REVIEW

Cocaine use and stroke

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Stroke is the third most common cause of death in developed countries. In England and Wales, 1000 people under the age of 30 have a stroke each year. Cocaine is the most commonly used class A drug, and the first report of cocaine-induced stroke was in 1977. Since the development of alkaloidal "crack" cocaine in the 1980s, there has been a significant rise in the number of case reports describing both ischaemic and haemorrhagic stroke associated with cocaine use. Cocaine is a potent central nervous system stimulant, and acts by binding to specific receptors at pre-synaptic sites preventing the reuptake of neurotransmitters. The exact mechanism of cocaine-induced stroke remains unclear and there are likely to be a number of factors involved including vasospasm, cerebral vasculitis, enhanced platelet aggregation, cardioembolism, and hypertensive surges associated with altered cerebral autoregulation. The evidence surrounding each of these factors will be considered here.

In 1859 the purification of cocaine was achieved by Albert Niemann, a German chemist. Towards the end of the 19th century, cocaine became widely available with no laws restricting sale or consumption. Cocaine was sold in a number of forms including cigarettes, inhalers and cocaine crystals.^{11 12} Angelo Mariani added cocaine to his own blend of wine, and supporters of his included a number of physicians including Sigmund Freud. At the end of the 19th century, John Styth Pemberton reformulated cocaine with caffeine which was advertised as a "brain tonic", and eventually became known as "Coca-cola". Until 1903, this contained approximately 60 mg of cocaine per serving.

Cocaine was also thought to be beneficial for a variety of medical problems. In 1884 Sigmund Freud published a paper advocating the therapeutic use of cocaine as a stimulant, an aphrodisiac, a local anaesthetic and a remedy for a number of disorders including asthma, wasting diseases and nervous exhaustion.¹³ Freud recommended cocaine in oral doses of 50–100 mg as a stimulant for depressive states.¹⁴ This increased availability led to misuse and subsequent addiction which resulted in the Harrison Narcotics Act of 1914, banning the distribution of cocaine except on prescription.

In the early 1970s a second epidemic began as cocaine was re-discovered as a recreational drug, and the previous dangers of cocaine use uncovered at the beginning of the century had long been forgotten. The perception at this time was that cocaine was safe and non-addictive. In fact, even the medical literature supported this idea stating that "used no more than two or three times a week, cocaine creates no serious problems".¹⁵ The hydrochloride salt is taken by nasal inhalation, though in the 1980s a more potent alkaloidal form called "crack" emerged which was relatively inexpensive and could be smoked.

Because of the illegality of cocaine, true prevalence rates are difficult to determine. In England and Wales cocaine is the most commonly used class A drug, and according to the 2004/5 British Crime Survey, 2.0% of the population had claimed to use cocaine within the last year, and a little over two million people were estimated to have used it ever.¹⁶

Stroke is the single biggest cause of severe disability and the third most common cause of death in developed countries.¹ It affects between 174 and 216 people per 100 000 population in the UK each year,² and accounts for 11% of all deaths. Each year in England and Wales, 10 000 people under the age of 55 and 1000 people under the age of 30 have a stroke.³ In the younger age group, thromboembolism and intracranial small vessel disease are more unlikely, and so a higher proportion of the less common causes of stroke occur, including substance misuse. The relationships between cigarette smoking and alcohol consumption with stroke are previously well documented.^{4 5} Of the illicit substances used, opiates,⁶ amphetamines,⁷ phencyclidine,⁸ and marijuana⁹ have all been reported in association with stroke; however, it is the use of cocaine which carries the most substantial data regarding an aetiological link, and will therefore be considered here.

HISTORY

Cocaine is derived from the leaves of the *Erythroxylon* coca plant found in South America. Its use dates back thousands of years, and remnants of chewed coca leaves which have a 1% cocaine content have been found near gravestones as far back as 2500 BC. Coca leaves have been chewed by Peruvian Indians for centuries and were said to prevent hunger and increase stamina.¹⁰ The amount of cocaine ingested was probably small with a total dosage of around 200–300 mg each day.

