Neurologic Complications of Cocaine

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INTRODUCTION

Coca leaves have been chewed by South American Indians for several centuries, and cocaine hydrochloride (HCl) has been used since it was isolated in the middle of the 19th century by Niemann (Grinspoon and Bakalar 1981; Holmstedt and Fredga 1981; Petersen 1977). However, untoward effects related to the chewing of the leaves or intranasal insufflation of cocaine HCl had been rare. When used for the only remaining medical indication, local anesthesia, complications are uncommon. In a survey of over 100,000 rhinoplasties performed using cocaine HCl as a local anesthetic, 191 mild and 34 severe reactions were reported, and 5 deaths were attributed to its use (Feehan and Mancusi-Ungaro 1976).

The introduction in 1983 of the alkaloidal form of cocaine known as crack (Jekel et al. 1986) has led to a tremendous increase in its use followed by a rise in the incidence of medical, neurologic, and psychiatric complications. From the lung epithelium, the effect on the central nervous system (CNS) of inhaled free-base cocaine is faster than that produced by intranasal or intravenous (IV) routes and results in a higher serum concentration (Johanson and Fischman 1989; Jones 1984; Verebey and Gold 1988). Local vasoconstriction in the oral or nasal mucosa slows down the absorption of cocaine and, therefore, produces lower plasma levels than IV administration of cocaine HCl or intrapulmonary absorption of crack. The mucosal (oral or nasal) administration has been associated with less intense excitement but also has a lower incidence of complications.

The rise in the rate of complications related to the increasing use of crack cocaine has been reflected in the medical literature: Initial isolated case reports were replaced by a series of accounts of medical and neuro-psychiatric complications of crack cocaine. These accounts were followed by publications describing specific complications such as strokes, seizures, myocardial infarctions, and rhabdomyolysis (Brust 1993; Sanchez-Ramos 1993).
The CNS effects of cocaine seem to result from the reuptake blockade of NE DA, and serotonin, which can potentiate the action of these

three neurotransmitters, leading to serious complications (Dackis and Gold 1988; Johanson and Fischman 1989). Although emergency room visits and hospital admissions due to cocaine-induced symptoms are more commonly related to medical and psychiatric problems, neurologic sequelae are frequent and severe. In two studies of cocaine-related emergency room visits (Brody et al. 1990; Rich and Singer 1991), neurologic symptoms accounted for 17.4 percent and 39.1 percent, respectively, of patients' complaints.

Neurologic complications related to cocaine use can be classified as neurovascular events (cerebral or spinal), seizures, abnormal movements, headache, hyperpyrexia, and rhabdomyolysis, as well as rarer miscellaneous complications involving the nervous system.

NEUROVASCULAR COMPLICATIONS

The first report of a cocaine-related stroke by Brust and Richter (1977) was accepted with skepticism. The few isolated case reports in the next few years (Caplan et al. 1982; Lichtenfeld et al. 1984; Lundberg et al. 1977; Schwartz and Cohen 1984) suggested that this was an extremely rare complication. However, since 1985 the incidence of cocaine-related strokes has reached epidemic proportions (table 1).

Although intracranial hemorrhages following cocaine use were more frequent in the early reports, the number of ischemic and hemorrhagic strokes seem to be equal in the more recent series of reviews (Daras et al. 1994b; Jacobs et al. 1989; Levine et al. 1990, 1991; Peterson et al. 1991; Van Viet et al. 1990). This probably reflects the change in the preferred route of administration, since hemorrhagic strokes seem to be more frequent with cocaine HCl while use of the alkaloidal form of cocaine is equally associated with both ischemic and hemorrhagic events (Levine et al. 1991).

Cocaine abuse is a significant risk factor for cerebrovascular complications in young adults (Kaku and Lowenstein 1990) in whom traditional risk factors are frequently missing (Daras et al. 1994a; Levine et al. 1990). Anticardiolipin antibodies, which increase the risk for stroke (Asherson et al. 1989), have been detected in 27.3 percent of asympto-matic cocaine users (Fritsma et al. 1991) and some patients with

TABLE 1. Reports of cocaine-related strokes.

