Toxicology Times

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Toxicology Times is written by a Certified Specialist in Poison Information (CSPI) at the Ontario Poison Centre for practicing Critical Care and Emergency Nurses in Ontario. Medical content is approved by the Medical Director.

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Street Drugs: "Uppers"

Background:

Stimulant drugs have been used by humans for centuries. These include substances that cause a "sympathomimetic toxidrome," characterized by symptoms such as increased heart rate, blood pressure, and alertness. For this edition of Tox Times, we will focus on illicit stimulants like cocaine, amphetamines, and MDMA, while recognizing that drugs such as caffeine and nicotine also have stimulant effects but fall outside the realm of "street drugs." Prescription stimulants, such as those used to treat ADHD, are another category not covered here but are known for potential misuse.

Stimulant drug use has a long and complex history, often moving from medicinal and spiritual contexts to social and recreational use. Coca leaf (plant source of cocaine) chewing dates back to 8000 BCE among Indigenous populations in South America, and there is evidence of coca remains in mummies from 1500 AD. By 2000 BCE, coca appeared in China, where ephedra was also being used medicinally.

Coca leaves eventually made their way into over-the-counter (OTC) remedies like throat lozenges and toothache drops, and even Coca-Cola prior to 1900. Amphetamines and methamphetamines, synthesized in the late 1880s, had significant use during World War II to combat fatigue. MDMA, synthesized in the early 1900s, emerged in the 1970s and became popular in 1980s rave culture.

By the early 20th century, awareness of the harms associated with these substances led to increased regulation. Cocaine was among the first drugs to be scheduled as illegal and removed from commercial products. With MDMA use increasing in the 1970s and 80s, it was scheduled in the US and eventually Canada. Despite these restrictions, illicit stimulant use remains widespread today.

Case presentation:

An adult male was brought to the Emergency Department (ED) after being found by family with abnormal, agitated behaviour. He was last seen acting normally two hours ago while with friends at an event. The patient's family believed that he had been using illicit drugs prior to being found.

On arrival to the ED the patient was diaphoretic, restless, and agitated. He was speaking quickly with a "flight of thoughts". The patient was tachycardic (HR 135), hypertensive (BP 158/105), with a mildly elevated temperature (37.7°C).

The treating team promptly gave lorazepam (2mg) for his agitated state, and started IV fluids for hydration. Blood work was sent for acetaminophen (APAP), aspirin (ASA), ethanol (ETOH) levels, routine electrolytes, liver and renal panels, venous blood gas, lactate, and creatine kinase (CK). An ECG showed sinus tachycardia with a normal QRS complex and QTc interval.

The poison centre was contacted by the treating team due to the reported use of illicit drugs and the patient's presentation. Recognizing symptoms consistent with a sympathomimetic toxidrome, the poison specialist suspected stimulant exposure. Recommendations included continuous cardiac monitoring, IV hydration, and liberal use of benzodiazepines for agitation, seizures, tachycardia, and hyperthermia. For hyperthermia, they emphasized the importance of aggressive cooling measures and advised that the team call back for further treatment recommendations, including possible intubation and paralysis if necessary. They advised to treat dysrhythmias with ACLS protocols, and to avoid beta blockers.

An hour later, the poison centre was called back as the patient's temperature rose to 40.1°C, with worsening tachycardia (HR 190). The treating team had administered IV lorazepam (8mg) and midazolam (10mg) due to increased agitation, hyperthermia, and tachycardia.

The patient's level of consciousness had significantly decreased, with extremity twitching suggestive of seizure activity. A repeat ECG noted QRS widening (122 msec). The team was administering an IV fluid bolus, using cold packs, and applying a cooling blanket to cool the patient. The ICU team was consulted and they requested additional treatment recommendations from the poison centre.

After consulting the on-call toxicologist, intubation, sedation, paralysis and continued aggressive cooling were recommended due to the patient's hyperthermia and significant clinical changes. Sodium bicarbonate boluses were advised for the wide QRS, with repeat ECGs targeting a QRS duration of <100msec, while maintaining sodium levels below 155mmol/L and pH under 7.55. It was also noted that cocaine is fat soluble and if the patient were in extremis or pre-arrest, lipid emulsion therapy could be considered.

Lab results suggested a metabolic acidosis with elevated lactate and a high CK level. ETOH was detected, but APAP and ASA were negative. Cardiac enzymes were added due to the patient's deteriorating clinical status with evidence of ECG changes, and results were pending.

The patient was intubated, sedated, paralyzed, cooled, and admitted to ICU. He became hypotensive and was started on vasopressors. Multiple bolus doses of sodium bicarbonate were given for a wide QRS (>100msec) and he was started on a bicarbonate infusion due to continued acidosis.

Over the next 24 hours the patient's CK rose above 18,000 U/L. INR increased, platelets decreased, and bleeding was noted at IV sites, as well as around his nose and mouth. His creatinine was increasing, suggesting kidney injury. Despite continued aggressive supportive care and treatment with fresh frozen plasma and blood transfusions, the patient died within 12 hours of admission to the ICU.