CHEMISTRY

Cocaine, or benzoylmethylecgonine, is a weak base extracted from coca leaves of the *Erythroxylon* plant which is ground into a paste and contains 70% pure cocaine. It is usually treated with acid to form cocaine hydrochloride salt which is water soluble and so can be absorbed through the nasal mucosa. However, because of its high melting and boiling point it cannot be smoked.

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Box 1 Clinical manifestations of cocaine use**Cardiac**

- Myocardial infarction
- Cardiomyopathy
- Myocarditis
- Arrhythmias
- Sudden death

Pulmonary

- Pneumothorax
- Pneumomediastinum
- Pulmonary oedema
- Pulmonary haemorrhage
- Bronchiolitis obliterans

Psychiatric

- Anxiety/depression
- Paranoia
- Delirium
- Psychosis

Neurology

- Headache
- Seizures
- Stroke
- Cerebral atrophy
- Cerebral vasculitis

Gastrointestinal

- Ischaemic colitis

Head and neck

- Enamel erosion
- Gingival ulceration
- Chronic rhinitis
- Osteolytic sinusitis
- Abnormal olfaction
- Perforated nasal septum
- Midline granuloma

Endocrine

- Gynaecomastia
- Galactorrhoea
- Sexual dysfunction

Infections (in intravenous users)

- Bacterial endocarditis
- HIV
- Hepatitis
- Injection site abscess
- Cellulitis

Other

- Weight loss
- Optic neuropathy
- Rhabdomyolysis
- Arterial/venous thrombosis

Cocaine alkaloid exists as freebase and crack which are chemically identical, though differ in their method of preparation. The melting point is 98°C, and heating converts cocaine to a stable vapour which can therefore be inhaled.¹¹ Crack is made

by dissolving cocaine hydrochloride into water, mixing it with baking soda and then heating it, which results in a hard precipitant.¹⁷ The name derives from the popping sound it makes when heated.

PHARMACOLOGY

Cocaine can be absorbed through any mucous membrane.¹⁷ In the 1970s the most common method of administration was nasal insufflation of cocaine hydrochloride. This results in peak levels in about 50–60 min, as uptake is limited by the small available surface area, and associated vasoconstriction in the nasal mucosa.^{17–18} Crack cocaine, which became available in the 1980s, is rapidly absorbed by the pulmonary vasculature and reaches peak levels in about 5–10 min. However, bioavailability is higher via the nasal route, so prolonging the euphoric effect.¹⁸

Cocaine has a short half life of approximately 60 min and is metabolised predominantly into two products, benzoylecgonine and ecgonine methyl ester.^{17–18} In the presence of ethanol, a transesterification process leads to the production of cocaethylene, which has similar pharmacological properties to cocaine.¹⁹ This prolongs the euphoria associated with cocaine, which is why ethanol and cocaine are often consumed together.¹⁹

The short half life of cocaine means that it is usually fully metabolised by the time it is excreted, and therefore not usually found in the urine. Its two main metabolites, benzoylecgonine and ecgonine methyl ester, have half lives of approximately 6 h, and can be detected in the urine for 6–14 days after cocaine use.²⁰ Screening reagents are therefore designed to detect these metabolites.

The known pathophysiological effects of cocaine include vasoconstriction, local anaesthesia and central nervous system stimulation. Cocaine binds to specific receptors at pre-synaptic sites preventing the reuptake of neurotransmitters. Sympathomimetic effects are therefore achieved by blocking the reuptake of catecholamines at the pre-synaptic sympathetic nerve terminals.¹⁹ Cocaine induces euphoria and central nervous system stimulation by preventing the reuptake of dopamine and serotonin into pre-synaptic neurones within the mesolimbic and mesocortical areas of the brain.¹⁹ The anaesthetic effect of cocaine results from slowing of nerve conduction due to blockage of fast sodium channels.¹⁹ Following chronic use, the body's reservoirs of neurotransmitters may deplete and therefore chronic users may experience features of tolerance and withdrawal.²¹

CLINICAL FEATURES

Cocaine is a potent central nervous stimulant. Initial euphoria is associated with restlessness, hyperactivity, increased sensory awareness, enhanced self confidence, and reduced appetite. Sexual pleasure may be amplified, and the euphoria is occasionally followed by feelings of discomfort and depression. Sympathomimetic effects result in elevated blood pressure and heart rate, and cause symptoms of sweating, palpitations, tremor and hyperthermia. Cocaine toxicity can manifest in a variety of ways.^{12–39} The precise nature of these complications can be difficult to determine for a number of reasons. Clinical manifestations often depend on the dose and route of administration, the purity of the sample and the chronicity of use. Also, multi-drug use and adulterants mixed with cocaine may have direct toxic effects themselves. Information regarding cocaine toxicity is derived primarily from individual case reports and small observational case series, where the history regarding the substances ingested may be unreliable. The medical and psychiatric complications associated with acute cocaine toxicity and chronic use are numerous, and table 1 outlines the major clinical manifestations.

