.
- The use of methamphetamine often leads to increased sexual risk taking behaviour, which could fuel the spread of HIV infection. This is of particular concern in areas with high HIV prevalence.

Introduction

Methamphetamine, popularly known as 'tik' in South Africa and 'speed' or 'crystal meth' in the United States, is a sympathomimetic amine that has stimulant, anorexiant, euphoric, and hallucinogenic effects. It was first synthesized in 1893 and is clinically used for the treatment of attention deficit disorder with hyperactivity, short-term treatment of obesity, and as an off-label treatment for narcolepsy. It is the most widely abused drug worldwide after cannabis and can be synthesized using readily available chemicals and adrenaline or pseudoadrenaline.[1]

MDMA (3,4-methylenedioxymethamphetamine), popularly known as 'ecstasy' in the United States, is a synthetic compound with pharmacologic similarities to amphetamines. It was first introduced by Merck in 1914 as an appetite suppressant for animals and later used in psychotherapy.[2] Since the late 1970s, it is primarily used as a recreational street drug to produce euphoric effects, in particular at urban dance parties.

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Despite the high prevalence of the usage of methamphetamine and its derivative MDMA, relatively few people experience serious adverse events.[3,4] Emergency practitioners must be able to both recognize that these drugs have a significant risk of physical harm and psychological disturbances and to assess and manage intoxication.[5–8]

Epidemiology

The use of amphetamines has reached epidemic proportions around the world.[9] In Africa, methamphetamine has become a major drug of abuse.[10] The United Nations estimates that 280,000–780,000 South Africans used amphetamines in 2011.[1] The South African Medical Research Council estimates that 7% of the population in Cape Town is using methamphetamine.[11] There has been an increase in both drug treatment and psychiatric admissions related to the use of methamphetamine in South Africa, especially in adolescent populations.[12,13]

Lifetime use of MDMA in Canada for those older than 15 years was 3% and 5.2% for women and men, respectively, and in the United States was reported at 5.8% in grade 9–12 students.[14,15] Australian surveys report up to 20% of those aged 20–29 years have used MDMA.[16] The United Nations estimates that 190,000–300,000 South Africans used MDMA in 2011. Estimates are not available for other parts of Africa.[1]

Pharmacology

Methamphetamine acts as an indirect neurotransmitter by displacing adrenaline, noradrenaline, dopamine, and serotonin into the cytosol, which then diffuse into the synapse activating postsynaptic receptors. Reuptake systems are also disturbed. The release of adrenaline and noradrenaline activates alpha and beta receptors causing hypertension, tachycardia, hyperthermia, and vasospasm. Serotonin release leads to mood changes and alterations in hunger and thirst responses. The observed drug-craving and drug-seeking behaviour and psychiatric symptoms can be attributed to the excessive dopamine receptor stimulation. The half-life is 12–34 h but the duration of effect may persist beyond 24 h.[17]

MDMA differs from traditional amphetamines in that it is structurally similar to serotonin and therefore carries a higher risk of serotonin syndrome. It is typically ingested in a tablet form and dosages in the illicit forms vary widely.

Clinical evaluation

Patient presentations are varied due to the wide range of physical, psychological, and physiological effects of amphetamines. Methamphetamine or MDMA intoxication should be considered in any patient with diaphoresis, severe agitation, psychosis, tachycardia, and hypertension. As in all emergent situations, airway, breathing, and circulation should be considered initial priorities prior to obtaining a clinical history.

Medical history

If the patient can provide a history, the emergency centre health professional should determine the route of exposure and frequency of use. The patient should be asked about the amphetamine identity, quantity consumed, and time of exposure. The location of exposure is also important as those in crowded clubs are at increased risk of metabolic disturbances and hyperthermia.[18] Patients who complain of chest pain, palpitations, headache, visual disturbance, or other focal neurological symptoms will require immediate assessment. A history of co-ingestants should be obtained as other stimulant drugs, monoamine oxidase inhibitors, and tricyclic antidepressants are synergistic. Certain prescribed medications, such as ritonavir, reduce hepatic metabolism of amphetamines and thus prolong their toxicity.[19] Personal medical history is important as those with underlying cardiorespiratory disease or seizure disorders will likely be less tolerant of amphetamine toxicity.

