Cerebrovascular Effects Of Cocaine
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Citation

Abstract
Over five million Americans using cocaine regularly, and a survey in South London showed an increase in crack cocaine use from 16% to 59% amongst drug users. Common manifestations such as chest pain, hypertension, and psychiatric disturbances occur, but we must be alert for other serious unexpected presentations. Misdiagnoses are likely, especially as an accurate history may not be forthcoming, with cocaine toxicity masquerading as other common diseases. Subarachnoid haemorrhage, strokes of varying aetiologies, seizures, headache and sudden death are recognised associations of cocaine abuse. Seizures, for instance, have been reported to make up almost 10% of cocaine related admissions to emergency departments, and patients with prior seizure history, poor compliance with antiepileptic medication, alcohol abuse and poor diet or sleep habits are at greater risk. Simple management principles coupled to a high index of suspicion, are efficacious in the assessment and treatment of cocaine toxicity.

INTRODUCTION
Cocaine is one of the major drugs of abuse in the United States, with over five million Americans using the drug regularly. This has recently become a problem in Great Britain, with a survey among injecting drug users in south London showing an increase in crack cocaine use from 16% in 1990 to 59% in 1993. In the North Thames region of London in 1995-6, 4% of young people used cocaine as their main drug of abuse, with a further 7% using crack cocaine. When asked if it were either the main or secondary drug of abuse, these figures rose to 12% & 16% respectively. 1 in 50 young people in Great Britain have tried cocaine and 1 in 100 have tried crack. A Department of Health study revealed that the only drug in Great Britain to show a significant increase in proportion of misuse was cocaine, increasing from 1% of 16 – 24 year olds in 1994 to 3% in 1998.

Cocaine has commonly recognised manifestations such as chest pain, hypertension, and psychiatric disturbances such as psychosis, paranoia, agitation, anxiety and depression, but more unexpected presentations may occur, many neurological, which may commonly be ascribed to other causes. Subarachnoid haemorrhage, strokes of varying aetiologies, seizures, headache and sudden death are all relatively common associations of cocaine abuse. This review summarises the relevant literature in relation to cerebrovascular effects of cocaine, and makes recommendations on important areas of management.

METHODOLOGY
A medical literature search was carried out using Medline (1966 to 2003), in both Ovid and Pubmed versions, and Internet search engines, using the keywords below. Papers were identified and evaluated, and further references were drawn from hand-searches of their bibliographies. Key words used were: cocaine, crack cocaine, cocaine-related disorders, toxicity, drug toxicity, overdose, cerebrovascular accident, and cerebrovascular disorders.

HISTORY, TYPES & PATTERNS OF USE
Cocaine, or benzoylmethylecgonine, is an alkaloid derived from the leaves of the coca plant, Erythroxylon coca. It acts as a local anaesthetic with sympathomimetic and vasoconstrictor properties and has been widely abused as a mental stimulant. The Indians of Peru, Bolivia and Colombia have traditionally chewed coca mixed with lime for 2000 years, to reduce fatigue and hunger and to enable sustained periods of heavy labour. Coca Cola, and tonic drinks such as Vin Mariani, contained cocaine until 1903. Thirty years after the isolation of alkaloidal cocaine by the German chemist Gaedke in 1855, Sigmund Freud praised the use of cocaine as a central nervous system stimulant. The Harrison Narcotics Act of 1914 finally forbade its inclusion in proprietary medicines and restricted its use to prescription only. Cocaine was little used until the 1960s when its popularity underwent a resurgence, along with other illicit drugs. The common route of use at this time was sniffing or snorting the hydrochloride salt. This period peaked in the
early 1980s, with the National Household Survey on Drug Abuse reporting that, in 1982, more than twenty million Americans had tried cocaine, with half of these reporting use in the preceding year. In the mid 1980s, crack cocaine was introduced, which coincided with the start of epidemic abuse of huge doses.