The first report of cocaine-associated stroke was in 1977. Intramuscular administration in a male user was followed 1 h later by aphasia and right sided hemiparesis.⁴⁰ During the 1980s, increased production of alkaloidal "crack" and the subsequent epidemic led to a significant increase in the number of case reports of cocaine-related stroke. The onset of symptoms is usually immediate or within 3 h of cocaine use,⁴¹⁻⁴⁴ and 73% of patients with cocaine-induced stroke have no prior cardiovascular risk factors.⁴¹ Cocaine is associated with both ischaemic and haemorrhagic stroke. Early studies suggested a higher proportion of haemorrhagic events related to cocaine use, though in a multi-centre series in 1990, Levine *et al* reported a higher proportion of infarcts.⁴⁴ Since then, reports of cocaine-induced stroke have demonstrated roughly equal proportions of ischaemic and haemorrhagic events. Daras *et al* studied 54 patients over a 6 year period who developed either acute neurological deficit, or headache with signs of meningeal irritation after cocaine use.⁴¹ Ischaemic and haemorrhagic strokes occurred in roughly equal proportions with 25 infarcts and 29 haemorrhages. The differences noted are primarily due to the type of cocaine used. Eighty per cent of strokes related to nasal insufflation of the hydrochloride form are haemorrhagic, as compared to alkaloidal "crack" which was later developed in the 1980s, and results in equal numbers of ischaemic and haemorrhagic stroke.⁴⁵

Cocaine-induced ischaemic strokes have been reported in both anterior and posterior arterial territories, and have included retinal infarction, spinal cord infarction and transient ischaemic attacks.^{41 44 46-51} Haemorrhagic strokes have been intraparenchymal, intraventricular and subarachnoid.^{41 44 48 51-53}

MECHANISM OF VASCULAR INJURY

The exact mechanism of cocaine related stroke remains unclear and there are likely to be a number of factors involved. The issue is complicated further by the fact that contaminants such as procainamide, quinidine and antihistamines, which are often mixed with the cocaine, may contribute to the effects seen and influence the underlying pathophysiology.

There does not appear to be any direct neurotoxic action,⁵⁴ and potential mechanisms involved in cocaine induced stroke include vasospasm, cerebral vasculitis, enhanced platelet aggregation, cardioembolism, and hypertensive surges associated with altered cerebral autoregulation and cerebral blood flow.

Cocaine induced vasospasm has been suggested by cerebral angiography in several patients with cocaine related ischaemic strokes^{42 44-46 55}; this response has also been reported in several animal studies, where angiographic evidence of vasospasm severe enough to cause vascular occlusion was demonstrated.⁵⁶⁻⁶¹ Histological findings elsewhere which support vasospasm as a mechanism for cocaine-induced ischaemic stroke include tunica media disruption,⁶² periarteriolar fibrosis in the nasal mucosa,⁶² elastic disruption in submucosal intestinal arterioles,⁶³ and coronary artery intimal hyperplasia.⁶⁴

Cocaine is a potent vasoconstrictor due to its sympathomimetic action, preventing the reuptake of noradrenaline, serotonin and dopamine at pre-synaptic nerve terminals. However, it also has direct effects on calcium channels, promoting intracellular calcium release from the sarcoplasmic reticulum in cerebral vascular smooth muscle cells.^{65 66} Zhang *et al*⁶⁷ demonstrated a significant increase in free calcium concentration in cultured canine cerebral vascular smooth muscle cells treated with cocaine.