Physical examination

After initial assessment of airway, breathing, and circulation, patients should be assessed for signs of life-threatening disturbances. Clinical signs indicating significant amphetamine toxicity include seizure, focal neurological deficits, reduced level of consciousness, abnormal motor movements, hyperthermia, dysrhythmias, hypotension, hypertension, acute coronary syndrome, and autonomic instability.[20] Prognostic factors for mortality include shock, coma, temperature $> 39\ ^{\circ}C$, acute renal failure, metabolic acidosis, and hyperkalaemia ($K > 5.6$).[21] Virtually all intoxicated patients will have tachycardia and hypertension.

The most common manifestations in patients with MDMA intoxication include restlessness, agitation, confusion, hypertension, and headache. The other common manifestations of MDMA intoxication are similar to those seen in methamphetamine intoxication (see Table 1). The most common serious complications are hyperthermia, Hyponatraemia, and rhabdomyolysis (see Table 2).[22] Acute coronary syndrome is a potential complication and presentation may be delayed.[23,24] Hyponatraemia may be due to drug-mediated anti-diuretic hormone release or marked increase in fluid intake, the latter of which is seen in some MDMA users due to the belief that drinking large amounts of water will avoid hyperthermia.[25,26] Patients using MDMA are at increased risk of serotonin syndrome, which presents as the triad of autonomic dysfunction, abnormal neuromuscular activity, and altered mental status.

Deaths due to methamphetamine or MDMA intoxication occur in young, healthy people and are likely underreported.[27,28] Most deaths are secondary to hyperthermia complicated by multi-organ failure (severe dehydration, renal failure, liver failure, and/or disseminated intravascular coagulation).[29,30]

Differential diagnosis

There are both toxicologic and non-toxicologic conditions that mimic methamphetamine and MDMA intoxication (see Table 3). In order to distinguish from methamphetamine intoxication, particular attention should be paid to duration of action and clinical signs specific to intoxication with other substances.[31]

Laboratory evaluation

When available, routine testing should include fingerstick glucose, paracetamol and salicylate levels, electrocardiogram, and pregnancy test in women of childbearing age. A urine drug screen is of limited value as not all sympathomimetic drugs are identified and the test will be positive for days after use. Serum and urine assays for MDMA are not useful. When significant toxicity is suspected, serum laboratory tests are recommended. Additional studies may be indicated based on the clinical presentation (See Table 4).[20]

Table 1 Common manifestations of MDMA intoxication.

Aggression	Agitation	Anger
Anxiety	Confusion	Dehydration
Depression	Diaphoresis	Dilated pupils
Disorientation	Dulling of senses	Fainting
Hallucinations	Headache	Hypertension
Lack of judgment	Loss of consciousness	Mood changes
Nausea	Paranoia	Psychosis
Restlessness	Sleep disturbance	Speech disturbance
Tachycardia	Teeth grinding	Tremulousness

Table 2 Serious complications with methamphetamine or MDMA intoxication.

Cardiac arrhythmia	Cerebral oedema	Coma
Death	DIC	Hyperthermia
Hyponatraemia	Intracranial haemorrhage	Liver failure
Metabolic acidosis	Myoglobinuric renal failure	Pneumonia
Respiratory arrest	Rhabdomyolysis	Seizure
Serotonin syndrome[a]	Stroke	Trauma

[a] More common in MDMA intoxication.

Management

Aggressive supportive care is essential. Close attention to and correction of hypotension, hyperthermia, hypoxia, and acid–base and metabolic abnormalities will significantly reduce morbidity and mortality. As such, vital signs need to be obtained in a timely fashion and patients should be kept on continuous cardiovascular monitoring if available.

