Gregory G. Davis,[1] *M.D. and Christopher I. Swalwell,*[2] *M.D.*

The Incidence of Acute Cocaine or Methamphetamine Intoxication in Deaths Due to Ruptured Cerebral (Berry) Aneurysms

REFERENCE: Davis, G. G. and Swalwell, C. I., **"The Incidence of Acute Cocaine or Methamphetamine Intoxication in Deaths Due to Ruptured Cerebral (Berry) Aneurysms,"** *Journal of Forensic Sciences,* JFSCA, Vol. 41, No. 4, July 1996, p. 626–628.

ABSTRACT: Acute intoxication with either cocaine or methamphetamine may contribute to formation and rupture of a berry aneurysm by causing transient hypertension and tachycardia. We report the results of a retrospective study to determine the incidence of acute cocaine or methamphetamine intoxication in deaths due to ruptured berry aneurysm in our jurisdictions. We reviewed all deaths from ruptured cerebral aneurysms that fell within our jurisdictions during the seven years from 1 January 1987 to 31 December 1993 and found 83 cases. The mechanism of death invariably involved subarachnoid hemorrhage, although some cases also had intracerebral hemorrhage. A history of drug abuse was found in 13 cases. Toxicological analysis was performed in 39 cases. Of these methamphetamine was detected in six cases and cocaine in three cases—an incidence of 21%. (In one case both methamphetamine and cocaine were detected.) The incidence of acute cocaine intoxication in all autopsies in Jefferson County was 13.6%. The incidence of methamphetamine intoxication in all autopsies in San Diego County was 4.9%.

Although the exact mechanism by which berry aneurysms form remains undetermined, research indicates that propagation and rupture of the aneurysm are aggravated by hypertension and tachycardia, both of which are pharmacologic side effects of cocaine and methamphetamine. Based on the preponderance of methamphetamine associated with deaths due to ruptured berry aneurysms it appears that methamphetamine is more toxic than cocaine, perhaps owing to the longer half-life of methamphetamine.

KEYWORDS: forensic science, forensic medicine, forensic pathology, cerebral aneurysm, berry aneurysm, saccular aneurysm, cocaine, methamphetamine, subarachnoid hemorrhage

In an earlier paper (1), we reported that acute intoxication with either cocaine or methamphetamine can contribute to rupture of a berry aneurysm by causing transient hypertension and tachycardia. Attributing a contributory role to acute cocaine or methamphetamine intoxication raises several questions. What is the incidence of acute cocaine or methamphetamine intoxication in deaths due to vascular rupture? Is the rate of cocaine intoxication similar to or different from the rate of methamphetamine intoxication? Does a history of chronic drug abuse have any effect on development or rupture of an aneurysm, or is the rupture solely related to acute intoxication? To answer these questions we performed a retrospective study of all deaths due to ruptured cerebral aneurysm that fell within our jurisdictions during the 7 years from 1987 through 1993.

Methods

A retrospective search of the files of the Medical Examiner's offices of Jefferson County, Alabama and San Diego County, California was performed via computer for all cases of death due to a ruptured cerebral aneurysm or due to subarachnoid hemorrhage not associated with trauma. The search included cases from 1 January 1987 through 31 December 1993. We found 83 cases, including three cases of spontaneous subarachnoid hemorrhage in which aneurysmal rupture was presumed, though not specifically identified, because other causes were excluded. The autopsy protocols and any microscopic slides of the central nervous system were reviewed.

Toxicological analysis was performed in 39 cases. In San Diego County toxicological screening was done by radioimmunoassay of blood. Screening in Jefferson County was by both enzyme multiplied immunoassay technique (EMIT) and thin layer chromatography when urine was available. When urine was unavailable the Jefferson County cases were screened by EMIT performed on a supernatant of whole blood from which the protein had been precipitated by acetone. In both counties the identity of compounds detected by screening was confirmed and quantified by gas chromatography/mass spectrometry.

Results

Our search revealed 83 deaths due to ruptured berry aneurysm. The decedents ranged in age from 17–93 years (mean 49 years ± 15 years). The ratio of males to females was 39:44. By race the population showed the following characteristics: 67 Caucasian, 11 Negroid, and 5 Asian (5 of the Caucasians were Hispanic). Hypertension was present in 38% of the decedents (32 of 84); this hypertension was either detected clinically earlier in life (20 cases) or inferred from cardiac hypertrophy detected at death (12 cases). A postmortem diagnosis of hypertension was made in any case where the heart weighed more than 450 g in the absence of cardiac dilatation, valvular disease, or ischemic heart disease (2). The age range, mean age, slight female preponderance, and incidence of chronic hypertension are in keeping with previous reports (3,4).

