
01 Jan 1982

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Recommended Citation

L. R. Caplan et al., "Current Concepts of Cerebrovascular Disease - Stroke: Stroke and Drug Abuse," *Stroke*, vol. 13, no. 6, pp. 869 - 872, Lippincott, Williams & Wilkins; American Heart Association, Jan 1982. The definitive version is available at <https://doi.org/10.1161/01.STR.13.6.869>

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Current Concepts of Cerebrovascular Disease — Stroke

Current Concepts of Cerebrovascular Disease — Stroke: Stroke and Drug Abuse

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DRUG abuse is a very serious problem. Because of man's search for new and different ways of inducing pleasurable feelings, the number of available pharmaceuticals has grown exponentially during the last few decades, as has societal use and dependence on medicines. Clearly, increased use has led to frequent abuse. Physicians should be aware of the many facets of drug abuse. It is now clear that drug abuse is a significant cause of stroke, especially in young adults and adolescents.

Addicts frequently abuse more than one substance. Furthermore, the drugs are mixed with a variety of different diluents and usually injected without sterile precautions. Drugs may be taken orally, inhaled nasally, or injected subcutaneously or intravenously. Drug abusers do not always honestly report the details of their usage, and they do not always appear for follow-up evaluations. As a result it is difficult to assess the role of an individual agent or adulterant and to determine the effect of dosage, foreign body or infectious contamination, avenue of entry, or incidence of long-term sequelae. Neurologists have only recently been active in the clinical or laboratory study of drug abuse so that information on neurological complications of many of the drugs used is fragmentary and incomplete. This review will summarize available information concerning cerebral vascular complications of the most commonly abused substances (Table 1) and discuss possible mechanisms of vascular injury and cerebral damage. Although alcohol is frequently abused and may have important cerebrovascular effects, its consideration is beyond the scope of this review.

Abused Drugs

Heroin. Often diluted with a variety of adulterants, including talcum, starch, curry powder, Vim, Ajax, caffeine ("Chinese heroin"), strychnine, mannitol, quinine, or lactose, heroin is injected subcutaneously (skin popping) or intravenously. Nine patients have been reported in detail in the literature whose stroke was directly attributable to the use of heroin. All had injected the drug intravenously. In each case the stroke was due to cerebral infarction. In four patients unre-

sponsiveness directly followed the heroin injection, and the patients entered the hospital with severe cerebral hemispherical defects (right hemiplegia and aphasia or left hemiparesis with neglect).¹ In the other patients focal deficits followed intravenous use immediately or six² to twenty-four³ hours later. Choreiform movements have occasionally been observed at onset but subsequently have improved. Arteriography in several patients demonstrated narrowing of the internal carotid artery at the siphon^{1,2} and poor opacification or beading of smaller intracranial arteries, which was called "arteritis" by the authors. The strokes have usually left significant residues, but most reported patients who stopped heroin abuse suffered no subsequent strokes. At times the injection which led to the stroke had followed a period of abstinence from heroin. In some patients the stroke was preceded by a general sense of feeling ill or nausea. Laboratory findings have included eosinophilia,² hypergammaglobulinemia, and positive latex fixation tests. Heroin abuse can also lead to infective endocarditis with the cerebrovascular complications of embolization and subarachnoid hemorrhage due to rupture of a mycotic aneurysm. One patient with abuse presumably limited to heroin had a documented intracerebral hemorrhage¹ but that patient also had azotemia and severe hypertension, and the hemorrhage was not known to follow injection. On postmortem evaluation of 96 heroin addicts dying of overdose,⁴ five had small cystic infarcts in the globus pallidus.

Amphetamines. In contrast to heroin, amphetamines are often taken orally as well as by injection. These drugs, most often in the form of methamphetamine, may cause intracerebral or subarachnoid hemorrhage.^{5,6} Approximately half of the reported cases have followed oral use, the remainder following intravenous injection. Headache, confusion, and seizures occur within minutes of drug use. In some patients, despite large lateralized intracerebral hemorrhages, there are surprisingly few focal signs, a phenomenon explained by edema, infarction, and diffuse vasculopathy found in nonhemorrhagic brain regions. Some patients have had severe transient hypertension, but when first examined, most have no obvious signs of sympathetic overactivity such as hypertension, tachycardia, or fever. Citron⁷ studied 14 polydrug abusers, almost all admitting to methamphetamine use, and found fibrinoid necrosis of the media and intima of medium-sized and small arteries in the brain and viscera. Elastic arteries, veins, and capillaries were spared. The perivascular regions had infiltrates of neutrophils, lymphocytes, and eosinophils; involved ves-

