Clinical Pharmacology

Coke, tik and 'E' – managing psychomotor-stimulant intoxication

Increasingly, doctors working in emergency medicine are faced with the management of young otherwise healthy patients presenting with manifestations of acute psychomotor-stimulant intoxication.

The current update from the South African Community Epidemiology Network on Drug Use (SACENDU) describes the demand for treatment for illicit substances. Although alcohol is still the primary substance of abuse, data show a steady increase in the use of recreational drugs, such as cocaine and the 'club drugs' including methamphetamines.

Amphetamines have a number of therapeutic indications including aiding weight loss and treating narcolepsy. Cold and flu preparations often include pseudoephedrine and caffeine. Caffeine and nicotine are some of the most widely used psychostimulants. All of the above may be abused for their psychostimulant effects. However, the vast majority of presentations to the emergency room are the result of abuse of illicit, recreational 'street' drugs.

Psychostimulants available on the drug market in South Africa comprise cocaine and the amphetamines including chemically related substances such as methamphetamine and ecstasy (3,4-methylenedioxymethamphetamine). This review will discuss the pharmacology, clinical presentation and management of the acute intoxication with these drugs.

Background on psychomotor stimulants

Cocaine

Cocaine (popular names include coke, nose candy, charlie, snow and shnaaf) is an alkaloid extracted from the leaves of the coca plant, found most commonly in South America. Its original uses were for mystical ceremonies and medicinal purposes. It was also used in times of famine to ward off hunger, enhance performance and promote a sense of well-being. Currently there is still limited use of cocaine as local anaesthetic by otolaryngologists and ophthalmologists.

Recreational cocaine is available in 2 forms:

- Cocaine hydrochloride, a bitter tasting powder, most commonly 'snorted'. It is the most expensive form.
- 'Free-base' cocaine or 'crack', obtained by heating cocaine with sodium bicarbonate until the water evaporates to form a 'rock'. This substance can then be smoked in a pipe or broken bottle making a cracking sound – this is known as 'free-basing'. 'Free-basing' is the most widespread form of cocaine use.

Amphetamines

Amphetamines is an umbrella term used to describe the chemically similar amphetamines (e.g. Benzedrine), dextroamphetamines, methamphetamines (popular names include ice, crystal, crystal meth, tik, straws, globes) and 3,4-methylenedioxymethamphetamine, MDMA (ecstasy, E, X).

The most readily available are methamphetamines which are simply produced by reduction of easily acquired over-the-counter medications, such as decongestants, containing ephedrine and pseudoephedrine.

These drugs sold illegally contain not only the pure amphetamines, but are also 'cut' with talcum powder, baking powder and other substances that can be easily disguised within the drug and ensure greater profit for the dealers. Methamphetamine or 'tik' use is increasingly rife in greater Cape Town, where it is consumed by placing the crystals or powder in a glass pipe or broken globe, heating it and inhaling the fumes.

MDMA is a hallucinogenic amphetamine, usually sold in tablet form and taken orally, but may also be crushed and snorted or inserted rectally.

Pharmacology and toxicokinetics

The onset of action and duration of effect depends on the formulation taken and route of administration. Intravenous, inhaled and intranasal consumption will have rapid distribution and effect, whereas oral use may have a longer lag time due to absorption.

Amphetamines and MDMA which are taken orally have an onset of action around 30 minutes (longer if taken after food) and reach peak concentrations within 1 - 3 hours. Duration of effect is approximately 6 - 12 hours.

Cocaine taken intravenously or by the nasal route will have effects within minutes and its action will last between 30 and 60 minutes. Smoking 'crack' will result in effects within seconds. Use of inhaled methamphetamines will result in effects within seconds and lasting 8 - 24 hours.

Psychostimulants are all sympathomimetic agents resulting in central nervous system stimulation. These substances are used to elicit feelings of euphoria, excitement, increased energy and decreased appetite.

Their effects are predominantly mediated by an increase in monoamine neurotransmitters, i.e. noradrenaline, dopamine and serotonin to different degrees.

Amphetamines predominantly promote noradrenaline release from adrenergic nerve terminals thereby stimulating the adrenergic system. They are also reported to have a direct action on alpha- and beta-receptors. Amphetamines are associated with an initial 'rush' when smoked; however, when snorted the 'high' is described as long lasting – this particular feeling of 'rush' or 'high' is thought to be the result of elevated dopamine levels.