Cocaine, C_{17}H_{21}NO_{4}, is imported into Europe and the USA as the hydrochloride salt, a white, water-soluble powder prepared by dissolving the alkaloid in hydrochloric acid. Alkaloidal cocaine is a colourless, odourless, crystalline, almost water-insoluble substance. Treating the hydrochloride salt with ammonia or sodium bicarbonate and then heating the mixture gives “crack” cocaine, named for the distinctive popping noise made by the crystals on heating. Dissolving the hydrochloride salt in water and ammonia, extracting into ether and then heating off this organic phase gives “freebase” cocaine. The production of this is predictably dangerous, with the associated fire and explosion risks, and so crack cocaine is today the most commonly produced. Both of these are volatile, very pure forms of cocaine that are usually smoked.

Cocaine, in its various forms, may be inhaled, ingested, smoked or injected, either subcutaneously, intramuscularly or intravenously. It is commonly used by polydrug users coincidentally with heroin injection & alcohol drinking which may be important in its toxicity. A 1994 study interviewing subjects in south London, using a Privileged Access Interviewer technique, found that 32% of regular users took cocaine intranasally, 40% smoked cocaine and 24% injected the drug. In 1993 in the USA, an NHSDA report indicated that 77% of users snorted, 36% smoked and 7% injected.

The route of administration has implications for both the likely demographic profile of the user, and the pathological effects. Injecting users are more likely to be older, white and male, whereas smoking and snorting abusers are more likely to be younger, black, and with a more equal male to female ratio. Evidence also suggests those smoking and injecting show greater abuse liability and greater propensity for dependence. Individuals are occasionally seen demonstrating pathological effects after “body packing” or “body stuffing”. Body packers are drug couriers who smuggle large amounts of the drug in their gastrointestinal tract, up to 460g, in supposedly sealed containers such as condoms, balloons or plastic bags. Body stuffers are usually users who hurriedly swallow various quantities of cocaine because of fear of police apprehension. These amounts tend to be flimsily wrapped and are very likely to lead to symptoms.

PHARMACODYNAMICS

LOCAL ANAESTHETIC EFFECTS
Like other local anaesthetic compounds, cocaine slows or disrupts sensory neural impulse transmission by inhibition of the voltage gated fast sodium channels. Similar mechanisms allow cocaine to affect the cardiac action potential, slowing conduction and impairing contractility.

NEUROTRANSMITTER EFFECTS
Cocaine has a sympathomimetic effect, blocking presynaptic neuronal uptake of catecholamines, and thus inhibiting the primary clearance mechanisms from the synaptic clefts. In the brain, the dopamine receptor appears to be a specific binding site for cocaine. Once again, its actions appear to be mediated by blockade of the receptor, preventing reuptake and leading to elevated dopamine concentrations. This has been suggested to be an important element in the reward mechanisms in cocaine abuse as it partly occurs in axons leading from the brainstem to the limbic system, the area responsible for emotional behaviour and pleasure perception. Cocaine transiently increases the amount of dopamine available by this reuptake inhibition, but this is followed shortly afterward by depletion of dopamine to below normal levels that may explain the craving following use. Serotonin levels in the brain are also thought to be affected by cocaine, preventing its synthesis from tryptophan, and increasing the actions of the hydroxylase that breaks it down. Serotonin is involved in sleep, appetite and mood regulation.

Figure 1
Figure 1: Blockade of presynaptic reuptake of dopamine by cocaine

PHARMACOKINETICS / ROUTES OF INGESTION

ABSORPTION / ADMINISTRATION
The onset and duration of effect of cocaine are dependent on the method of intake.
Orally ingested cocaine has a bioavailability of 30 – 40% and a relatively slow onset of action of approximately 15 minutes. Subcutaneous or intramuscular injection is not favoured today as the vasoconstrictor effect of the drug prevents a rapid effect. Intravenous injection is favoured by some groups, as mentioned earlier, and produces an intense euphoria in 1 – 2 minutes, after the injection of approximately 15mg. Intranasal cocaine use generally produces euphoria in 3 – 5 minutes, after the inhalation of 20 – 30 mg. The use of crack cocaine involves the heating of 50 – 120mg of the freebase in a water pipe or modified tin can, and inhalation of the smoke. Because of the rapid absorption in the extensive pulmonary vascular bed, crack produces an intense high in approximately 8 seconds. An addict may repeat this process every 5 – 10 minutes, consuming up to 150g of cocaine in a 72 hr period.