Animal studies suggest that endothelin-1 is an important mediator of cocaine-induced cerebral vasospasm.⁶⁸ Johnson *et al*⁶⁹ established that cocaine induced cerebral vasospasm was relatively specific to dopamine rich brain areas and hypothesised

that dopamine pathways play a central role in controlling cerebral blood flow. Vasospasm and ischaemia in cocaine users may therefore be related to the increased availability of dopamine in these areas. Cocaine induced reductions in cerebral metabolism may also lead to feedback down regulation of blood flow.⁷⁰ London *et al* demonstrated reduced glucose metabolism following cocaine administration,⁷¹ and Volkow *et al* found there to be more areas of decreased cerebral blood flow in chronic cocaine users compared to healthy volunteers.⁷² However, the significance of abnormal patterns of cerebral blood flow in cocaine users in relation to associated stroke remains unclear.

Cerebral vascular thrombosis may occur secondary to vasospasm, and it has been suggested that vasospasm results in endothelial injury and platelet aggregation with subsequent release of smooth muscle growth factor and obstructive intimal hyperplasia.⁶⁴ Advanced atherosclerosis has been observed in the renal arteries and aorta of cocaine users.⁷³ The arteriosclerotic toxicity of cocaine has also been demonstrated in rabbits,⁵⁸ and the same pathophysiological process may also occur in intracerebral vessels leading to cocaine-induced lacunar infarction. Konzen *et al* reported three cases whose angiographic and pathological data suggested that vasospasm with secondary thrombus formation may be an important mechanism of cocaine-induced cerebral infarction.⁶¹ Histology in one of these cases showed small calibre intracerebral arteries with infolded and irregular internal elastica lamina in multiple territories, presumably related to cocaine induced vasoconstriction. Staining techniques did not reveal any other potential cause for these changes.

Cocaine in vitro causes an enhanced response of platelets to arachidonic acid, leading to increased thromboxane production and platelet aggregation.⁷⁴ However, data on the interaction of cocaine with platelet function and the haemostatic system are conflicting and inconclusive. In vitro studies have reported an increase,⁷⁵ no change,⁷⁶ and decrease⁷⁷ in aggregation, whereas animal studies have shown increased platelet activation.^{74 78}

Acute platelet rich thrombi have been described in fatal cocaine related infarcts in both normal and atherosclerotic coronary vessels.⁷⁹ However, interpretation of data from cocaine users may be complicated by the fact that these cases may have been chronically exposed to other toxins. It has also been suggested that in the setting of chronic cocaine use, the repeated release of cell growth factors by cocaine activated platelets might promote atherosclerosis, thus predisposing to thrombosis and ischaemia in the absence of acute intoxication.⁸⁰ Reduced regional cerebral blood flow has been demonstrated in association with increased platelet aggregation in cocaine dependant patients, with significant improvement of hypoperfusion after abstinence.⁸¹ Heesch *et al*⁸² demonstrated platelet activation, α granule release and platelet containing microaggregate formation with decreased bleeding time following in vivo cocaine administration to healthy volunteers, even at low doses.

Ischaemic stroke may also be less commonly associated with cerebral vasculitis following cocaine use. Cerebral vasculitis has been attributed to cocaine misuse on the basis of the typical angiography findings of arterial beading.^{43 83} However, angiographic arterial beading should not be specifically attributed to vasculitis since it is a non-specific sign of vascular injury.⁸⁴ Krendel *et al*⁸⁵ demonstrated two cases of histologically confirmed cerebral vasculitis associated with cocaine use. Angiography was normal in one patient, and in the other showed multiple large vessel occlusions, though without the described pattern of vascular beading.

Vasculitis has been demonstrated in other drug-induced strokes, especially those related to amphetamines.⁸⁶ These can cause an inflammatory vasculopathy with vessel wall necrosis

potentially leading to vessel wall rupture.⁸⁷ Amphetamines have a similar mechanism of action to cocaine by increasing the availability of catecholamines at nerve terminals, and so there may be similarities in terms of the aetiology of the vasculitic changes. It should be noted that amphetamines may also be present as adulterants in cocaine preparations.