Associated with the prolonged 'high' is a feeling of extreme confidence and elation. Tolerance develops to the amphetamines resulting in increasing doses being required. As with all of the street drugs, the purity of the substance may be poor and therefore dosing is not reliable. This increases the risk of unsuspected overdose.

MDMA acts mainly by inhibiting serotonin re-uptake, but has additional effects on the adrenergic system. This drug has also been called an 'empathogen' which is why it was first produced for use in psychotherapy. Users describe a sensation of being connected to everyone around them with associated feelings of joy, exhilaration, ecstasy and love. It is also associated with excessive energy, stamina and loss of appetite, which are the desired effects; however, users are often not aware of the potentially serious adverse effects. Several fatalities have been described in the literature, and there is ongoing debate about long-term neurological sequelae.

Cocaine inhibits the re-uptake of catecholamines at pre-synaptic receptor sites. It may also increase the release of noradrenaline from sympathetic nerve terminals. Cocaine is known to block fast-sodium channels, resulting in the local anaesthetic effects and pro-arrhythmic potential. This drug is associated with feelings of extreme self-confidence, usually extroversion and increased stamina. A psychological dependence can form quickly in which users may occupy all their time and energy pursuing the 'high'.

Clinical signs of intoxication (Table I)

Considering the poorly quantified use of these illicit drugs, relatively few serious adverse events result in a hospital admission. However, serious and sometimes fatal complications do occur.

The common adverse effects are demonstrated by an exaggerated sympathetic response. All systems may be affected by the flood of neurotransmitters.

Amphetamine and cocaine intoxication presents with overlapping clinical pictures; however, cocaine intoxication is of shorter duration.

MDMA poisoning has been associated with both severe dehydration and water intoxication. Dehydration occurs in the setting of extreme physical exertion, often in poorly ventilated venues, with reduced awareness of thirst. Alternatively, hyponatraemia may result from overzealous consumption of water in an attempt to prevent dehydration in addition to inappropriate ADH secretion. Cocaine use causes intense arterial constriction which may be associated with myocardial ischaemia. This is made worse in patients with underlying cardiovascular disease, but may present in previously healthy individuals.

Clinical assessment

A thorough drug history should be elicited from the individual or collateral sources. Most often, more than one illicit drug will have been taken. The initial assessment should include past medical history of cardiovascular, central nervous system or psychiatric disease and concurrent medication which may point to relevant drug interactions (MDMA in particular is prone to drug interactions due to its cytochrome P450 iso-enzyme metabolism).

Clinical review should document vital signs, in particular temperature, heart rate and blood pressure. Pupil size should be noted.

Investigations that may be indicated include serum electrolytes, creatine kinase and liver function tests. An electrocardiogram may expose cardiac ischaemia. Urine may be sent for screening to confirm suspected exposure; however, this does not assist in the acute management of psychomotor-stimulant intoxication.

Table I. Clinical signs of intoxication

Organ system	Clinical features
Cardiovascular system	Hypertension, intense peripheral vasoconstriction, palpitations, cardiac dysrhythmias, cardiac ischaemia and aortic dissection
Central nervous system	Restlessness, agitation, hypervigilance, mydriasis, seizures, haemorrhagic and thrombotic cerebrovascular accidents, coma
Psychiatric	Aggression, delirium, psychosis with paranoid delusions
Respiratory	Localised burns of airways from smoking, bronchospasm, pulmonary hypertension, non-cardiogenic oedema
Gastrointestinal	Mesenteric ischaemia, diarrhoea, hepatotoxicity
Renal	Acute renal failure
Musculoskeletal	Jaw-clenching and bruxism, skeletal muscle over-activity, rhabdomyolysis
Other	Hyperthermia, serotonin syndrome (especially if taken with other serotonergic agents), hyponatraemia secondary to the syndrome of inapproprite antidiuretic hormone (ADH) secretion, disseminated intravascular coagulopathy (DIC)

Management of the acute presentation

General

There is no specific antidote for psychomotor-stimulant overdose and the management is symptomatic and supportive.