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TABLE 1 *Relative Incidence of Documented Cerebrovascular Complications of Abused Drugs**

Drug	Intracerebral hemorrhage	Subarachnoid hemorrhage	Emboli	Ischemic stroke	Hypertension
Heroin	—	—	—	+	—
Amphetamines	+++	+++	—	—	++
T's & Blues	++	—	+++	+	—
Cocaine	+	—	—	—	++
Methylphenidate	—	—	+++	—	+
LSD	—	—	—	+	+
PCP	+	—	—	—	++

*Not including complications of endocarditis.

sels were often thrombosed or had local bulging regions producing a nodose-like appearance. Rumbaugh and colleagues⁸ analyzed the angiographic features of a group of methamphetamine abusers and described beaded arteries, segmental changes in vessel caliber, and regions of slow flow. In monkeys given intravenous methamphetamine for two weeks,⁹ angiography showed similar beading and segmental changes, and necropsy revealed small cerebral hemorrhages, zones of infarction, and microaneurysms. In a single patient with subarachnoid hemorrhage after oral dextroamphetamine and methylphenidate abuse, beading of arterial branches was no longer apparent on angiograms repeated after a three-week course of prednisone.¹⁰ We are unaware of a well-studied patient presenting with a purely ischemic stroke after amphetamine use, but ischemic damage has been documented pathologically. Recent information indicates that the use of amphetamines is declining rapidly, perhaps because of its known serious complications.

T's & Blues. Talwin and pyribenzamine (T's & Blues) are tablets made for oral use but often injected intravenously after being crushed, suspended in water, and filtered through a cigarette filter or cotton. Two users developed cerebral infarctions: one patient had a seizure directly after injecting T's & Blue and was hemiplegic when he awakened from the seizure, and one patient awakened from sleep with hemiplegia after injecting the previous night.¹¹ Cerebral infarcts were small and deep and produced a clinical picture of pure motor hemiplegia. Two other T's & Blues addicts developed intracerebral hemorrhage.¹¹ In one patient with hemorrhage, angiography revealed occlusion of small middle cerebral branches, beading of arteries, and extravasation of contrast. Brain tissue contained regions of infarction, hemorrhage, and perivascular lymphocytic pleocytosis. Lung tissue in this and other series¹¹ has shown severe granulomatous reaction to microcrystalline cellulose or magnesium silicate (talc). Cerebral vessels may also contain birefringent foreign material which represents filler material used in the pills. Endocarditis and cerebral infection may also complicate the use of T's & Blues. These drugs are inexpensive and readily available and can give a high similar to heroin. They are now in wide use in Chicago and New Orleans and will probably spread further throughout the United States.

Other Drugs. Information concerning neurological or cerebrovascular complications of abuse of other substances is even more fragmentary. *Methylphenidate* (Ritalin) tablets are taken orally and occasionally injected intravenously. A young woman developed dyspnea and generalized weakness immediately after injecting methylphenidate into a neck vein.¹² In this patient quadriplegia and paralysis of the lower cranial nerves were shown at necropsy to be caused by bilateral medullary infarction in the distribution of the anterior spinal arteries, branches of which were occluded by foreign body emboli detected by polarizing microscopy. The lungs, liver, spleen, and kidneys also contained foreign body granulomas. Methylphenidate is made with native magnesium silicate, cornstarch, and some gum residues. In one series¹³ 17 methylphenidate abusers had retinopathy due to talc and cornstarch emboli visible on ophthalmological examination. Probable intracarotid injection of methylphenidate (missing the intended jugular vein)¹⁴ led to transient hemiparesis on two occasions in one other abuser. Others have reported subcutaneous foreign body nodules and abscesses and visceral granulomas in methylphenidate abusers.

