

Cocaine-related vascular headaches

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Abstract

The records of 21 patients admitted to hospital from January 1985 to December 1988 for acute headache associated with cocaine intoxication were reviewed. Fifteen patients were identified who experienced headaches with migrainous features in the absence of neurological or systemic complications. None of them had a history of cocaine-unrelated headaches or a family history of migraine, and all had a favourable outcome. Three possible mechanisms of cocaine-related vascular headaches are discussed which depend on the interval between cocaine ingestion and development of the headache. We postulate that acute headaches following cocaine use may relate to the sympathomimetic or vasoconstrictive effects of cocaine, while headaches following cocaine withdrawal or exacerbated during a cocaine "binge" may relate to cocaine-induced alteration of the serotonergic system.

Among cocaine abusers up to 60-75% report severe headaches which they relate to use of the drug,^{1,2} and there may be a relationship between the cocaine dose ingested and the prevalence of headaches.² In some cases, those experiencing chronic headache may begin using cocaine as self-medication for pain.³ The acute onset of new headaches in cocaine addicts can signal intracranial haemorrhage,⁴ ischaemic stroke,^{5,6} endocarditis,⁷ brain abscess,^{8,9} or other psychiatric or medical illnesses⁹ and should be taken seriously. The majority of such patients seem to have a more benign cause of the headache with a favourable outcome.^{1,2,9-11} The headache in these patients frequently has migrainous features and can be attributed to either acute cocaine intoxication or withdrawal.^{9,11,12} This retrospective study investigated cocaine-related vascular headaches in relation to time and pattern of cocaine use and to define their possible mechanisms.

Methods

Between January 1985 and December 1988 all patients admitted to Hennepin County Medical Center (HCMC) with a primary diagnosis of acute headache in the setting of cocaine intoxication were identified using the computerised register of the hospital. A positive urine toxicology screen for cocaine was required in all patients.

The patients' age and sex were recorded, and the character of the headache, associated symptoms, and pattern of cocaine abuse were

analysed. The headache was described according to the following variables: description of the pain, temporal profile of pain onset and duration, history of headaches, family history of migraine, associated symptoms (nausea, vomiting, visual disturbances, photo- and phono-phobia, focal neurological symptoms, nuchal rigidity, fever), and findings on the physical examination. The following variables of cocaine addiction were analysed: duration of abuse, relationship of pain onset to cocaine ingestion, acute dose, route, and pattern of cocaine use. All patients were evaluated with cranial CT and most had CSF analysis.

Results

Of the 1188 admissions to HCMC with medical, psychiatric and neurological complications associated with acute cocaine intoxication, we identified 21 patients hospitalised for acute headache evaluation. Six patients were excluded since their headache could be attributed to subarachnoid haemorrhage (2), acute sinusitis (2), endocarditis (1), or pneumonia (1).

The remaining 15 patients, nine women and six men, presented with headaches with migrainous features (table). Their mean age was 28.3 years (range 20-37 years). Five had snorted the cocaine, five injected it intravenously, and five smoked it as "crack". All patients were habitual cocaine users. None of them had a personal or family history of migraine, but two of them described similar cocaine-associated headaches in the past. The neurological examination on admission was normal in all patients. All patients had normal CT scans; the CSF was normal in the seven patients in whom it was analysed; none of them had cerebral angiogram performed. All patients had a normal outcome.

The interval between the cocaine ingestion and the onset of the headache was known in 12 of these 15 patients. This allowed the definition of three different patterns of cocaine-related headaches with migrainous features (table): acute onset of the headache within minutes of cocaine use (pattern 1), increasing headache during a cocaine "binge" (pattern 2), and onset of increasing headache with cocaine abstinence (pattern 3).

Pattern 1 (table) was found in five patients; two women had smoked crack and one woman and two men had injected the cocaine intravenously. All five were chronic, habitual cocaine abusers (five to eight years of cocaine use, three to seven times per week) who denied previous headaches after snorting cocaine. In all of them the headache developed immediately (maximum within five minutes) after a "usual" cocaine dose, and lasted for two

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Table Summary of cocaine use and headache characteristics for 15 patients with cocaine-related vascular headaches. The patients are classified into four groups according to the timing of the onset of the headache in relationship to the cocaine ingestion: acute onset of the headache within minutes of cocaine use (pattern 1), increasing headache during a cocaine "binge" (pattern 2), and onset of increasing headache with cocaine abstinence (pattern 3), insufficient data available (uncertain).