Year	Types and # of Strokes	Reporting Researchers and Incidents Reported
1977	Infarct: 1	Brust and Richter
	SAH: 1	Lundberg et al.
1982	ICH: 1	Caplan et al.
1984	Infarct: 1	Schwartz and Cohen
	SAH: 2	Schwartz and Cohen; Lichtenfeld et al.
	ICH: 2	Schwartz and Cohen; Lichtenfeld et al.
1986	Infarcts: 2	Chasnoff et al.; Golbe and Merkin
	SAH: 2	Rogers et al.; Cregler and Mark
1987	Infarcts: 4	Levine et al.,3; Lowenstein et al.,1
	TIA: 8	Lowenstein et al.
	SAH: 6	Altes-Capella et al.,1; Wojak and Flamm,2; Kaye and Fainstat,1; Mittleman and Wetli,1; Lowenstein et al.,1
	ICH: 11	Wojak and Flamm,4; Mittleman and Wetli,4; Lowenstein et al.,2; Lehman,1
1988	Infarcts: 9	Devenyi et al.,1; Mody et al.,4; Weingarten,1; Toler and Anderson,1; DeVore and Tucker,1; Tenorio et al.,1
	TIA: 2	Mody et al.
	SAH: 6	Mangiardi et al.,5; Henderson and Torbey,1
	ICH: 7	Mangiardi et al.,4; Mody et al.,3
1989	Infarcts: 27	Mast et al.,8; Rowley et al.,2; Jacobs et al.,8; Engstrand et al.,8; Meza et al.,1
	TIA or infarcts: 21	Moore and Peterson
	SAH: 4	Jacobs et al.
	ICH: 19	Nalls et al.,4; Mast et al.,6; Rowley et al.,1; De Broucker et al.,1; Jacobs et al.,4, Mercado et al.,1; Nolte and Gelman,1; Spires et al.,1
	IVH: 7	Mast et al.
	ICRH: 29	Peterson and Moore,13; Tardiff et al.,9; Klonoff et al.,7
	Strokes: 13	Dixon and Bejar

TABLE 1. Reports of cocaine-related strokes (continued).

Year	Types and # of Strokes	Reporting Researchers and Incidents Reported
1989	Unspecified Periventr. Leuko-malacia: 5	Mast et al.
1990	Infarcts: 38	Seaman,1; Levine et al.,18; Deringer et al.,1; Krendel et al.,2; Hall,1; Petty et al.,1; Kaku and Lowenstein,7; Hoyme et al.,1; Kramer etal.,1; Guidotti and Zanasi,2; Sloan et al.,3
	SAH: 31	Levine et al.,5; Kaku and Lowenstein,6; Hoyme et al.,1; Simpson et al.,17; Sloan etal.,2
	ICH: 16	Levine et al.,5; Green et al.,1; Kaku and Lowenstein,10
1991	Infarcts: 62	Peterson et al.,19; Sauer,1; Daras et al.,18; Hamer et al.,1; Heier et al.,17; Fredericks etal.,1; Dominguez et al.,5
	SAH: 10	Peterson et al.,8; Hamer et al.,1; Chadan etal.,1
	ICH: 10	Harruff et al.,2; Peterson et al.,7; Ramadan etal.,1
1992	Infarcts: 3	Sloan and Mattioni,1; Konzen et al.,1; Nwosu et al.,1
1993	TIA: 1	Libman et al.
	Infarct: 2	Massachusetts General Hospital; Morrow and McQuillen
1994	Infarcts: 25	Daras et al.
	SAH: 9	"
	ICH: 16	"
	IVH: 5	"

KEY: SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; ICRH = intracranial hemorrhage; IVH = intraventricular hemorrhage; TIA = transient ischemic attack.

cocaine-related strokes (Daras et al. 1994b; Sloan et al. 1990; Toler and Anderson 1988). Ethanol intoxication has also been associated with strokes (Gorelick 1987). Combining cocaine with ethanol, the drug most commonly used with cocaine, leads to formation of cocaethylene (benzoylecgonine ethyl ester) (Dean et al. 1992), which induces more adverse cardiovascular effects than cocaine alone in healthy volunteers (Perez-Reyes and Jeffcoat 1992) and leads to higher mortality in mice (Hearn et al. 1991).