[1]Associate Coroner/Medical Examiner, Jefferson County Coroner/Medical Examiner's Office, Birmingham, AL and Assistant Professor of Pathology, University of Alabama at Birmingham.

[2]Deputy Medical Examiner, Office of the Medical Examiner, San Diego, CA.

Presented in part at the 47th Annual Meeting of the American Academy of Forensic Sciences, Seattle, Washington, February 1995.

Revised manuscript received 5 Sept. 1995; revised manuscript received 3 Nov. 1995; accepted for publication 7 Nov. 1995.

Autopsy revealed subarachnoid hemorrhage as a mechanism for death in each case. Histologic samples of the central nervous system were available for review in 45 of 83 cases. In 39 cases sections of the central nervous system were available, in 20 cases sections were taken of the ruptured aneurysm, and in 12 cases both central nervous system and aneurysm were taken. Review of the histologic samples showed that the arterial wall was attenuated, with replacement of the muscular layer by a thin, fibrous shell. The sections of the aneurysmal wall showed absence of both the muscular tunica media and of the internal elastic lamina. In no section was either the dilated cerebral vessel or the cortical vessels inflamed.

Toxicological analysis for cocaine and methamphetamine was performed in 39 of the cases (47%). Cocaine was detected in three of these cases and methamphetamine in six cases. The total number of cases in which these drugs of abuse were detected was eight, since in one case both cocaine and methamphetamine were detected. The cases in which either cocaine or methamphetamine was detected are recorded in Table 1. (In case No. 1 cocaine was detected in urine only; no cocaine was detectable in the blood. The post mortem interval was approximately 24 hours.) Separation of the deaths by county shows that the incidence of acute intoxication with either cocaine, methamphetamine, or both in deaths due to ruptured berry aneurysms was 15% (2 of 13) in Jefferson County and 23% (6 of 26) in San Diego County.

Discussion

Ruptured berry aneurysms are the most common cause of primary subarachnoid hemorrhage, accounting for approximately half of all cases (5). The mean annual incidence of primary subarachnoid hemorrhage is 10–15 per 100,000 (5). Death occurs prior to admission to a hospital in 8–15% of cases (4). Calculation of 8–15% of 5–7.5 per 100,000 gives an estimated annual rate of sudden and unexpected deaths owing to rupture of an unsuspected berry aneurysm of 0.4 to 1.1 /100,000 per year, a rate in keeping with the number of cases seen by our jurisdiction during the seven years of this study.

While the precise details by which berry aneurysms form remain uncertain, it is believed that these aneurysms are an acquired lesion caused by degenerative changes at arterial branch points brought on by hemodynamic stress (6). The specific degenerative change is disruption and loss of the internal elastic lamina, a feature present in every berry aneurysm (7). Hemodynamic stress is a rubric for the various forces that adversely affect blood vessels as a consequence of their function as channels for blood flow. Turbulence, shear, pressure, and vibration are all borne by the vascular walls as blood circulates continuously through the vascular tree, and these forces continually wear at the vessel (7,8). This hemodynamic stress causes physiologic fatigue (6). Fatigue is the lessening or failure of the capacity of an organ because of excessive stimulation or prolonged exertion. Increased pressure augments hemodynamic stress, and for this reason Stehbens (6) considers hypertension a predisposing factor to aneurysm formation. Stehbens believes hypertension contributes to the formation of aneurysms by contributing to hemodynamically induced fatigue. The concept of vascular fatigue as the seed from which a berry aneurysm develops has important repercussions. The attenuated wall of the artery is prone to rupture owing to fatigue, and fatigue is aggravated by hypertension (6). Since vascular fatigue is cumulative, every bout of transient hypertension contributes to the eventual rupture of the aneurysm, whether the patient is experiencing hypertension at the moment of aneurysmal rupture or not (6). In fact, since fatigue is cumulative, rupture of an aneurysm need not be precipitated by an individual episode of hypertension brought about by any factor, be it emotion, exertion, or traumatic stress (6). Austin et al. (9) have found that the inside of a saccular aneurysm can endure only a certain volume and pressure; their work *in vitro* shows that beyond this certain threshold of increased pressure an aneurysm is prone to sudden, expansive dilatation. Moreover, this expansive dilatation occurs at a smaller aneurysmal volume when the increased pressure is coupled with an increased pulse rate. Both cocaine and methamphetamine cause transient tachycardia and hypertension (10,11). In theory, then, each of these drugs of abuse contributes by its pharmacologic side effects to the propagation and eventual rupture of a berry aneurysm. Several authors have suggested that this theory takes place with cocaine (10,12,13). Wojak and Framm (14) reviewed ten cases of death due to intracranial hemorrhage in patients with a history of cocaine abuse. Four of these patients had a berry aneurysm demonstrated either by angiography or autopsy. Wojak and Flamm suggest that the transient elevation in systemic blood pressure that occurs following cocaine use places increased stress on vascular lesions. Harrington et al. (15) have suggested that repeated episodes of hypertension owing to methamphetamine intoxication may contribute to intracerebral hemorrhage, but they did not consider the relationship of methamphetamine and berry aneurysms. Since both cocaine and methamphetamine cause vascular fatigue by virtue of hypertension and tachycardia, and since this fatigue is cumulative, the previous use of these drugs may be a factor in the formation of the aneurysms in the five patients with a history of drug abuse in whom neither cocaine nor methamphetamine was detected at autopsy. If so, then a history of cocaine or methamphetamine abuse may be as