Age (yrs)	Sex	Cocaine use				Headache characteristics						
		Route	Pattern	Dose (gm)	Onset	Duration from last cocaine dose	Location	Quality	Photo-phobia	Nausea/vomiting	Visual disturbances	Other symptoms
<i>Pattern 1</i>												
27	F	crack	single dose	?	minutes after dose	2 hrs	occipital	throbbing	yes	yes	blurring	numbness & weakness of legs
30	F	crack	single dose	1	immediately after dose	?	bi-temporal	throbbing	yes	yes	no	lt. leg weakness
28	F	iv	3 doses in 4 hrs	1.5	seconds after 3rd dose	4 hrs	occipital	throbbing	yes	yes	spots & trails	neck stiffness
23	M	iv	single dose	0.5	immediately after dose	18 hrs	generalised	stabbing	yes	yes	no	unsteadiness
35	M	iv	single dose	1	5 min after dose	2 days	lt occipital	burning	yes	yes	wavy lines	rt arm numbness & weakness
<i>Pattern 2</i>												
24	F	crack	"binge" 4 days	3/day	increasing during "binge"	?	rt sided	throbbing	yes	no	no	no
20	F	nasal	"binge" 2 wks	?	2nd wk of "binge"	3 days	"top of head"	throbbing	yes	yes	blurring	episodic vertigo & diplopia
36	F	nasal	"binge" 8 days	?	4th day of "binge"	6 hrs	frontal	throbbing	yes	yes	no	no
20	M	crack	"binge" 2 wks	2/day	2nd wk of "binge"	1 wk	frontal	throbbing	yes	yes	blurring	no
31	M	nasal	"binge" 2 wks	1-2/day	6th day of "binge"	?	frontal	pounding	yes	yes	flashing spots	no
<i>Pattern 3</i>												
30	F	crack	daily use	> 1/day	1 day after stopping	6 days increasing pain	frontal	throbbing	yes	yes	blurring	no
30	M	iv	daily use	2-3/day	4 days after stopping	6 days increasing pain	frontal	throbbing	yes	yes	no	neck stiffness
<i>Uncertain</i>												
24	F	nasal	daily use	2/day	?	?	generalised	throbbing	yes	yes	no	no
37	F	nasal	daily use	?	?	?	?	throbbing	yes	yes	no	no
30	M	iv	?	?	?	?	generalised	throbbing	yes	yes	no	dizziness

to 48 hours. The headache was occipital or bilateral, throbbing, associated with photophobia, nausea and vomiting in all of them. Three subjects had extremity paraesthesia or weakness, one complained of unsteady gait, one of neck stiffness and two of scintillating scotomata. All these symptoms were transient, and all symptoms resolved within 12–24 hours.

Pattern 2 (table) was found in five patients; three intranasal cocaine abusers and two crack users. All had been on a "binge" for four to 14 days with unusually large amounts of cocaine (1–3 gm/day). They all described onset of the headache after a few days and experienced increasing severity of the pain during the course of the "binge". Most headaches in this group were frontal, throbbing, and associated with nausea. Only one patient reported vomiting associated with transient vertigo and diplopia. No information about the immediate effect of each cocaine dose on the headache was available for any of the patients.

Pattern 3 (table) was seen in one male intravenous cocaine user and one female crack smoker. Both had been using cocaine for years and before presentation had been using cocaine daily for several months. Both abruptly stopped using cocaine and developed headaches one to four days following the last cocaine dose. The headache progressively worsened over six days with continued drug abstinence. Both described the pain as frontal, throbbing, and associated with photophobia, nausea, and vomiting. One subject subsequently developed neck stiffness. The CT and CSF analysis were normal in both, and neither had clinical evidence of depression.

The following three cases illustrate the three patterns of cocaine-related headaches with migrainous features.

Case 1 (pattern 1)

A 23 year old man developed a severe, stabbing, generalised headache associated with photophobia, nausea, vomiting, and unsteadiness of

gait "within seconds" of injecting 0.5 gm of cocaine intravenously. His neurological examination, CT, and CSF analysis were normal. The headache resolved spontaneously after 18 hours. He was a habitual cocaine user who denied headaches after snorting the drug, but reported similar headaches on the three previous occasions in which he had used intravenous cocaine. Chronic intravenous heroin use had never triggered a headache. He had never had cocaine-unrelated headaches and his family history was negative.

Case 2 (pattern 2)

A 31 year old man had been snorting 1–2 gm of cocaine daily for two weeks. Six days into the "binge" he developed a pounding, frontal headache with nausea, photophobia, and "flashing spots in front of the eyes". He stated that he kept using cocaine "to relieve the headache", but that the pain "keeps getting worse the more I use". The severity of the pain finally brought him to the hospital. His neurological examination, CT, and CSF analysis were normal. He denied a previous history of similar cocaine "binges". He had no history of headaches and his family history was negative for migraine.

Case 3 (pattern 3)

A 30 year old man presented to the hospital with a three day history of increasing headache which was maximal around the eyes, associated with nausea, vomiting, photophobia, and mild neck stiffness. He was a habitual intravenous cocaine abuser who had been using 2–3 gm of cocaine daily for several months. He denied habitual or recent use of any other drugs. He stopped using cocaine suddenly and four days later developed a headache that kept worsening in the absence of additional cocaine use. His neurological examination, CT, and CSF analysis were normal. He had no history of headaches and his family history was negative

for migraine. The headache kept increasing in severity for three days (total of six days after onset) and eventually resolved spontaneously.