Several reports describe cerebrovascular accidents in neonates exposed in utero to cocaine (Chasnoff et al. 1986; Dixon and Bejar 1989; Dominguez et al. 1991; Heier et al. 1991; Hoyme et al. 1990; Kramer et al. 1990; Mast et al. 1989; Spires et al. 1989). Low serum cholinesterase levels in the fetus (Johanson and Fischman 1989) may increase susceptibility to the vascular effects of cocaine. Although pregnancy is also associated with low cholinesterase levels (Johanson and Fischman 1989), reports of strokes in pregnant women are rare (Henderson and Torbey 1988; Levine et al. 1991; Mercado et al. 1989; Tuchman et al. 1992).

The exact mechanism of cocaine-related stroke remains incompletely understood because of the multiple effects of cocaine on the cardiovascular system. By blocking the reuptake of norepinephrine (Herrting et al. 1961), cocaine increases sympathetic activity leading to hypertension, tachycardia, and vasoconstriction (Johanson and Fischman 1989). A dose-related rise in arterial pressure and heart rate has been noted in humans (Fischman et al. 1976) and experimental animals (Wilkerson 1988).

Subarachnoid hemorrhage (SAH) from rupture of an underlying aneurysm or arteriovenous malformation (AVM) (Daras et al. 1994b; Levine et al. 1990; Mangiardi et al. 1988; Tardiff et al. 1989; Wojak and Flamm 1987) may be due to acute hypertension induced by cocaine. The absence of hypertension in the initial emergency room examination in most cases of cocaine-induced intracranial hemorrhage can be explained by the short half-life of cocaine (Johanson and Fischman 1989).

Intracerebral hemorrhage may be due to an underlying lesion such as AVM (Daras et al. 1994b; Jacobs et al. 1989; Kaku and Lowenstein 1990; Levine et al. 1990; Lichtenfeld et al. 1984; Lowenstein et al. 1987; Mangiardi et al. 1988; Mittleman and Wetli 1987; Mody et al. 1988; Simpson et al. 1990) or a glioma (Wojak and Flamm 1987). The location of hemorrhages in the territory of penetrating arteries,

such as the basal ganglia/internal capsule or pons, in a large number of patients suggests a pathophysiology similar to that of hypertensive intracerebral hemorrhage. Habitual cocaine abuse may expose small vessels to episodic hyper-tension, leading to accelerated arteriosclerotic changes. Advanced atherosclerosis has been observed in the aorta and the renal arteries of cocaine users (Bacharach et al. 1992; Fogo et al. 1992) and in rabbits exposed to cocaine (Langner et al. 1988). An alternate explanation for the occurrence of intracerebral bleeding is hyperperfusion in an area made ischemic by cocaine-induced vasoconstriction (Caplan 1988). These two pathogenetic mechanisms are not necessarily mutually exclusive and may, in fact, coexist.

Ischemic infarctions related to cocaine use can involve any level of the neuraxis, including the spinal cord (Daras et al. 1991; Mody et al. 1988; Peterson et al. 1991) and the retina (Devenyi et al. 1988; Libman et al. 1993). Multiple overlapping mechanisms may be responsible. The vasoconstriction from sympathetic overstimulation due to blocking of epinephrine reuptake may be aggravated by the simultaneous increase of systemic arterial pressure, which can alter cerebral autoregulation (Burke et al. 1987). Changes in autoregulation have been observed in the rat neocortex following cocaine administration (Kelly et al. 1993). Hypertensive opening of the blood-brain barrier may increase vasocon-striction (Owman and Hardebo 1985). Cocaine may also block the reuptake of serotonin (Dackis and Gold 1988), the most potent vasoconstrictor amine in the brain (Edvinson and MacKenzie 1976), particularly in large and medium-size vessels (Hardebo et al. 1978). Cocaine-induced vasoconstriction has been observed in the retinal artery of a patient with monocular blindness (Libman et al. 1993) and cerebral arterioles of rats (Altura et al. 1988), and it can be ameliorated by mag-nesium ion (Mg^{2+}) (Huang et al. 1990). However, the observation that topical cocaine application dilated pial arterioles in cats (Dohi et al. 1990) contradicts previous findings and has added confusion.