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Mechanism and Kinetics:

Stimulants typically act by increasing catecholamine release from presynaptic neurons or by decreasing their reuptake into that same presynaptic neuron: the net result is a substantial increase in the concentration of the affected neurotransmitter in the synapse, leading to continuous downstream effects. Increased norepinephrine causes a sympathetic response: increased heart rate (beta stimulation) and increased blood pressure (alpha stimulation). Dopamine surges lead to feelings of euphoria and contribute to the addictive and psychoactive effects of these drugs. Increased serotonin levels contribute to some of the emotional effects like increased empathy and sociability, as well as hallucinogenic effects.

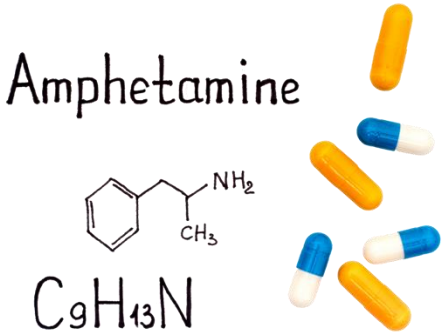
Cocaine blocks the reuptake of dopamine, norepinephrine, serotonin, and epinephrine. It also can block fast inward- sodium channels on cardiac myocytes, increasing the width of the QRS complex and worsening cardiotoxicity. When consumed together, cocaine and alcohol produce a metabolite called cocaethylene which has similar effects to cocaine but has a longer half-life (2hrs vs 1hr for cocaine), potentially exacerbating cardiotoxicity.

Amphetamines are groups of compounds with stimulant effects due to their structural similarity to norepinephrine. They enhance neurotransmitter activity by promoting the release of norepinephrine, dopamine and serotonin, while also inhibiting monoamine oxidase (MAO), the enzyme responsible for breaking down these catecholamines. Some amphetamine compounds are approved for medical use and prescribed to treat attention deficit disorder (ADD) and narcolepsy.

Methamphetamine is a particularly potent stimulant in the amphetamine class that is long-lasting. It has significant abuse potential.

MDMA (also known as “ecstasy”, “molly”, or several other names) primarily increases serotonin, leading to its psychoactive effects, and also increases norepinephrine release which causes its physiological effects.

Other phenethylamine derivatives, including NBOMe compounds and 2C designer drugs, have effects similar to MDMA, acting on serotonin receptors and causing sympathetic stimulation. However, their exact mechanism of action is not well understood.



Symptoms:

Symptoms of stimulant exposure may include:

- Increased heart rate, respiratory rate, and blood pressure
- Mydriasis (dilated pupils), agitation, restlessness, tremors, hallucinations and/or psychosis, seizures
- Dysrhythmias, MI, vasospasms
- Life-threatening hyperthermia
- Rhabdomyolysis
- Hyponatremia (MDMA)
- Serotonin syndrome (more likely if co-ingested with another serotonergic substance)
- Death can occur from dysrhythmias, cardiovascular collapse, hyperthermia, or complications such as DIC

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Management:

Management of stimulant poisoned patients prioritizes addressing the sympathetic overstimulation caused by these drugs. The stimulant poisoned patient can present with life-threatening symptoms (listed above) but can also pose a safety risk to staff because of agitation and aggression. Benzodiazepines are the first-line treatment. They improve the hyper-adrenergic state contributing to tachycardia, hypertension and agitation leading to life-threatening hyperthermia. Large and frequent IV doses may be necessary. In severely poisoned patients, intubation can be required to allow for adequate sedation with benzodiazepines and other second-line agents.

IV fluids are necessary to maintain hydration, as these patients are at risk of developing rhabdomyolysis due to overstimulation and muscle breakdown. Beta blockers are typically avoided as there is a theoretical risk of unopposed alpha stimulation which can lead to a hypertensive crisis, and because benzodiazepines are more effective at addressing the cause of tachycardias.

ACLS protocols should be followed for the management of dysrhythmias. QRS widening can be treated with sodium bicarbonate boluses (more typical for cocaine exposures). Electrolytes should be monitored and corrected, as necessary. If a patient is deteriorating and unresponsive to standard therapies, the poison centre should be re-contacted for additional recommendations that could be considered for a variety of specific stimulant drugs.

Body Packers/Stuffers:

Ililcit drugs are often smuggled across borders by individuals who ingest multiple well-wrapped packages of the substance, a process known as “body packing”. These packages are carefully prepared for “safe” transport, making rupture or leakage less likely. In contrast, some individuals may quickly swallow poorly wrapped packages of illicit drugs (often to hide them from authorities), a practice referred to as “body stuffing”. These poorly wrapped packages carry a higher risk of rupture leading to severe, life-threatening effects. For these cases, consult the poison centre for treatment recommendations, as these patients may require specific decontamination and observation time frames.

Clinical Pearls:

- Managing agitation is key; if not managed this increases risk of hyperthermia, rhabdomyolysis, and further complications.
- Hyperthermia is life-threatening with stimulant exposures and should be treated aggressively.
- Severe complications can occur and may require aggressive critical care treatments.

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