Another potential mechanism for ischaemic stroke associated with cocaine use is cardioembolism. Petty *et al* reported a case of a 39-year-old woman with onset of left hemiparesis caused by embolic upper division middle cerebral artery branch occlusion 3 h after smoking crack cocaine.⁸⁸ Cerebral emboli with subsequent infarction can originate from cardiac thrombi which form during cocaine induced myocardial infarction,⁸⁹ and case reports have also documented embolic stroke secondary to cocaine related cardiomyopathy.^{88–90} These disease processes are established causes of cardiac arrhythmia which may also predispose to cardioembolism. Prolongation of the QT interval has been noted in patients presenting with cocaine toxicity,⁹¹ and experiments on isolated myocytes exposed to cocaine resulted in a modest prolongation of the transmembrane action potential demonstrating a possible mechanism for cocaine arrhythmogenesis.⁹² Contaminants mixed with cocaine may provide a further mechanism for cardioembolism due to arrhythmia. As with any substance injected intravenously, cocaine administered by this route can result in embolic vessel occlusion due to endocarditis.^{35–36} Stroke resulting from endocarditis may also be haemorrhagic, following rupture of a septic aneurysm.^{93–95}

Cocaine use is associated with both intracerebral haemorrhage⁹⁶ and subarachnoid haemorrhage.^{97–98} As with ischaemic stroke, the exact mechanism involved is not fully understood, though may involve cocaine-induced haemodynamic changes in susceptible individuals.

By blocking the reuptake of catecholamines at pre-synaptic nerve endings, cocaine use results in tachycardia and pronounced transient increases in blood pressure.^{99–100} Cerebral autoregulation maintains constant cerebral blood flow despite fluctuations in arterial blood pressure, although above this upper limit blood flow may increase resulting in a risk of arterial rupture.^{101–102} Cocaine disturbs cerebral autoregulation by lowering this upper limit of blood pressure at which constant cerebral blood flow is maintained,¹⁰³ therefore increasing flow and predisposing to vascular rupture. Cocaine-induced disturbance of cerebral autoregulation may also result in reperfusion injury and haemorrhagic transformation of an infarct.^{96–104}

In a prospective autopsy-based study, Nolte *et al* demonstrated positive toxicology for cocaine in 59% of 17 non-traumatic

haemorrhagic strokes.⁵² No pathological evidence of vasculitis was identified in any of these cases, suggesting the role of haemodynamic change and hypertensive surges rather than a cocaine-induced vasculopathy.

Seventy-eight per cent of patients with cocaine-related subarachnoid haemorrhage and 48% of patients with cocaine-related intracerebral haemorrhage have an underlying vascular abnormality.⁹⁶ Autopsy studies have also demonstrated a higher incidence of hypertensive cardiovascular disease in cocaine-induced haemorrhagic stroke.^{52–53} This suggests that cocaine-induced haemorrhagic stroke may result as a consequence of the haemodynamic effects of cocaine in a susceptible subgroup of individuals.

SUMMARY

Cocaine is the most commonly used class A drug in England and Wales. Toxicity can result in a variety of clinical manifestations including both ischaemic and haemorrhagic stroke. Potential mechanisms involved in cocaine-induced stroke include vasospasm, cerebral vasculitis, enhanced platelet aggregation, cardioembolism, and hypertensive surges associated with altered cerebral autoregulation.

The growing number of case reports describing cocaine-related stroke, and the increasing evidence supporting this aetiological link, suggests that cocaine use should always be considered as a possible cause of stroke, especially in the younger age group, and in patients who lack other known vascular risk factors. Toxicology screening should therefore be included alongside standard investigations in this group of patients, or when a history of substance misuse is suspected.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES

1. Cocaine stimulates the release of catecholamines at pre-synaptic sympathetic nerve terminals.
2. Cocaine is a potent vasoconstrictor, and cerebral vasospasm has been demonstrated in cocaine users.
3. In the majority of cases of cocaine-induced stroke, symptoms occur within 3 h of cocaine use.
4. "Crack" cocaine is associated with significantly more haemorrhagic rather than ischaemic strokes.
5. Approximately three-quarters of patients with cocaine-induced stroke have no known vascular risk factors.

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ANSWERS

1. F: Cocaine's sympathomimetic effects are achieved by blocking the reuptake of catecholamines at pre-synaptic sites.
2. T
3. T
4. F: "Crack" cocaine is associated with haemorrhagic and ischaemic strokes in roughly equal proportions. It is the hydrochloride form which carries the higher risk of haemorrhagic events.
5. T

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