Experimentally, cocaine enhances the response of platelets to arachidonic acid, which leads to increased production of thromboxane A and promotes platelet aggregation (Togna et al. 1985). Thrombocytopenia has been reported in six human immunodeficiency virus (HIV)-negative cocaine users, none of whom developed a stroke (Leissinger 1990).

Myocardial infarction, cardiac arrhythmias, and cardiomyopathy increase the risk of embolic infarcts, but only two cases of proven

embolic strokes have been reported (Petty et al. 1990; Sauer 1991). Vasculitis, which is common in strokes related to other drugs and particularly amphetamines (Citron et al. 1970), has been attributed to cocaine on the basis of angiographic findings (Kaye and Fainstat 1987). These findings, however, could also indicate vasospasm following undiagnosed SAH (Levine et al. 1988). Biopsy-proven vasculitis has been documented in only five cases (Fredericks et al. 1991; Krendel et al. 1990; Massachusetts General Hospital 1993; Morrow and McQuillen 1993); all had normal cerebral angiography.

COGNITIVE DEFICITS

The question of mental impairment in cocaine users was brought up first by Gordon (1908). Sixty years later, Buck and colleagues (1968) described psychological impairment and poor work performance in South American coca leaf chewers. Subsequent studies demonstrated subtle deficits in auditory recall, concentration, and reaction time (Ardila et al. 1991; O'Malley et al. 1992; Weinrieb and O'Brien 1993). The main problem in all these studies is the unavailability of information about the premorbid performance of the patients.

Electroencephalographic investigation of cocaine users revealed diffuse theta activity that increased with continuous use (Pascual-Leone and Dhuna 1990a). Cerebral atrophy has been reported in chronic habitual cocaine users on computed tomography (Pascual-Leone et al. 1991). The exact explanation of these findings is not clear. It is, however, tempting to speculate that the atrophy is ischemic in origin based upon several positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies performed on cocaine users. Studies have demonstrated decreased cerebral blood flow, particularly in the frontal and temporal cortex of cocaine users (Tumeh et al. 1990; Volkow et al. 1988), small focal cortical defects (Holman et al. 1991), and decreased glucose utilization (London et al. 1990). Cognitive impairment accompanied by cerebral hypoperfusion on SPECT has been noted even after 6 months of abstinence (Strickland et al. 1993).

HEADACHES

The incidence of headaches related to cocaine use varies significantly from study to study. Among cocaine users, up to 60 percent reported

headaches following its use (Washton and Gold 1984). Lipton and colleagues (1989) reported that 13.1 percent of hospitalized cocaine users complained of headaches. Lowenstein and colleagues (1987) found that only 0.8 percent of emergency room patients suffered from headaches. Among patients with cocaine intoxication, 1.8 percent presented with acute headache (Dhuna et al. 1991a). Migraine-like headaches occasionally complicated by neurological deficit have been reported (Lipton et al. 1989; Satel and Gawin 1989). In one case report, a patient became dependent on cocaine because it relieved migraines (Brower 1988).

Dhuna and colleagues (1991a) identified three patterns of headaches following cocaine use: acute onset of headaches within minutes of cocaine use, increasing headache during a binge, and headaches during abstinence. Withdrawal headaches have been reported as late as 4 weeks to 9 months after cessation of cocaine use (Baker and Dilavou 1989). A possible connection between cocaine-induced headaches and serotonin may exist, in view of the blocking of serotonin reuptake by cocaine (Cunningham and Lakoski 1988). Acute headache following use of cocaine is not always benign. It may be an ominous sign and herald the onset of an acute cerebrovascular event, particularly hemorrhage (Daras et al. 1994a; Levine et al. 1990).