Discussion

Studies based on cocaine telephone helplines report that up to 60–75% of callers complain of cocaine-related headaches.^{1,2} El-Mallakh¹³ in a questionnaire survey administered to 120 consecutive admissions to an alcohol and drug treatment programme found that all 30 cocaine abusers that completed the questionnaire reported headaches. The relative frequency of headaches as primary admitting diagnosis in our study was 1.8%. Other hospital based studies report highly variable prevalences of headache among cocaine users ranging from 0.8%¹⁰ to 13.1%.⁹ Due to our methodology we cannot make a statement about the prevalence of headaches among cocaine abusers admitted to hospital. In addition, it is likely that a much larger number of cocaine users experience less severe headaches and either do not seek medical attention or are seen in the casualty department and not admitted to hospital.

Acute onset of severe vascular headaches without neurological complications immediately after cocaine ingestion (pattern 1) has been previously reported by Lipton *et al.*⁹ In accordance with their description,⁹ we found this type of headache only in patients who had used cocaine intravenously or as crack. The headache began immediately after the ingestion of cocaine, in the expected time for the drug to reach peak levels in the brain.¹⁴ The sudden cocaine surge produced by crack or intravenous routes leads to a rapid block of presynaptic norepinephrine reuptake with potent sympathomimetic effects,^{15,16} and to a calcium dependent acute constriction of vascular smooth muscle.¹⁷ Derangements of norepinephrine and vasomotor control have been advocated as important factors in the pathogenesis of migraine.^{18–20} An important role of cocaine-induced vasospasm with transient ischaemia in the pathogenesis of this pattern 1 headache is suggested by the finding of focal neurological symptoms in all our patients. Similar findings are reported by Lipton *et al* in three patients.⁹ Most reported cases of cocaine-associated strokes are preceded by headaches^{5,6,10} suggesting a common underlying mechanism for some cocaine-associated ischaemic strokes and pattern 1 headaches.

Five of our patients presented with headaches of increasing severity during “binges” with cocaine (pattern 2). Satel and Gawin¹¹ describe three patients who developed headaches 45–90 minutes after cocaine ingestion, when the brain cocaine levels are expected to be declining.¹⁴ Two of them, during a cocaine “binge”, experienced acute, temporary pain relief immediately following each additional dose of cocaine, but the headaches reoccurred with increasing severity. Nasal application of cocaine solution is advocated as treatment for cluster headaches,²¹ the presumed mechanism of action is a local anaesthetic effect on the sphenopalatine ganglion.²² This mechanism

may play an important role in the nasal cocaine abusers with this pattern 2 headache. Alternatively, since serotonin has been implicated in migraine,^{18–20} the transient relief of the headache by cocaine ingestion may be related either to the blockade of presynaptic serotonin-reuptake by cocaine^{11,23} or by a specific competitive antagonism at 5-HT₃ receptors.²⁴ The role of the latter mechanism of cocaine is questionable since firstly 5-HT_{1D} and/or 5-HT_{1A} receptors have been implicated in migraine,²⁵ secondly specific 5-HT_{1D} receptor agonist (Sumatriptan) has been found to be a highly effective acute antimigraine agent²⁶ whereas 5-HT₃ antagonists have been disappointing in clinical trials for the treatment of migraine headaches.²⁷ Prolonged cocaine use may eventually lead to a secondary presynaptic serotonin depletion²⁸ and account for increased severity of the headache.²⁹ In this context it is interesting that the patient described by Brower³ whose cocaine habit was reportedly initiated for self-medication of his headaches.

The third pattern of cocaine-related headaches described appears to be associated with drug withdrawal in longterm habitual users. Lipton *et al*⁹ describe five patients with headaches following cocaine withdrawal all of whom were depressed and had suicidal ideations. Our two patients were not clinically depressed. Baker and Dillavou¹² describe six patients with onset of self-limited headaches four weeks to nine months following cessation of cocaine. In our patients the headache developed one to four days after the last dose and kept increasing in severity for the following six days. Chronic cocaine use leads to presynaptic depletion of serotonin, dopamine, and norepinephrine.¹⁵ The time required for these different neurotransmitter systems to recover following cocaine withdrawal may be responsible for this type of cocaine-related headache. Baker and Dillavou¹² report that the headache in their patients can be prevented by doxepin. Doxepin prevents the presynaptic reuptake of norepinephrine and serotonin³⁰ and may prevent the transient hypoactivity of these neurotransmitters during cocaine withdrawal. Alternatively, doxepin’s action may be less specific and related to the prevention of depression.

To develop consistency in the future study of cocaine-related headaches with migrainous features it is important to classify them in accordance with the New International Headache Classification.³¹ Pattern 1 headaches best fit “Headache induced by acute substance use or exposure” (group 8.1). Pattern 3 headaches should be classified as “Headache from substance withdrawal (chronic use)” (group 8.4). Headaches corresponding to pattern 2 are more difficult to classify. They are generally associated with “binge” use superimposed on chronic exposure and therefore may represent a variant in group 8.1. They could also be classified under “Headache induced by chronic substance use or exposure” (group 8.2) since they share many of the features of ergotamine-induced headache (group 8.2.1).¹⁸

Further investigation into the characteristics and basic mechanisms of cocaine-related

headaches may lead to a better understanding of other headache disorders.

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