CLINICAL UPDATE

Cocaine use and cardiovascular complications

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ABSTRACT

- In Australia, the lifetime use of cocaine is rising, with 3% of the population aged over 14 using cocaine in 1991, increasing to 4.5% in 1998, and cocaine use accounting for 10% of all deaths secondary to illicit drug use in 1998.
- Cocaine is prepared from the leaves of the plant *Erythroxylon coca*, and is available as cocaine hydrochloride (a water-soluble powder or granule which can be taken orally, intravenously or intranasally) and as "freebase" or "crack" cocaine (heat stable, melting at high temperatures, thus allowing it to be smoked).
- Acute myocardial infarction (AMI) is the most commonly reported cardiac consequence of cocaine misuse, usually occurring in men who are young, fit and healthy and who have minimal, if any, risk factors for cardiovascular disease.
- The mechanism by which cocaine induces AMI is largely not understood.
- Cocaine effect should be seriously considered in any young patient with minimal risk factors for cardiac disease presenting with AMI, dilated cardiomyopathy, myocarditis or cardiac arrhythmias.

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IN AUSTRALIA, in 1998, illicit drug use caused more than 1000 deaths and about 7% of all hospital admissions. Cocaine accounted for 10% of these illicit drug related deaths;[1] some 42% of these were in the 14–34-years age group. Although cocaine is a relatively uncommon drug of misuse in Australia (with only about 1% of Australians over the age of 14 having used cocaine within the past 12 months), it nevertheless has a very high rate of addiction, morbidity and mortality, with the proportion of Australians aged over 14 years ever having used cocaine (lifetime use) increasing from 3% in 1991 to 4.5% in 1998. This is similar to lifetime heroin use of 4% in Australia, but is significantly less than the 12% lifetime use of cocaine in the United States.[1]

Cocaine use is a major problem worldwide, and, although it may not be at the forefront of Australia's drug problems, it causes significant morbidity, mortality and cost to the healthcare system. Cardiovascular complications account for most cocaine-related deaths. Its pharmacology is described in the Box.

Cocaine and the heart

Acute myocardial infarction (AMI) is the most commonly reported cardiac consequence of cocaine misuse, but significant arrhythmias are also reported. More than 100 case reports of cocaine-induced AMI have been published since the early 1980s.[2,5] Cocaine appears to cause acute myocardial ischaemia or infarction in patients with and without pre-existing coronary artery disease. Indeed, 33% of those with apparent cocaine-induced AMI had no coronary artery damage at angiography.[6] Affected patients are relatively young (mean age, 34 years) and more than 90% are men,[3] for whom retrospective data show that they are healthy. The risk of having an AMI secondary to cocaine use is maximal in the first hour after ingestion, having been reported as 24 times[7] or 31 times[8] the baseline risk. However, lifetime-risk increase has been reported in recent prospective studies to be much lower, with an average risk increase (over non-users) of about 6%.[6,9]

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There are a number of proposed mechanisms of cocaine-induced myocardial infarction. Firstly, in-vitro studies have shown that cocaine activates platelets, increases platelet aggregation and potentiates platelet thromboxane production. The mechanism is thought to be by induction of α-granule release from platelets leading to subsequent thrombosis — a recent randomised, double-blind, crossover study found that there was a fourfold increase in both platelet factor 4 and thromboglobulin and an increase in platelets containing microaggregates (α-granules) at 40 and 80 minutes.[10] This is supported by the postmortem findings of acute platelet-rich thrombi in fatal cocaine-related infarcts in both normal and atherosclerotic coronary vessels.[11] A further procoagulant effect has also been demonstrated by the finding of lower protein C and antithrombin III levels among cocaine users.[10] This anticlotting-factor deficiency predisposes to in-situ thrombosis, causing acute myocardial infarction in the presence of previously normal or minimally diseased coronary arteries. Finally, no increase in von Willebrand factor is found in cocaine users.[10]

Secondly, the sympathomimetic effects of cocaine induce an increase in heart rate and blood pressure, leading to a resultant increase in oxygen demand by the heart. Cocaine could lead to myocardial ischaemia and subsequent infarction, particularly in the presence of underlying coronary artery disease.[2]

Thirdly, coronary artery vasospasm has been suggested as another mechanism for cocaine-induced AMI. The mechanism by which cocaine may induce vasospasm is not understood. There are two schools of thought suggesting a wide role for cocaine as a general vasoconstrictor, and another suggesting a more specific role for cocaine on the vascular smooth muscle leading to vasoconstriction.[2] Of particular note is a study showing the possible role of endothelin-1, the most potent endogenous, endothelium-derived vasoconstrictor factor.[12] That study showed a significantly increased concentration of endothelin-1 in actively intoxicated and chronic users of cocaine over healthy control subjects. However, it was difficult to determine whether this increase alone was sufficient to induce coronary vasospasm. The study went on to hypothesise that, because endothelin-1 increases the calcium sensitivity of arteries, it may sensitise the vasculature to other vasoconstrictor stimuli and prolong coronary vasoconstriction or vasospasm, causing acute myocardial infarction even in people without coronary stenosis.[12]