Cocaine may be inhaled or injected subcutaneously, intramuscularly, or intravenously. One addict developed a hemiparesis one to two hours after intramuscular cocaine injection,¹⁵ and transient severe hypertension (BP 180/130) was documented. Cocaine prevents the uptake of sympathomimetic neurotransmitters and may sensitize to epinephrine and norepinephrine. Also cocaine may be "cut" with amphetamines. Both explanations have been offered for occasional hypertensive crises seen after the use of cocaine. We have examined a 22-year-old man who developed a right parietal lobe hemorrhage 30 minutes after snorting cocaine. He was only transiently hypertensive. A cerebral angiogram was normal.

Phencyclidine (PCP), often called angel dust, can be taken orally, inhaled nasally, or injected intravenously. It is often given to the unsuspecting teenager as "acid" loosely concealed or mixed with other agents. Phencyclidine use also has been shown to lead occasionally to hypertensive encephalopathy.^{16, 17}

A single report describes a 14-year-old boy who suffered a hemiplegia after ingestion of four tablets of *lysergic acid diethylamide* (LSD).¹⁸ Narrowing of the

internal carotid artery at the siphon was attributed to the vasospastic effect of this ergotamine derivative.

The evidence seems clear that a variety of different drugs or combinations can cause stroke. Furthermore, stroke types range from ischemic lesions to subarachnoid and intracerebral hemorrhages. Because of poly-drug abuse and the frequent lack of clear historical data, it is often impossible to identify the offending agent.

Mechanisms of Vascular Injury

Let us now turn to a discussion of possible unifying themes or causes of vascular damage and examine the evidence for each. Possible mechanisms include (1) endocarditis with secondary central nervous system vessel changes, (2) direct toxic injury to vessels, (3) embolization of foreign material, (4) pharmacological alteration of vascular function, and (5) immunogenic vascular injury — "vasculitis."

Endocarditis. The pathology and clinical features of central nervous system vascular changes in endocarditis are well known and have been reviewed elsewhere.^{19, 20} In narcotic addicts the organisms are often coagulase positive *Staphylococcus aureus* or fungi; the tricuspid valve is frequently involved, and usually there is no underlying congenital or rheumatic valvular disease.¹⁹ Mortality is high.^{19, 20}

Direct Toxic Injury. Direct toxic injury to blood vessels is not likely to be a common mechanism of stroke in drug abusers. Cerebral vascular lesions are relatively rare considering the frequency of injection and can be caused by diverse agents. Furthermore, by the time the drug reaches the cerebral vessels, it would be considerably diluted. A severe reaction in the injected veins and a diffuse systemic vascular response would be expected and would be dose related if a direct toxic effect were present. Since this mechanism is unlikely and the vascular changes of endocarditis are well known, we will not consider these issues in further detail.

Embolization of Foreign Matter. Most of the drug substances injected by abusers contain contaminants in the form of particulate foreign matter. In one patient after methylphenidate injection¹² and in one T's & Blues addict,¹¹ foreign material identified within small cerebral arteries had evoked an inflammatory response. In many other patients foreign materials have been noted within pulmonary arterioles with a resultant severe granulomatous reaction and obliteration of the small pulmonary arterioles. Similar reactions have been seen in systemic vessels in other organs but less frequently. The pulmonary changes are often sufficient to produce pulmonary hypertension and to open functional pulmonary arteriovenous shunts. When the lungs cease to become efficient filters of incoming venous blood, intravenously injected particulate matter can be released unfiltered into the systemic circulation and can block brain and visceral arteries. Because of the small size of the particles, small vessels would be blocked. Two patients who abused T's & Blues had clinical and CT evidence of small deep infarcts

compatible with such small vessel blockage. Embolization could also explain ischemic deficits after arterial injection.¹⁴ In other patients the abrupt onset with seizures of an ischemic stroke after injection is compatible with an embolic mechanism.

The offending particulate matter is usually only identified by the demonstration of birefringent crystals on polarizing microscopy. Cotton fibers, talc, cornstarch, or other adulterants would be specifically identified only by special staining techniques. Foreign body embolization has not been documented in patients whose drug abuse is limited to heroin or amphetamines, and yet these patients do suffer ischemic deficits. It is doubtful that an embolic mechanism is the likely underlying cause of cerebral and subarachnoid hemorrhage in abusers. Embolization of material has not been documented as a cause of hemorrhage except in the special circumstance of endocarditis and mycotic aneurysm formation. Further careful tissue studies with the polarizing microscope will be needed to define the true incidence and importance of systemic and cerebral foreign body embolization as a mechanism of drug-induced vascular damage.