TABLE 1—*Deaths caused by rupture of cerebral aneurysm associated with cocaine or methamphetamine.*

Case	Age, race, and sex	Drug concentration[a]	Heart weight	Evidence of hypertension	History of drug abuse
1.	25 yo WF	$Cocaine_u$ detected, $cocaine_b$ not detected	340 g	No	Yes
2.	36 yo WM	$Cocaine_b$ 0.94 mg/mL, cocaethylene detected	310 g	No	Yes
3.	27 yo WF	$Methamphetamine_b$ 0.70 mg/mL	375 g	Yes	Yes
4.	26 yo BM	$Cocaine_b$ 0.48 mg/mL, $Methamphetamine_b$ 0.05 mg/mL	330 g	No	Yes
5.	57 yo WM	$Methamphetamine_b$ 1.81 mg/mL	500 g	Yes	Yes
6.	42 yo WM	$Methamphetamine_b$ 0.59 mg/mL	400 g	Yes	Yes
7.	38 yo WF	$Methamphetamine_b$ 0.09 mg/mL	295 g	No	Yes
8.	43 yo WM	$Methamphetamine_b$ 2.55 mg/mL	290 g	No	Yes

[a] u = urine, b = whole blood.

NOTE:—Cases 1 and 2 are from Jefferson County; cases 3–8 are from San Diego County.

important in a death owing to rupture of a cerebral aneurysm as finding the drug of abuse in the decedent's blood.

Although methamphetamine and cocaine have similar pharmacologic effects, the metabolism of the drugs differs. We think this difference is also important in understanding the contribution of cocaine and methamphetamine to berry aneurysm formation and rupture. The number of cases available for review in our study is insufficient to draw definite conclusions, but methamphetamine was associated with aneurysmal rupture more often than was cocaine. This is not due to differences in the rate of intoxication in medical examiner cases. The incidence of acute cocaine intoxication during this 7 years in Jefferson County was 13.6% (376 of 2764 autopsies). Jefferson County had no cases of methamphetamine intoxication during this time. In contrast, the rate of cocaine intoxication in all adult autopsies in San Diego County was 5.1% (685 of 13,362 autopsies). The rate of methamphetamine intoxication in San Diego County in all autopsies was 4.9% (653 of 13,362 autopsies). Therefore, the increased incidence of methamphetamine intoxication in cases of ruptured cerebral aneurysms is not a consequence of the increased incidence of the drug in our patient population. What other factor might account for the disparity? The two drugs are similar in some ways; both block reuptake of norepinephrine to bring about their sympathomimetic effect (10,11). The drugs differ, however, in their half-lives. The half-life of cocaine is around 40 minutes, while the half-life of methamphetamine is roughly 12 hours (16). Cocaine is hydrolyzed in blood, but methamphetamine is only slowly metabolized, if at all (16). The longer half-life of methamphetamine allows more time for vascular fatigue, and we suggest that this additional time for vascular fatigue may make methamphetamine more likely than cocaine to be associated with the formation or rupture of a berry aneurysm.