ELIMINATION
Cocaine is rapidly cleared from the bloodstream in humans, with a half-life of approximately 40 minutes. It is cleared by two, or occasionally three, separate mechanisms;

SPONTANEOUS HYDROLYSIS
This process converts cocaine, benzoylmethylecgonine, into benzoylecgonine.

ENZYMATIC HYDROLYSIS
This process utilises plasma pseudocholinesterase to convert benzoylmethylecgonine into ecgonine methyl ester.

ALCOHOL
A third metabolic pathway becomes important when cocaine is taken with alcohol. Ethanol and benzoylmethylecgonine are transesterified in the liver to produce cocaethylene. This is found in high concentrations in the blood, brain and liver, and is as powerful a dopamine receptor blocker as cocaine itself, but has a longer half-life so that the effect of repeated doses may have a cumulative effect.

CEREBROVASCULAR EFFECTS OF COCAINE
The evidence for the cerebrovascular effects of cocaine is derived mainly from multiple case series. Although causation may not be inferred from these types of studies, significant and important associations may be as follows:

- Subarachnoid Haemorrhage
- Haemorrhagic Cerebrovascular Accident
- Ischaemic Cerebrovascular Accident
- Transient Ischaemic Attack
- Seizures
- Headaches
- Subarachnoid Haemorrhage

There have been multiple case reports of subarachnoid haemorrhage (SAH) associated with cocaine abuse. The presentation typically consists of a severe headache starting usually several minutes, but occasionally up to a few hours, after cocaine use. Most cases, up to 70% in one series, have been found to be due to a pre-existing vascular malformation, such as a berry aneurysm of the Circle of Willis. Patients are often young, one series reporting a mean age of 26 years old at admission. There is often an association with alcohol abuse, but the precise mechanisms remain unknown. In animals, cocaine is known to potentiate both the blood pressure and cerebral blood flow in response to norepinephrine and also in response to head trauma. A dose dependent elevation of arterial blood pressure has been reported in humans and animals. Fessler et al, in 1997, compiled a large case series of 65 patients suffering from SAH. They concluded that cocaine use is a risk factor for early rupture of intracerebral aneurysms. They suggested that the mechanism probably involves prolonged periods of marked hypertension. These changes in blood pressure would be transmitted essentially unchanged to the structurally abnormal, inelastic and nondistensible saccular aneurysm wall, causing up to ten times as much wall stress as in the cerebral arteries. Kiyabashi et al prospectively studied autopsy data in 52 patients who died of intracerebral haemorrhage secondary to cocaine abuse, 26 of whom had cerebral aneurysm rupture and 26 who did not. They found the group without the aneurysms showed more evidence of cerebrovascular changes associated with increased blood pressure, leading them to consider changes in cerebral autoregulation as important. Above the upper limit of autoregulation, forced dilatation of blood vessels occurs, and blood flow increases with consequent risk to vessel walls and any defects within them. The upper limit of autoregulation is not a fixed point, and cocaine shifts this upper limit downwards towards lower blood pressure levels, leading to increased flow at these pressures. Animal studies administering cocaine to rats found a focal 200 – 400% increase in blood flow below the normal limit of autoregulation. Also, dopamine is known to lower the upper limit of autoregulation.
HAEMORRHAGIC CEREBROVASCULAR ACCIDENT

Many cases of haemorrhagic cerebrovascular accident (HCVA) have been reported to be associated with cocaine abuse forming the largest proportion of pathological mechanisms, in some studies up to 54%. 71% of CVA's temporally associated with cocaine abuse in an early study were due to haemorrhage. In their case series Fessler et al reported 29 cocaine related HCVA patients with a mean age of 39.2 years, in contrast to earlier series quoting a mean age of 34 years. They suggested that the mechanisms underlying HCVA's are probably similar to those underlying ischaemic cerebrovascular accidents (ICVA) in many instances.

