

Current Concepts of Cerebrovascular Disease

Cocaine and Stroke

Steven R. Levine, MD, and K.M.A. Welch, MD

Drug abuse is a major social and medical problem and has become a significant cause of stroke, especially in young adults.¹ Cocaine is already a commonly used drug, and its new form, "crack," has an enhanced risk of cerebrovascular complications. Because cocaine is now used in nearly epidemic proportions throughout the United States² and because crack is a high-potency, essentially pure form of cocaine, it is timely to review the known consequences of this drug on the cerebral and cardiac vasculature.

Background

Cocaine, or benzoylmethylecgonine, is derived from the leaves of the *Erythroxylum coca* plant, which is found primarily in the eastern mountains of Peru, Ecuador, and Bolivia. Street cocaine or the noncrack form is highly variable in purity, often "cut" with various agents.³

Crack cocaine is often made by mixing an aqueous solution of the drug with ammonia with or without baking soda.⁴ Sodium bicarbonate, heat, and water extracts crack from the cocaine powder as well.² This chemical reaction converts the cocaine hydrochloride to a volatile form of the drug, almost pure cocaine. Free-based cocaine (the basic cocaine alkaloid) is inhaled or smoked after the cocaine is mixed in the alkaline solution and precipitated as alkaloidal cocaine. This process provides a more rapid, intense euphoria as a result of higher blood concentrations. When smoked as free-base, cocaine is rapidly absorbed into the pulmonary circulation and is transmitted to the brain in <10 seconds.⁵ Cocaine in the blood is rapidly hydrolyzed to benzoylecgonine⁶ and may be present in the urine of an adult for up to 27 hours after intranasal use⁷ or up to 36 hours depending on the route of administration and the cholinesterase activity.⁸ The presence of cocaine metabolites can be accurately documented in the urine.⁹

Five million Americans use cocaine regularly,^{8,10} and an additional 5,000 daily try it for the first time. Reasons for the increased use of the drug include the currently lower prices, increased availability, improved purity, and the erroneous belief in its nonaddicting nature.

Cocaine-related deaths have risen steadily in recent years. Crack cocaine use has been associated with a greater incidence of overdose and medical and neuro-

logical complications, including death.^{8,11} Dealers of cocaine prefer to sell crack instead of the powder (cocaine hydrochloride) because of the former's higher addiction potential, low unit cost, and ease of handling.² Each "rock" of crack weighs approximately 100 mg and sells for \$5–10 on the street. In Detroit, "crack houses" supply vast amounts of the drug. Routes of administering cocaine include oral, vaginal, sublingual, rectal, and intranasal (snorting) and by smoking (inhaled free-base) and subcutaneous, intramuscular, or intravenous injection.⁸

Cardiovascular effects begin soon after cocaine use and include increased blood pressure, heart rate, body temperature, and metabolic rate.¹² The acute effects usually subside 20–30 minutes after intravenous administration or 45–60 minutes after nasal use.¹³ The peak effect of cocaine, based on experimental kinetic measurements, occurs 7.3 minutes after an intravenous bolus of cocaine.¹⁴

Pitts et al¹⁵ demonstrated a rapid, dose-dependent increase in mean arterial pressure of relatively short duration in rats given intravenous cocaine. Phentolamine (an α -adrenoreceptor antagonist) was able to antagonize the cardiovascular effects of cocaine at a dose previously shown to block centrally evoked increases in sympathetic tone. This finding suggests that the pressor effect of cocaine is probably mediated through a peripheral catecholaminergic mechanism.

The spectrum of cocaine-associated ischemia includes myocardial,^{12,16–24} renal,²⁵ intestinal,²⁶ and cerebral vasculature.^{27–33}

Cerebrovascular Complications

Table 1 summarizes the reported cerebrovascular complications associated with cocaine use. In 12 of the 13 patients, cocaine was either snorted or smoked as crack. In one patient the route was intramuscular. Ages of the 12 patients ranged from newborn (perinatal infarction) to 48 years. The six patients with bleeds (intracerebral or subarachnoid)^{1,33–35} were younger (mean 26 years, range 22–30 years) than the patients with ischemic complications (mean 34 years, range 25–48 years, excluding the newborn). Four of six with hemorrhage had underlying cerebral aneurysm or arteriovenous malformation (AVM), including all three women. This finding suggests that patients with AVM or aneurysms may be at increased risk of cerebral hemorrhage after cocaine use. Six other patients with intracranial hemorrhage associated with cocaine have been reported.^{36,37} Alcohol was also used in five cases, three ischemic and two hemorrhagic (both with un-

From the Department of Neurology, Henry Ford Hospital, Detroit, Michigan.