General management of any intoxication includes attention to decontamination and elimination. In the case of amphetamines, activated charcoal for decontamination plays a very limited role. It can potentially decrease absorption if administered within one hour of ingestion but the majority of patients present outside this timeframe.[32] As amphetamines are weak bases, urine acidification could potentially enhance amphetamine elimination. Despite this, it is contraindicated as urine acidification can potentiate adverse effects of rhabdomyolysis and worsen metabolic acidosis.[33]

Emergent consultations with a medical toxicologist are recommended if considering gastrointestinal decontamination in the case of recent large ingestion. Such consultations are available by telephone in certain locations worldwide. The World Health Organization lists all international poison centres. As of February 2012, African poison control centres exist in Algeria, Ghana, Kenya, Morocco, Senegal, South Africa, Tunisia, and Zimbabwe (see Appendix B).[34]

Hyperthermia has been associated with amphetamine related deaths and thus it should be treated promptly. Aggressive cooling with core body temperature monitoring should be initiated for hyperthermia since it is the most important determinant of mortality. Hyperthermia specifically due to MDMA intoxication will often be associated with other clinical signs of serotonin syndrome.[35,36] External cooling methods can be used to lower body temperature and intravenous crystalloids should be administered for dehydration. Administering benzodiazepines will control agitation and decrease muscle activity that leads to hyperthermia. Lorazepam dosed at 1–4 mg or diazepam 5–10 mg may be used and repeated every 8–10 min. If there is no IV access, midazolam 5–10 mg can be injected intramuscularly and this can be repeated every 10 min. If paralysis and tracheal intubation are necessary, succinylcholine should not be used for rapid sequence intubation due to the risk of rhabdomyolysis.

The use of dantrolene in the setting of MDMA induced hyperthermia has been controversial. A systematic review from 2010 of cases dating back to 2008 found the proportion of survivors to be higher in the dantrolene treated patients, especially in cases of extreme ($>42\ ^{\circ}C$) and severe ($>40\ ^{\circ}C$) fever. No adverse events were reported with the use of dantrolene except for a potential association with transient hypoglycaemia.[37] Despite this, it is unclear if the decreased mortality is due to dantrolene alone or a combination of interventions.[38] In instances of amphetamine-related refractory hyperthermia, serotonin toxicity should be considered. Cyproheptadine is a 5HT2a antagonist and has been used successfully in case reports.[39,40] One animal study explored the use of carvedilol in treating MDMA-induced hyperpyrexia.[41] A recent human study in healthy subjects suggests a potential role for carvedilol in reducing hyperthermia, hypertension and tachycardia caused by MDMA toxicity.[42] These are currently not standard treatments.

Agitation should be treated aggressively with patients cared for in a quiet environment. Physical restraints should not be used unless chemical restraint is not available as the muscle contractions associated with resisting restraints have been associated with lactic acidosis, hyperthermia, sudden cardiac collapse, and death. Benzodiazepines are considered first line pharmacologic management of agitation. The use of antipsychotics such as haloperidol or droperidol is controversial as they can interfere with heat dissipation, prolong QT interval, and reduce the seizure threshold.[43]

Seizures can be amphetamine-induced, secondary to hyponatraemia, or related to intracerebral pathology such as haemorrhage, ischaemia, or infarction. Most are amphetamine-induced and should be treated with benzodiazepines with the use of phenobarbitone as a second-line agent. If unresponsive to these interventions, general anaesthetic sedation using thiopentone, propofol, or midazolam can be used. Any patient with suspected intracranial pathology should have head imaging if available.[20]

Critical hypertension is managed with benzodiazepines. If additional blood pressure agents are needed, then nitroglycerin, nitroprusside, and phentolamine may be used. Pure beta-blocking agents should be avoided due to the risk of unopposed alpha-receptor stimulation and subsequent

Table 3 Differential diagnosis.