ISCHAEMIC CEREBROVASCULAR ACCIDENT

ICVA's are described in multiple case series in a proportion varying from 21.2% to 46%. The mechanism of ischaemic change following cocaine abuse is complex and multifactorial. Cocaine induces vasospasm and potential ischaemia by several pathways:

- Direct calcium mediated smooth muscle contraction in the arterial walls.
- Augmentation of the physiological effects of catecholamines.
- Autoregulatory vasoconstriction secondary to acute hypertension.
- Augmentation of autoregulatory vasoconstriction secondary to a decrease in cerebral metabolism.

These pathophysiological changes lead to ischaemia with subsequent haemorrhage following reperfusion of the affected tissues. Cocaine is often consumed concurrent with alcohol; itself an independent risk factor for stroke, and the result of the transesterification process, cocaethylene, produces an additive effect of both drugs. A study of single cocaine exposure in humans showed that an increase in blood pressure occurred within 2 minutes of administration, which peaked within 5 – 10 minutes when administered intravenously, and in 15 – 20 minutes when given intranasally. The effects lasted longer than 30 minutes. Injecting or snorting cocaine involves repeated doses over several hours, which results in higher, more sustained concentrations than would occur with a single exposure. As mentioned earlier, crack smoking also leads to very high levels of drug intake over a period of time. Although it remains to be studied further, it is possible that there may be an increased effect on arterial blood pressure with repeated doses of cocaine. Finally, it has been shown that there is impaired endothelium-dependent relaxation in cocaine arteriopathy, and also accelerated atherosclerotic changes in these vessels.

TRANSIENT ISCHAEMIC ATTACK

Cases have been reported of Transient Ischaemic Attacks (TIA's) in the middle cerebral and vertebrobasilar arterial territories, with resolution of neurological signs and symptoms by the time of examination. Vasospasm has been assumed to be the likely pathological mechanism.

SEIZURES

Cocaine induced seizures are one of the earliest recognised neurological complications of cocaine abuse, first reported in the 1920's. Seizures are thought to be the most lethal of these complications and have been commonly reported to be a pre-terminal event, especially in large overdoses in body packers. The proportion of seizures has been reported to be between 0.6 – 7.9% of emergency department presentations for cocaine toxicity. A large retrospective case note review studied the types, risk factors and confounding variables in 474 patients treated for acute cocaine associated complications. They defined cocaine-related seizures as those occurring up to 90 minutes from the ingestion of the drug. All patients had a positive urine toxicology screen for cocaine. They found that of patients with no prior history of seizures of any aetiology, seizures were single, generalised, induced by crack or intravenous cocaine, and were not associated with any long lasting neurological deficits. Of patients with a prior history of non-cocaine related seizures, most presented with multiple seizures, of the same type as those in their history, and induced even by nasal cocaine. Patients with a history of prior seizures had twice the frequency of seizures related to cocaine than those without such a history. Animal research has shown that seizures are associated with significantly elevated rectal temperatures, lactic acidosis and hypertension. Hyperthermia was the most important contributor to death in this group. Partial seizures may often be misdiagnosed as agitation, delirium or psychosis. Seizures are usually well controlled with Diazepam. Phenytoin may not be effective against cocaine-induced seizures.

HEADACHES

Severe headaches have been associated with cocaine use and they may provide a diagnostic dilemma. Early severe headaches occur in 50% of patients with cocaine related
stroke, and 18% of these have seizures. Cases have been reported of migraine-like headaches attributable to the after effects of cocaine bingeing. These headaches subsided immediately with the readministration of cocaine, but were sufficiently aversive to motivate quitting the use of the drug. The authors highlighted the effects of cocaine in first increasing and then decreasing the levels of serotonin, a potent vasoactive neurotransmitter. The resolution of the headache with further cocaine was consistent with the rapid response of migraine to serotonin enhancing agents like ergot.

DISCUSSION
The prevalence of cocaine use among young people is increasing in the United States and the United Kingdom. The potential for serious and severe pathological effects of cocaine use is large, and although the effects may be more likely with prolonged or cumulative use, some have been reported after a single episode.

In one of the quoted studies, 9 out of 33 patients died, of whom 78% presented with SAH. Put differently, 44% of patients presenting with cocaine related SAH died. SAH appears to have a higher mortality when associated with cocaine use, and appears to present at a younger age and with smaller aneurysms. Although severe elevations in blood pressure have been implicated in these and other cerebrovascular manifestations of cocaine abuse, only 1 of 55 patients were hypertensive on admission to the emergency department.