Seizures

Although seizures have been known to occur following cocaine use since 1922 (Pulay 1922) and have been notoriously associated with the "body packer" syndrome (Wetli and Mittleman 1991), it was only recently realized that seizures can be associated with recreational cocaine use (Alldredge et al. 1989; Choy-Kwong and Lipton 1989a; Harden et al. 1992; Kramer et al. 1990; Lowenstein et al. 1987; Myers and Earnest 1984; Pascual-Leone et al. 1990). In questionnaires given to adolescent cocaine users, loss of consciousness was reported by 2 percent and seizures by 1 percent of the light users, while 27 percent of heavy users reported loss of consciousness and 4 percent reported seizures (Schwartz et al. 1988). In clinical studies, the reported occurrence of cocaine-related seizures is also relatively low. Lowenstein and colleagues (1987) reported 29 seizures (2.8 percent) in 1,275 emergency room visits or admissions for cocaine-related complications. Pascual-Leone and colleagues (1990) reported 32 (7.9 percent) seizures among 403 cocaine- intoxicated patients. In two New York studies, seizures were found less frequently: 1.4 percent in the series reported by Choy-Kwong and Lipton (1989a)

and 0.6 percent by Harden and colleagues (1992). The majority of patients develop generalized tonic-clonic convulsions, but partial simple or complex seizures may occur. Seizures are usually isolated, but generalized status epilepticus can occur (Alldredge et al. 1989; Lowenstein et al. 1987). One case of complex partial status epilepticus has been described after crack use (Ogunyemi et al. 1989).

The mechanism of cocaine-related convulsions remains unclear. Eidelberg and colleagues (1963) postulated that cocaine produced seizures by blocking the reuptake of catecholamines. Their finding that dibenamine, chlorpromazine, and reserpine prevented cocaine-induced seizures in experimental animals further supported this hypothesis. They also documented onset of cocaine-related seizures in the temporal region in cats similar to lidocaine-induced seizures (Post et al. 1981).

Recurrent seizures have been described in experimental animals after repeated doses of subconvulsant levels of cocaine administered intraperitoneally; the term "pharmacologic kindling" has been proposed by Post and Kopanda (1975) to describe this phenomenon. In spite of the controversy surrounding kindling in humans, the finding by Harden and colleagues (1992) that 9 of 22 patients had recurring seizures only after repeated use of cocaine and the case report by Dhuna and colleagues (1991b) of possible kindling-induced epilepsy in a habitual cocaine user support this notion.

ABNORMAL MOVEMENTS

A possible association between cocaine and abnormal movements was first reported by Kumor and colleagues (1987), who noted an increased incidence of dystonic movements in cocaine users treated with neuro-leptics. This observation was also made by Hegarty and colleagues (1991). Dystonic reactions have been observed during both cocaine intoxication (Farrell and Diehl 1991; Merab 1988) and withdrawal (Choy-Kwong and Lipton 1989b; Rebischung et al. 1990) without use of neuroleptics.

Exacerbation of other abnormal movements, such as tics induced by cocaine in previously controlled patients with Tourette syndrome, has been noted (Cardoso and Jankovic 1993; Factor et al. 1988; Mesulam 1986; Pascual-Leone and Dhuna 1990b). Occurrence of tics has also been reported in previously asymptomatic patients (Pascual-Leone

and Dhuna 1990b). One case of opsoclonus-myoclonus following cocaine use has been reported (Scharf 1989).

Choreoathetoid movements clinically indistinguishable from those observed in Huntington's disease and lasting up to 6 days have been reported recently (Daras et al. 1994a). By blocking the reuptake of dopamine, cocaine produces a high availability of dopamine at the synaptic cleft, which can trigger choreoathetoid movements. Further inability to downregulate dopamine concentration may be responsible for the recurrence of these movements with repeated cocaine use in some patients. The existence of street names to describe these movements (crack dancing and boca turcida) suggests that they may be more common than physicians recognize.