Assessing temperature and providing appropriate cooling with a fan and tepid bathing is appropriate. Manage fluid intake and electrolytes adequately to treat possible dehydration or prevent further over-hydration. In extreme cases, the use of muscle relaxants and assisted ventilation may be necessary to alleviate seizure activity or the excessive heat production from overactive skeletal muscles.

Cardiovascular complications

For cardiovascular presentations, benzodiazepines are the agents of choice. Hypertension should be monitored and is usually transient, not requiring specific treatment other than a benzodiazepine. In the setting of refractory hypertension or when there are neurovascular complications, vasodilators should be chosen (e.g. sodium nitroprusside, hydrallazine or calcium channels blockers). Management of cardiac ischaemia, particularly as a result of cocaine intoxication, includes the use of oxygen, aspirin and nitrates.

It is crucial to remember that beta-blockers are absolutely contraindicated as initial management for cardiac complications. Their use may result in dangerous unopposed alpha stimulation and worsening of vasoconstriction.

Psychiatric complications

Patients may present with acute aggression, confusion and agitation. Therefore the initial management should include providing a quiet, non-confrontational environment. Benzodiazepines are the drug of choice in this setting, except in the face of acute psychosis, where the use of a neuroleptic such as haloperidol may be indicated.

The psychosis is often aggressive, associated with severe paranoia and hallucinations. Low mood is not uncommon in the days following the use of these agents. This is often manageable with supportive care but may result in overt depression requiring antidepressant prescription. Psychiatric referral and review are necessary prior to discharge from the emergency facility.

Table II. Urine tests for drugs of abuse

Drugs	Duration of detectability	Drugs that may cause false positive results
Amphetamines and methamphetamines	Up to 2 - 3 days	High concentrations of MDMA and methyl enedioxyamphetamine (MDA), amantadine, buproprion, chlorpromazine, desipramine, ephedrine, phenylephrine, pseudoephedrine, trazadone, ranitidine and selegiline
Cocaine	Short-term use 2 - 3 days; heavy use up to 8 days	

Neurological complications

There have been reports of both haemorrhagic and thrombotic strokes. Therefore maintain a low threshold for conducting CT scans when severe headache, protracted confusion or focal neurological complications are present. First-line treatment for seizures remains benzodiazepines.

The serotonin syndrome is a clinical syndrome diagnosed in the presence of hyperreflexia and clonus. Additional features include hyperthermia and rigidity which may be associated with rhabdomyolysis and DIC. When severe, this condition should be treated in an intensive care setting where rapid cooling, appropriate hydration and assisted ventilation can be monitored. The judicial use of the serotonin antagonist, cyproheptadine, may be indicated in serious cases.

Laboratory screening for drugs of abuse

Sensitive screening tests are available to assess exposure to several drugs of abuse. These laboratory tests are performed on urine samples using immuno-assay kits. The tests are poorly specific with the possibility of false positives and should therefore be used for screening only. Thresholds may differ between laboratories and results will only be provided as positive or negative, without quantifying the drug level. Urine tests for drugs of abuse are given in Table II.

Conclusion

National surveys suggest that abuse of psychostimulants is on the rise. We can therefore expect an increase of these cases presenting in the casualty setting.

The informed, expedient clinical management of patients with both mild and severe intoxication will help to optimise their care and minimise disorder in the emergency room. Ideally, there should be referral to an appropriate drug counselling service following the abatement of clinical symptoms.

Recommended reading and useful websites

Cape Town Drug Counselling Centre website: http://www.drugcentre.org.za/

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Herbal preparations don't relieve hot flushes

Black cohosh alone or combined with other botanical agents does not relieve the vasomotor symptoms of menopause any better than placebo, according to a report in the *Annals of Internal Medicine* late last year. The 5-arm trial was carried out in women aged 44 - 55 who had at least 2 vasomotor symptoms each day at the start of the trial. The women were randomised to receive black cohosh, a multibotanical containing black cohosh and 9 other herbs, a multibotanical along with counselling on soy intake, oestrogen, with and without progesterone, and placebo. None of the herbal interventions was any better than placebo at 3, 6 or 12 months of follow-up. But hormonal treatment reduced the symptoms compared with placebo.

Newton KM, *et al. Ann Intern Med* 2006; 145: 869-879.