Fourthly, several recent autopsy reports suggest prolonged cocaine misuse causes intimal hyperplasia and premature atherosclerosis in young patients who die from AMI following cocaine use.[11] Similarly, endomyocardial biopsy specimens from patients with cocaine-induced chest pain show marked thickening of small coronary vessels suggestive of previous arterial injury.[2]

There may also be a central nervous system role for the action of cocaine[13] whereby it affects the parasympathetic and sympathetic control of the heart. One study examined sympathetic nervous system activity after intranasal administration of a low dose of cocaine and found there was an immediate threefold increase in skin sympathetic nerve activity and by a sustained twofold increase in sympathetic nervous system activity for a further 90 minutes. It was proposed that cocaine acts centrally to increase sympathetic outflow both to the cutaneous and skeletal muscle bed, promoting peripheral vasoconstriction, and to cause cardiac sympathomimetic effects such as tachycardia.[13]

There is also evidence that cocaine can trigger cardiac arrhythmias, probably as a result of the enhanced sympathetic state and the direct effects of cocaine on the heart. The mechanisms are not fully understood, but several theories have been proposed: (i) alteration of myocardial automaticity by direct effect on myocardial tissue; (ii) central autonomic dysregulation by enhanced adrenergic and neurohumoral stimulation; (iii) induction of vasospasm and ischaemia with resultant electrical disturbances; and (iv) potentiation of re-entrant arrhythmias.[2,7,14,15]

At the cellular level, cocaine has a local anaesthetic effect and blocks the inward flux of sodium ions during depolarisation.[2,3,10] Neurotransmitters released from cardiac sympathetic nerves act on both α- and β-adrenoceptors.[4] Stimulation of β-adrenoceptors leads to the activation of adenylate cyclase, which increases the concentration of cyclic AMP, leading to an increased influx of calcium into myocardial cells.[1] This calcium influx can lead to depolarisation of the cardiac membrane, with sustained action potential generation and subsequent extrasystolic beats.[3]

Cocaine pharmacology

Cocaine is an alkaloid prepared from the leaves of the plant *Erythroxylon coca*. The crystalline or powder form of cocaine is prepared by dissolving the alkaloid in hydrochloric acid to form the water-soluble salt cocaine hydrochloride. "Freebase" or "crack" cocaine is the cocaine alkaloid in its basic, non-salt form and is prepared by organic extraction from a basic solution with ether. Crack cocaine melts at high temperature and vaporises at even higher temperatures without losing any of its potency, thus allowing it to be smoked.[2,3] When inhaled, cocaine crosses the alveolar endothelium and is rapidly absorbed into the bloodstream. In fact, cocaine is rapidly absorbed from all mucous membranes, allowing it to be administered sublingually, intravaginally, rectally and through the respiratory system, as well as by intramuscular or intravenous injection. Onset of action generally varies between three seconds and five minutes, depending on the route of administration. Peak effect is usually reached within 20 minutes and the duration of action is also variable, ranging from five to 90 minutes. Cocaine has a plasma half-life of 30–60 minutes in humans.[4] The drug is metabolised by plasma and hepatic cholinesterases to the water-soluble compounds benzoylecgonine and ecgonine methyl ester, which are excreted in the urine, thus enabling detection by urinary drug screening for these compounds.[4]

The primary mechanism of action underlying cocaine's central and peripheral effects is blockade of norepinephrine, serotonin and dopamine reuptake into the presynaptic terminals from which these transmitters are released.[3,4] This blockade potentiates and prolongs the central and peripheral actions of these catecholamines. In particular, prolongation of dopaminergic effects in the brain's "pleasure centre" (the limbic system) produces the intense euphoria that cocaine initially causes.[2] Chronic intake of cocaine depletes dopamine, leading to the intense depression experienced and described by cocaine addicts.[4] This depletion triggers a cycle of craving for cocaine and temporary relief of depression by further cocaine ingestion.

Actively intoxicated cocaine users been found to have increased circulating levels of noradrenalin and adrenalin secondary to cocaine blockade of the reuptake receptors on the presynaptic neuronal membranes.[3,7] Increased noradrenalin levels and increased sympathetic tone reduce cardiac electrical stability and predispose to lethal arrhythmias, particularly under ischaemic conditions. Further, recent studies have shown that long-term cocaine use is associated with increased left ventricular mass and wall thickness,[14] which is an independent risk factor for ventricular arrhythmias and ischaemia.[6,7]

Conclusion and clinical implications

Cocaine is a complex drug which can cause lethal cardiovascular events, including myocardial infarction and ventricular arrhythmias. The mechanisms for the cardiotoxic effects remain somewhat unclear. Some of the proposed mechanisms include cocaine-induced diffuse or local coronary spasm in normal or atherosclerotic arteries, and cocaine's effect in increasing platelet aggregation contributing to thrombus formation. Cocaine also increases oxygen demand by increasing heart rate and blood pressure, as well as affecting the heart's muscular architecture. Long-term use may cause repetitive episodes of spasm, and this may cause endothelial damage and subsequent acceleration of atherosclerosis.