Toxicologic	Nontoxicologic
Cocaine	Heat stroke
Phencyclidine (PCP)	Thyrotoxicosis
Theophylline/caffeine	Pheochromocytoma
Aspirin	Sepsis/meningitis/encephalitis
Monoamine oxidase inhibitors	Hypoglycaemia/hyperglycaemia
Serotonin syndrome	Intracerebral haemorrhage
Anticholinergic poisoning	

Table 4 Laboratory testing and other studies.

Fingerstick glucose	If reduced consciousness
Electrolytes, renal function	Exclude Hyponatraemia and hyperkalaemia
Creatinine kinase	Look for rhabdomyolysis
Coagulation screen	Exclude disseminated intravascular coagulation
Liver function tests	Look for hepatitis
Arterial blood gas analysis	To detect metabolic disturbances
Serial cardiac enzymes	Assess possible acute coronary syndrome (ACS)
Electrocardiogram	Assess for ACS/dysrhythmias
Chest radiograph	To rule out aortic dissection or pneumothorax
Abdominal radiograph	If suspicion of ingested packets of amphetamine
CT brain	If concern for stroke, cerebral oedema, trauma
Echocardiography	If concern for cardiomyopathy

Adapted from Greene et al.[20]

uncontrolled hypertension. The use of labetalol is controversial.[44,45] One study of cocaine users showed that it attenuated cocaine-induced increases in heart rate and blood pressure.[46]

Hyponatraemia can be a significant serious complication of amphetamine intoxication and should be excluded early, especially in patients with altered mental status or seizures. In one study, 38.8% of patients with MDMA ingestion presented with hyponatremia.[47] Mild to moderate hyponatraemia in a non-dehydrated patient can be treated with fluid restriction. Normal saline should be used if intravenous fluids are required. Severe hyponatraemia with seizures is treated cautiously with benzodiazepines and hypertonic saline with a goal of cessation of seizures. X mL/kg of 3% saline will raise the sodium by X mmol/L.[20] Mannitol has been used for symptomatic hyponatraemia secondary to MDMA ingestion but data are currently restricted to case reports.[48,49] The use of mannitol is not a currently standard treatment.

Rhabdomyolysis may result from increased muscle motor activity and can lead to severe hyperkalemia.[50] Fluid resuscitation should aim for a urine output goal of 1–2 cc/kg/hr to prevent myoglobinuric renal failure. Patients with concomitant myocardial dysfunction with a risk of pulmonary oedema or symptomatic hyponatraemia will need close fluid management monitoring due to competing goals.[51] Urinary alkalinization is not recommended as it inhibits amphetamine elimination. The use of bicarbonate to alkalinize the urine and the use of mannitol have not proven to improve end-point measures of morbidity, mortality, or the need for dialysis.[52]

Most patients can be safely discharged after a period of observation – up to 6 h or once asymptomatic. Some patients may require admission for vital signs monitoring, intravenous fluids, and administration of benzodiazepines. Those with serious complications may need to be managed in the intensive care unit for a prolonged period.[22] All patients should be educated about the dangers of amphetamine use.

Conclusion

Although the popular image of methamphetamine and MDMA is that of 'safe' drugs, clinical practice and data show otherwise. Knowledge of the clinical manifestations and immediate management of methamphetamine and MDMA intoxication is essential for emergency medicine practitioners worldwide, especially in Africa where use of these drugs has boomed in the past decade. Most intoxications do not require long-term admission, but acute and chronic use of these drugs presents the risk of serious complications including death. When patients present to emergency centres with symptoms of agitation and vital sign alterations, methamphetamine or MDMA use must be in the differential diagnosis. Amphetamine use is of particular concern as more adolescents are now using these drugs. Furthermore, some researchers are concerned that the use of methamphetamine leading to increased sexual risk-taking behaviour could fuel the spread of HIV infection.[10,11,53,54] Emergency centres in Africa should update or create protocols regarding the immediate assessment and management of amphetamine intoxication in order to provide efficient, standardized care that reduces associated morbidity and mortality.

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