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TABLE 1. Reported Cases of Cocaine-Associated Cerebrovascular Complications

Reference	Age	Sex	Vascular location	Method of cocaine use	Time to onset of symptoms	Other drugs
<i>Ischemic</i>						
Levine et al ²⁷	27	M	Cortical	Smoked crack	During	None
Levine et al ²⁷	25	M	Vertebrobasilar	Smoked crack	During	Alcohol
Levine et al ²⁷	48	M	Vertebrobasilar	Smoked crack	During, hours later	None
Brust and Richter ²⁸	43	M	Cortical	Intramuscular	Hours	Alcohol, methadone, ?ex-heroin addict
Schwartz and Cohen ³³	32	M	Cortical	Snorting	1 day	?
Chasnoff et al ²⁹	New-born	M	Cortical	Maternal snorting	15 hours before birth	Nicotine
Golbe and Merkin ³⁰	27	M	Cortical	Smoked crack	Unclear	Alcohol, nicotine, ibuprofen, ex-heroin addict
<i>Hemorrhage</i>						
Schwartz and Cohen ³³	23	F	Subarachnoid	Snorting	During	Alcohol
Schwartz and Cohen ³³	30	M	Intracerebral	Snorting	?	?
Lichtenfeld et al ³⁴	29	F	Subarachnoid	Snorting	Minutes	?
Lichtenfeld et al ³⁴	24	F	Intracerebral with subarachnoid extension	Snorting	5-10 minutes	?
Caplan et al ¹	22	M	Intracerebral	Snorting	30 minutes	?
Lundberg et al ³⁵	28	M	Subarachnoid	Snorting	During	Alcohol, hashish

Abbreviations: HTN, hypertension; MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery; SAH, subarachnoid hemorrhage; PCoA, posterior communicating artery; ACoA, anterior communicating artery; AVM, arteriovenous malformation; SCA, superior cerebellar artery; ?, unknown, not reported, not performed.

derlying aneurysms). Five of the seven ischemic events were cortical in the territory of the middle cerebral artery, and two were in the vertebrobasilar circulation. Vasculitis was not specifically identified on any of the arteriograms.

In 1977, Brust and Richter²⁸ reported the first patient with the possible association of cocaine with ischemic stroke. A 43-year-old hypertensive ex-heroin addict who had used cocaine occasionally for several years developed right-sided weakness and difficulty speaking 1-2 hours after his usual intramuscular cocaine dose and ingestion of alcohol. Clinically, the location of the stroke was probably cortical in the territory of left middle cerebral artery branches. Hypergammaglobulinemia was also present, raising the possibility of a drug-induced autoimmune reaction.

Schwartz and Cohen³³ briefly mentioned three patients with cerebrovascular syndromes associated with cocaine inhalation. Two had stroke due to aneurysmal subarachnoid or intracerebral hemorrhage. The other, a 32-year-old nonhypertensive man, developed a computed tomography (CT)-proven right temporal occipital ischemic infarct 1 day after cocaine use. Angiography showed a posterior cerebral artery occlusion and

narrowed ipsilateral anterior and middle cerebral arteries.

Chasnoff et al²⁹ reported a newborn male baby that developed a left cerebral hemisphere infarct within 24 hours of birth to a cocaine-abusing mother. The last dose of cocaine (1 g) was taken during the 15 hours before delivery. Cocaine metabolites were found in the baby's urine.