Pharmacologically Mediated Vascular changes. Amphetamines, methylphenidate, cocaine, PSP, and LSD share the potential for altering vascular tone. By preventing the uptake of sympathomimetic neurotransmitters by nerve terminals, cocaine sensitizes the end organ response of vessels to epinephrine and norepinephrine.¹⁵ Phencyclidine (PCP) produces a pressor response by directly stimulating alpha adrenergic receptors¹⁶ and also enhances the hypertensive response to infused epinephrine and levarterenol.¹⁷ LSD, PCP, and mescaline all have been shown to produce a potent contractile response when directly applied in the laboratory to isolated canine basilar and middle cerebral arteries.²¹ Methylphenidate and amphetamines have a potent catecholamine-like response.

Cardiac lesions in the form of subendocardial hemorrhages and focal areas of myocardial injury are commonly identified in patients dying of subarachnoid hemorrhage; one hypothetical mechanism of this damage is sudden catecholamine release with subsequent vascular injury.²² Similarly, then, could sudden catecholamine release or vascular hypersensitivity to pressor amines lead to stroke in drug abusers, and might some of the vascular effects be a sequel of chronic catecholamine hyperactivity or hypersensitivity? Although this could be the mechanism of some cases of stroke in drug abusers, the pathology of drug abuse differs significantly from that seen in patients with acute or chronic hypertension. Also, most strokes in abusers, even those due to amphetamines, are not accompanied by signs of catecholamine hyperactivity such as hypertension. If the mechanism of stroke was pharmacological, delayed onset of stroke would be difficult to explain unless the pharmacological effects of the drugs were also delayed. Thus, while pharmacologically mediated injury is applicable to some drug abuse states, it is clearly not likely to be a frequent or critical factor in most.

TABLE 2 Evidence Favoring Immune Etiology of Drug Abuse Stroke

<i>Clinical</i>	
	Delay in onset after injection
	Abstinence for period before reintroduction of drug
<i>Laboratory</i>	
	Eosinophilia
	Elevated gamma globulins and immune globulins
	Angiographically documented polyarteritis-like lesions
	Lymph node hypertrophy
	Morphine binding of gamma globulin fraction
	False positive serology
	Positive Coombs test
<i>Pathology</i>	
	Perivascular infiltrates of eosinophils, lymphocytes, and histiocytes
	Necrotizing angiitis
<i>Experimental</i>	
	In rabbits given morphine, increased serum binding of gamma globulins by morphine ⁴
	Monkeys injected with methamphetamines developed vasculitis ⁹

Immunological mechanisms. The frequent polymorphic vascular response and nodose distribution of the vascular lesions seen in drug abusers mimic the changes in vasculitic disorders usually considered to be autoimmune.⁷ Furthermore, the delayed onset of stroke after injection and the common occurrence of stroke after an unusually long period of abstinence suggest immune mediated factors. Immune phenomena could apply to all drugs whether ingested or introduced parenterally. Evidence for an immune etiology is summarized in Table 2.

Although frequent, recurrent intravenous injection of foreign matter would seem to be an ideal way of eliciting antibodies, surprisingly there are scanty data documenting the incidence and importance of this immunogenic stimulation in the drug abuse population. In narcotic addicts hypergammaglobulinemia,²³ false positive serology,²³ lymph node hypertrophy,⁶ and altered immunoglobulins have been noted.⁴ In rabbits in whom morphine pellets have been implanted, there is increased binding of serum globulins by morphine.⁴ In some narcotic addicts there is increased morphine binding of gammaglobulins.⁴ The level of C3 component of complement is reduced in patients with heroin-induced pulmonary edema.²³ Fever, leukocytosis, and elevated liver enzymes have been noted in T's & Blues addicts and could reflect a disseminated immune response.¹¹ Despite these fragmentary immunological observations no investigation to date has systematically studied the immune response of addicts and its pos-

sible role in the production of the complications of addiction. An immune mechanism could explain cerebrovascular injury from a host of different agents. Perhaps clarification of this aspect might guide treatment.

Although pharmacological and embolic mechanisms can occasionally be documented, we believe that immune mediated reactions are a more common and universal mechanism of vascular injury and stroke. Elucidation of the body's immune response to drugs is clearly the next important step.

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