In summary, we report 83 cases of sudden death due to rupture of a berry aneurysm seen in our offices in a seven-year span. In these 83 cases, we found eight patients who were acutely intoxicated at the time of death with either cocaine, methamphetamine, or both. Unfortunately, not all cases were tested for drugs. While the number of cases in our study is relatively low, we observed that the incidence of acute intoxication with cocaine or methamphetamine in cases of ruptured berry aneurysm is higher than is the background rate of acute intoxication with these drugs seen in our jurisdictions. We believe that this drug intoxication is an important factor in these deaths. Both cocaine and methamphetamine contribute to physiologic vascular fatigue by their pharmacological actions of hypertension and tachycardia. Vascular fatigue in a berry aneurysm leads to rupture and, often, to death. Furthermore, because vascular fatigue is cumulative, we think that chronic previous cocaine or methamphetamine use may be a significant factor in the development of berry aneurysms. We suggest that the longer half-life of methamphetamine is responsible for the increased incidence of aneurysmal rupture in association with methamphetamine compared to cocaine. Although we consider the knowledge of drug abuse important to our understanding of the evolution of cerebral aneurysms, we do not currently list "chronic drug abuse" as a contributing factor in deaths due to ruptured cerebral aneurysms if no drug is detected in the blood at the time of autopsy. If the decedent is acutely intoxicated with either methamphetamine or cocaine, we list this intoxication as a contributing factor.

References

(1) Davis GG, Swalwell CI. Acute aortic dissections and ruptured berry aneurysms associated with methamphetamine abuse. J Forensic Sci 1994;39(6):1481–85.
(2) Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. Am J Cardiol 1984;53(6):849–55.
(3) de la Monte SM, Moore GW, Monk MA, Hutchins GM. Risk factors for the development and rupture of intracranial berry aneurysms. Am J Med 1985;78(1):957–64.
(4) Barrow DL, Reisner A. Natural history of intracranial aneurysms and vascular malformations. Clin Neurosurg 1992;40:3–39.
(5) Toole JF, Robinson MK, Mercuri M. Primary Subarachnoid Hemorrhage. In: Toole JF, editor. Handbook of Clinical Neurology, Vol. 11, No. 55, New York: Elsevier Science Publishers, 1989;1–39.
(6) Stehbens WE. Pathology and pathogenesis of intracranial berry aneurysms. Neurol Res 1990;12:29–34.
(7) Yong-Zhong G, van Alphen HAM. Pathogenesis and histopathology of saccular aneurysms: review of the literature. Neurol Res 1990;12:249–55.
(8) Stehbens WE. Haemodynamic production of lipid deposition, intimal tears, mural dissection and thrombosis in the blood vessel wall. Proc R Soc Lond B Biol Sci 1974;185(1080):357–73.
(9) Austin G, Schievink W, Williams R. Controlled Pressure-Volume Factors in the Enlargement of Intracranial Aneurysms. Neurosurgery 1989;24(5):722–30.
(10) Cregler LL, Mark H. Medical Complications of Cocaine Abuse. N Engl J Med 1986;315(23):1495–99.
(11) Buchanan JF, Brown CR. Designer drugs, a problem in clinical toxicology. Med Toxicol Adverse Drug Exp 1988;3(1):1–17.
(12) Nolte KB, Gelman BB. Intracerebral hemorrhage associated with cocaine abuse. Arch Pathol Lab Med 1989;113(7):812–13.
(13) Oyesiku NM, Colohan ART, Barrow DL, Reisner, A. Cocaine-induced aneurysmal rupture: an emergent negative factor in the natural history of intracranial aneurysms? Neurosurgery 1993; 32(4):518–26.
(14) Wojak JC, Flamm ES. Intracranial hemorrhage and cocaine use. Stroke 1987;18(4):712–15.
(15) Harrington H, Heller HA, Dawson D, Caplan L, Rumbaugh C. Intracerebral hemorrhage and oral amphetamine. Arch Neurol 1983;40(8):503–07.
(16) Karch SB. The pathology of drug abuse. Boca Raton: CRC Press, 1993.

Address requests for reprints or additional information to
Gregory G. Davis, M.D.
Jefferson County Coroner/Medical Examiner's Office
1515 Sixth Avenue South, Room 205
Birmingham, AL 35233-1924