There have been two patients with ischemic stroke due to angiographically proven internal carotid artery occlusion in conjunction with cocaine use (W. Anderson, Stroke Service, Emmanuel Hospital, Portland, Oregon; personal communication). Rogers et al³⁷ reported a 34-year-old woman who died of a ruptured berry aneurysm and had an autopsy blood cocaine metabolite concentration of 420 ng/ml.

Golbe and Merkin³⁰ recently reported a 27-year-old man with ischemic stroke who had used free-based cocaine. A right middle cerebral artery territory infarct developed after using two vials of crack and a large amount of alcohol and ibuprofen.

Ischemic stroke was associated with crack cocaine use in several of our patients who had no other definite stroke risk factors.²⁷ All had acute onset of frontal headache while inhaling the drug followed either

TABLE 1. (Continued)

Other risk factors	Head CT scan	Angiogram
None	L temporoparietal infarct	Probable L angular branch occlusion with delayed filling
None	Normal	Refused
Hyperglycemia	Normal	Normal
HTN, mitral valve disease	?	Refused
?	R temporoparietal infarct	R PCA occlusion, narrowed R ACA and R MCA
Cyanotic episodes	L frontoparietal infarct	?
?thrombocytosis, ?mild hypertension	R MCA territory infarct	R supraclinoid ICA narrowing with distal branch occlusion (2 weeks after ictus)
?	SAH	L PCoA aneurysm
?	R temporoparietal bleed	No lesions seen
?	Normal	ACoA aneurysm
?	Deep R temporoparietal bleed	Large R hemisphere AVM
?	R parietal bleed	Normal
?	Autopsy	R SCA berry aneurysm

immediately or shortly thereafter by focal neurological deficits attributed to cerebrovascular disease. One had a documented left cerebral cortical ischemic infarction on CT. Cerebral angiography 48 hours after the stroke did not reveal vasculitis, AVM, or aneurysm but did show narrowing of the posterior cerebral artery and a distal branch occlusion in the middle cerebral artery territory. Amphetamine-like vascular beading was not seen, suggesting that the mechanisms of cocaine-induced angiographic abnormalities may be different.

Our other two patients had vertebrobasilar strokes. The angiogram in one was normal within 48 hours of the ictus, consistent with vasospasm. A 32-year-old woman was brought to the emergency room with severe dysphasia and right-sided weakness. No further history was obtainable. CT revealed infarction in the territory of the left anterior cerebral artery and middle cerebral artery (inferior trunk only). Complete urine toxicology revealed only cocaine metabolite. She died 72 hours later of progressive central herniation. Autopsy revealed a normal heart, narrowed anterior and middle cerebral arteries, and a hemorrhagic region within the anterior cerebral artery territory. The second patient was a 37-year-old woman who developed severe headache, photophobia, nuchal rigidity, and backache after free-basing cocaine. She had also used intravenous heroin 10 days before. Head CT and cerebral angiography were normal. Cerebrospinal fluid revealed

23 white blood cells (54% polymorphonucleocytes) and 121 red blood cells with normal protein, glucose, and immunological studies. She improved.

Cocaine-Induced Myocardial Ischemia and Infarction

Evidence relating cocaine to clinical ischemic heart disease continues to accumulate.^{12,16-24} Isner et al¹⁹ reported seven cases of cocaine-related cardiac events and reviewed the 19 previously reported cases. Two of their patients had pathological data. One had a normal myocardium and coronary arteries. The other, a 37-year-old man with a history of drug abuse, was found dead in bed. He was an insulin-dependent diabetic who had propoxyphene as well as cocaine metabolites in his urine. A fresh thrombus was present in the left anterior descending artery at a point narrowed 90% by atherosclerotic plaque. One other patient had an endomyocardial biopsy that revealed substantial numbers of eosinophils. This finding has been described in other drug-related vasculitides,³⁸ lending further support to a cocaine-induced hypersensitivity or inflammatory cause. Mathias¹² recently reviewed the clinical and angiographic features of 12 patients with cocaine-associated myocardial ischemia. All had taken cocaine nasally or intravenously. All but two coronary angiograms revealed arterial narrowing of one or more vessels. Half also smoked cigarettes, and three used intravenous heroin in addition to cocaine. Autopsy of one patient revealed thrombotic occlusion of the proximal left anterior descending artery.