By 1993, a total of over 300 cocaine related strokes had been reported, 50% HCVA and 50% ICVA. Of the HCVA patients, approximately 50% were due to underlying aneurysms or vascular malformations. Although patients with a HCVA or ICVA appear to have a better prognosis than those presenting with SAH, in the USA more than 10 000 people under the age of 44 suffer a stroke each year. 25% of these patients die during their initial hospitalisation, and many of the survivors suffer permanent neurological handicaps. Levine et al noted a strong temporal association between use of alkaloidal or crack cocaine and both ischaemic and haemorrhagic events. They also remarked that crack cocaine abuse was reported to be associated with ICVA’s and HCVA’s in equal frequency, but cocaine hydrochloride abuse was more often (approximately 80% of reports) associated with HCVA’s. The relative risk for stroke in drug abusers was 6.5 in one study, increasing to 50 for patients whose symptoms began within 6 hours of drug administration.

Seizures have been reported to make up almost 10% of cocaine related admissions to emergency departments, and patients with prior seizure history, poor compliance with antiepileptic medication, poor diet, poor sleep habits, and alcohol abuse are at greater risk. Authors have identified that the incidence of seizures due to cocaine may be higher than estimated, and that there exist likely limitations to history taking from drug users or friends, with medical attention seeking behaviour probably proving an important factor.

Early severe headaches occur in half of patients with cocaine related stroke, and almost a fifth of these have seizures. Cases have been also reported of migraine-like headaches.

Cocaine, in various forms, has been reported to contain a plethora of adulterants. These include local anaesthetics such as lidocaine, sugars, stimulants such as amphetamine, toxins such as strychnine and quinine, and inert compounds such as talc and cornstarch. All of these, especially the toxins and stimulants, may have multiple side-effects of their own, many of them possibly lethal.

Acute cocaine abuse is an increasing problem in the United Kingdom. Awareness of the problem is essential as patients will often not volunteer information, and presentations may not be attributed to cocaine without clinical suspicion. Aggressive resuscitation following early diagnosis is essential in preventing death. Using a prioritised ABCDE system of assessment and treatment gives the best chance of detecting life-threatening illness. Activated charcoal actively adsorbs cocaine, and is therefore an important element of early treatment.

MANAGEMENT
- A high index of suspicion must be maintained, especially in young people with any neurological presentation.
- A careful history, including a full candid drug history, must be taken in all circumstances.
- A full examination, looking for signs of neurological or cardiovascular involvement should be performed.
- Assessment and treatment of patients using an ABCDE structured approach will ensure minimum likelihood of life-threatening conditions being missed on examination, and minimise the
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occurrence of secondary insult or injury.

- Investigation of collapsed patients should include:
  - Diagnostic electrocardiogram
  - Arterial blood gases, searching for metabolic acidosis
  - Bedside blood glucose
  - Rectal temperature

- Ventilatory support with correction of acidosis are key elements of management.

- Administration of activated charcoal

- Seizures and hypertension should be controlled with Diazepam.

- A low threshold must be maintained for computed tomography scanning of patients with any neurological complaints.

There is no clear evidence of benefit in undertaking a urine toxicology screen in these circumstances. Urine toxicology screens measure benzoylecgonine, which may show positive results for up to 30 – 40 hours, and although the main metabolites of cocaine, benzoylecgonine and ecgonine methyl ester are excreted primarily unchanged in the urine, with average half-lives of 7.5 and 3.6 hours respectively, the emergency treatment of a collapse due to cocaine is likely to be unchanged by a positive result.

CONCLUSION

Cocaine abuse is a growing problem in the UK, and the manifestations of overdose and toxicity are many. The cerebrovascular effects in particular may be seen in unexpected groups of patients, particularly the young. Misdiagnoses are very possible, especially an accurate history may not be forthcoming, and cocaine toxicity may masquerade as other common presentations, including grand mal convulsions, collapse and psychiatric disturbance. Simple management principles coupled to a high index of suspicion, are efficacious in the assessment and treatment of cocaine toxicity.

References

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