The increase in cocaine misuse has resulted in an increase in cocaine-related emergency department visits, hospital admissions and mortality. Regular cocaine use is associated with an increased likelihood of AMI in younger patients. Indeed, about 25% of AMIs in people aged 18–45 years in the United States were attributable to frequent cocaine use.[15] So, the possibility of cocaine use should be seriously considered in any young patient with minimal risk factors for cardiac disease presenting with AMI, dilated cardiomyopathy, myocarditis or cardiac arrhythmias.[2] Pharmacological management of such patients is also problematic, as there have been no well designed, prospective, randomised controlled trials to compare treatment strategies for cocaine-induced myocardial ischaemia. Benzodiazepines attenuate the cardiac and central nervous system effects of cocaine, and clinical experience supports their use in cocaine-intoxicated patients to reduce anxiety and decrease blood pressure and heart rate, thereby reducing myocardial oxygen demand.[16] Antiplatelet therapy with aspirin, if not contraindicated, may also be warranted in view of the procoagulant properties of cocaine (although there are no clinical data to support this). Nitrites may also be indicated to reduce infarct size, reduce pain related to ischaemia and reverse coronary vasoconstriction secondary to cocaine use.[16]

Secondary prevention by behaviour modification (cessation of cocaine use) through public awareness and education campaigns may reduce cardiovascular and other morbidity associated with cocaine use. Further research is indicated, as past research has been limited by the nature of patient samples (usually only healthy participants) and by the limited experimental doses of cocaine used (for ethical reasons) — in general, only the acute effects have been studied.

References

1. Miller M, Draper G. Statistics on drug use in Australia. Canberra: Australian Institute of Health and Welfare, 2000. <www.aihw.gov.au>.
2. Mouhaffel AH, Madu EC, Satmary WA, Fraker T. Cardiovascular complications of cocaine. *Chest* 1995; 107: 1426-1434.
3. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001; 345: 351-357.
4. Mycek MJ, Harvey RA, Champe PC, editors. Lippincott's illustrated reviews: Pharmacology. 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 2000.
5. Zimmerman FH, Gustafson GM, Kemp HG Jr. Recurrent myocardial infarction associated with cocaine abuse in a young male with normal coronary arteries: evidence for coronary artery spasm culminating in thrombosis. *J Am Coll Cardiol* 1987; 9: 964-968.
6. Hollander JE, Hoffman RS, Burstein JL, et al. Cocaine associated myocardial infarction: mortality and complications. *Arch Intern Med* 1995; 155: 1081-1086.
7. Mittleman MA, Mintzer D, Maclure M, et al. Triggering of myocardial infarction by cocaine. *Circulation* 1999; 99: 2737-2741.
8. Cheung, TO. Risk of acute myocardial infarction in cocaine abusers [letter]. *Circulation* 2000; 101: 227.
9. Amin M, Gabelman G, Karpel J. Acute myocardial infarction and chest pain syndrome after cocaine use. *Am J Cardiol* 1990; 66: 1434-1437.
10. Heesch CM, Eilhelm CR, Ristich J, et al. Cocaine activates platelets and increases the formation of circulating platelet containing microaggregates in humans. *Heart* 2000; 83: 688-695.
11. Kolodgie FD, Farb A, Virmany R. Pathobiological determinants of cocaine associated cardiovascular syndromes. *Hum Pathol* 1995; 26: 583-586.
12. Wilbert-Lampen U, Selinger C, Zilker T, Arendt R. Cocaine increases the endothelial release of immunoreactive endothelin and its concentrations in human plasma and urine: reversal by co-incubation with sigma-receptor antagonists. *Circulation* 1998; 98: 385-390.
13. Vongpatanasin W, Mansour Y, Chavoshan B, et al. Cocaine stimulates the cardiovascular system via a central mechanism of action. *Circulation* 1999; 100: 497-502.
14. Chokshi SK, Moore R, Pandian NG. Reversible cardiomyopathy associated with cocaine intoxication. *Ann Intern Med* 1998; 111: 1039-1040.
15. Qureshi AJ, Fareed M, Suri K, et al. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. *Circulation* 2001; 103: 502-506.
16. Hollander JE. Current concepts: the management of cocaine-associated myocardial ischaemia. *N Engl J Med* 1995; 333: 1267-1272.

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