Small amounts of inhaled cocaine may cause myocarditis as well as myocardial infarction and arrhythmia.²⁴ Histology has shown mononuclear cell infiltrates with myocyte necrosis. Both patients with cardiomyopathy had interstitial fibrosis, which appears to accompany chronic cocaine use. Early results of an unpublished study indicate that cocaine can cause coronary artery spasm in normal individuals, resulting in myocardial infarction.²⁴ Cardiovascular events seem to occur in people who use cocaine on at least a part-time basis. Angiography in one patient within 6 hours of admission for cocaine-related chest pain showed an intraluminal clot in the coronary artery without underlying coronary artery disease.

Rupture of the ascending aorta in the absence of Marfan's or similar conditions has also been described following cocaine use.³⁹

Potential Mechanisms of Stroke

Although cocaine is a known vasoconstrictor, it is not known whether the sympathomimetic action of cocaine is specifically responsible. Focal coronary arterial spasm could not be elicited with ergonovine maleate in any patient to date.¹²

Cocaine in vitro causes an enhanced response of platelets to arachidonic acid, leading to increased thromboxane production and platelet aggregation.⁴⁰ The two reported autopsy cases of cocaine-related acute myocardial ischemia support a platelet-thrombus mechanism.^{22,23} Simpson and Edwards²³ described a

21-year-old man with no coronary risk factors who had platelet thrombosis in the left main and proximal anterior descending arteries as well as unique non-atherosclerotic intimal proliferation of vascular smooth muscle cells. This proliferation alone caused significant obstruction of two coronary arteries.

In sheep, cocaine alters fetal oxygenation by reducing uterine blood flow and impairing oxygen transfer to the fetus.⁴¹ Direct cocaine administration to the fetus produces smaller increases in fetal heart rate and blood pressure than the dose-dependent effect observed after maternal cocaine injection. Uterine arterial vasoconstriction could lead to ischemic cerebral injury in the fetus.

Cocaine does not appear to have a direct neurotoxic action.⁴² "Street-drug" contaminants, such as procainamide, quinidine, amphetamines, phencyclidine, antihistamines, and strychnine, have cardiovascular effects³ that could contribute to the effects seen with cocaine. The presence or absence of these adulterants in cocaine may be documented with urine toxicology. The known pathophysiological effects of cocaine include vasoconstriction, local anesthesia, and central nervous system stimulation. The enhanced sympathetic activity accompanied by acute elevation of blood pressure following cocaine use could be a major factor contributing to the pathogenesis of stroke by causing cerebral vasoconstriction or vasospasm. This could be compounded by hypertensive opening of the blood-brain barrier,⁴³ causing circulating catecholamines to enter the brain parenchyma. Cocaine itself has been shown to decrease cerebral metabolism *in vivo*⁴⁴ and may thus secondarily decrease cerebral blood flow.

Alternatively, cocaine may potentiate neurotransmission of serotonin⁴⁵ by blocking its reuptake,^{46,47} thereby increasing synaptic levels of serotonin. Serotonin is one of the most potent vasoconstrictor amines in the cerebral circulation,⁴⁸ especially for large and medium-sized arteries.⁴⁹ Headache, common to our three cases and to cocaine users in general,^{50,51} raises the possibility of cocaine-induced complicated migraine. Perhaps relevant is the fact that disturbed sympathetic, serotonergic, and platelet function has been reported in migraine patients.⁵²

The long-term prognosis of patients with cerebral or myocardial ischemia associated with cocaine use is unknown, primarily because of the lack of data. Isolated case reports in the cardiology literature suggest that continued abuse is associated with recurrent events despite maximal medical therapy. Abstinence carries an excellent prognosis.

Although the exact mechanisms of cocaine-related stroke remain uncertain, crack cocaine may contribute to ischemic cerebral infarction in both the anterior and posterior circulation in the absence of known stroke risk factors. Cerebral hemorrhage from cocaine has been recognized for some time. Whatever the mechanism, crack cocaine is a new and increasingly prevalent cause of cerebral ischemia. Physicians as well as cocaine users should be alerted to this possibility.

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