RHABDOMYOLYSIS AND HYPERPYREXIA

The alkaloidal form of cocaine has been added to the list of drugs that produce rhabdomyolysis. However, the other routes of administration can also trigger muscle damage (Daras et al., in press-b; Merigian and Roberts 1987; Nolte 1991; Parks et al. 1989; Roth et al. 1988; Skluth et al. 1988). Rhabdomyolysis can occasionally recur (Horst et al. 1991) or can occur simultaneously with skin infarction (Zamora-Quezada et al. 1988). Elevated serum creatine kinase levels may be present in up to 34percent of cocaine users without other muscle symptoms (Welch et al. 1991).

Hyperpyrexia, which has been described in cocaine intoxication, has been noted in several cases of cocaine-induced rhabdomyolysis (Merigian and Roberts 1987; Roth et al. 1988; Skluth et al. 1988). Hyperthermia alone or in combination with agitation may cause muscle damage. In addition, ischemia from cocaine-induced vasoconstriction of muscle arteries has been proposed to induce muscle injury (Roth et al. 1988; Skluth et al. 1988). A direct toxic effect has been shown on cardiac (Peng et al. 1989) but not on striated muscle. High catecholamine levels from cocaine- induced reuptake blockade may release calcium from the sarcoplasmic reticulum, leading to high intracellular calcium. This can trigger a series of events leading to cell death (Parks et al. 1989).

The association of hyperthermia, rhabdomyolysis, and agitation has led Kosten and Kleber (1988) to propose a mechanism similar to that responsible for the neuroleptic malignant syndrome (NMS). Chronic use of cocaine may produce dopamine depletion (Dackis and Gold

1985) or decrease dopamine receptors (Volkow et al. 1990) and lead to inadequate dopamine availability. The observation of higher incidence of NMS in cocaine abusers treated with neuroleptics (Akpaffiong and Ruiz 1991) supports this notion. It seems, however, that these multiple mechanisms are not mutually exclusive but may combine to produce this frequently fatal complication.

MISCELLANEOUS COMPLICATIONS

In addition to the increased risk of infection associated with IV use, non-IV cocaine users tend to expose themselves to the risk of HIV and other sexually transmitted infections because of their sexual practices. Increased sexual activity, promiscuity, or exchange of sex for crack can lead to higher incidence of infection (Marx et al. 1991). Cocaine has immunosuppressant properties and IV cocaine users are at a higher risk of infectious endocarditis than are other parenteral drug users (Chambers et al. 1987). Enhancement of HIV-1 replication by cocaine has been noted in human peripheral mononuclear blood cells (Peterson et al. 1993).

Anosmia, rhinitis, and perforation of the nasal septum are well known complications of cocaine-induced vasoconstriction from nasal insufflation, but extreme cases of cerebrospinal fluid rhinorrhea from erosion of the cribriform plate (Sawicka and Trosser 1983) and bilateral optic neuritis with osteolytic sinusitis have also been reported (Newman et al. 1988).

In addition to the cases of anterior spinal artery infarction (Daras et al. 1994a; Mody et al. 1988; Peterson et al. 1991), spinal cord involvement from a spinal epidural hematoma has been described (Huff 1994).

Impairment of the neuromuscular junction by cocaine would not be expected, but cocaine use unmasked and then exacerbated symptoms of myasthenia gravis in a young woman (Berciano et al. 1991). The author has also observed recurrent exacerbation of myasthenic symptoms with repeated cocaine use in a young man (Daras et al., in press-a).

CONCLUSIONS

The neurologic complications of cocaine abuse may be the tip of an iceberg in view of the medical and psychiatric side effects as well as the social problems related to its use. In particular, the violence associated with crack surpasses that of other illegal drugs and makes cocaine not a panacea, as Freud had suggested, but a societal nightmare.

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