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Acute Aortic Dissections and Ruptured Berry Aneurysms Associated with Methamphetamine Abuse

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ABSTRACT: Sudden, unexpected death can occur following rupture of an artery weakened by aneurysmal dilatation or by medial dissection. In both of these diseases the arterial abnormality is exacerbated by hypertension. This arterial weakness could also be aggravated by the use of drugs with a hypertensive effect. We report seven cases of sudden death in patients abusing methamphetamine—four cases of ruptured berry aneurysms and three cases of aortic dissection with cardiac tamponade. The autopsy findings are reviewed, and various mechanisms are considered by which methamphetamine may contribute to death in such cases.

KEYWORDS: pathology and biology, methamphetamine, berry aneurysm, cerebral aneurysm, aortic dissection, cocaine

Methamphetamine is a popular drug of abuse in San Diego. Since 1987 the San Diego County Medical Examiner's Office has had seven cases of sudden death due either to a ruptured cerebral (berry) aneurysm or aortic dissection in which we also found acute methamphetamine intoxication. These cases were examined to consider the relationship between arterial rupture and methamphetamine.

Background

Methamphetamine is a methylated form of amphetamine; the addition of the methyl group improves the central nervous system penetration of the drug [*1*]. Methamphetamine, which has been a drug of abuse since shortly after its invention over 50 years ago, goes by several street names, including speed, meth, crystal, and crystal meth. Several characteristics make methamphetamine an attractive drug of abuse. Distributors like the drug because it is easily synthesized from phenyl-2-propanone or ephedrine, compounds that were unregulated for many years in the United States and that remain unregulated in Mexico and Canada [*2*]. The pharmacologic action of methamphetamine is similar to that of cocaine; both promote release of norepinephrine and prevent norepinephrine reuptake [*3*]. Methamphetamine addicts enjoy an excitatory high similar in sensation to that of cocaine but with a duration of 2 to 4 hours, a duration much longer than the high from crack cocaine.

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This high can be obtained by taking racemic methamphetamine orally, intranasally, or intravenously. Methamphetamine may also be smoked if it is in the form of pure (+) methamphetamine hydrochloride, a compound known as "ice" on the streets [2]. Regardless of the form in which it is taken, the high of methamphetamine produces alterations in color, color intensity, perception of texture, and the elaboration of fantasy states. Methamphetamine is a sympathomimetic, and thus its side effects are tachycardia, hypertension, intracranial hemorrhage, hyperthermia, seizure, arrhythmia, and death [1].

Methods

A retrospective search was made via computer for cases of death owing either to ruptured cerebral aneurysm or aortic dissection from 1987 through 1992. A total of 23 cases were found. Review of these 23 cases revealed seven cases in which the decedent's blood contained methamphetamine at the time of death. The protocols and microscope slides of these seven cases were reviewed. If needed, an additional section of pons was submitted to evaluate for vasculitis within the central nervous system.

Toxicologic analysis was performed on whole blood by gas chromatography and mass spectrometry following the formation of the pentafluoroproprionic anhydride derivative.

Results

Of the seven cases of sudden vascular death associated with acute methamphetamine intoxication, four deaths were due to ruptured berry aneurysm and three deaths were due to ruptured aortic dissection. In all seven cases the decedent had a history of drug abuse. The male to female ratio was 5:2. The age range of the decedents was 27 to 57 years with a mean of 41 years. Two cases are illustrative of the histories obtained in each case.

Case 1

The decedent was a 42-year-old Hispanic male who smoked 1 pack of cigarettes per day. It is unknown whether the decedent had a history of hypertension. The decedent complained of headache for one week prior to death as well as on the day of his death. The decedent was lying on a bed watching television with a friend when the decedent gasped and became unresponsive. Autopsy showed a ruptured aneurysm a "few mm" in diameter at the junction of the left internal carotid artery and the posterior communicating branch. Although no section was taken of the aneurysm, a section of the brain showed no small vessel vasculitis. Whole blood methamphetamine level was 0.59 μg/mL.

Case 2

The decedent was a 52-year-old white, male, apartment manager with a history of intravenous drug abuse. It is unknown whether the decedent had a history of hypertension. The decedent was repairing a roof at the apartment complex when he complained of pain in the back of his neck. He descended the ladder, went into his apartment, told his wife of his neck pain, and laid down to rest. When his wife checked on him a few minutes later he was unresponsive. Autopsy showed a dissection of the ascending aorta with an intimal tear at the ostium of the right coronary artery, an adventitial tear of the aorta 6 cm distal to the aortic valve, and 450 mL of hemopericardium. Microscopic examination of the aortic dissection showed medial dissection with neither medial necrosis nor disarray of fibers on elastin stain. Toxicologic analysis of the whole blood revealed a methamphetamine level of 0.62 μg/mL. Although cocaine was not detected, the blood contained 0.12 μg/mL of benzoylecgonine; blood morphine was 0.96 μg/mL.

Methamphetamine alone was detected in five of the seven cases. In addition to Case 2 described, one female had a blood codeine level of 0.05 μg/mL. The methamphetamine levels are given in Table 1, and ranged from 0.09 μg/mL to 1.81 μg/mL with an average of 0.67 μg/mL. For comparison, a 10 μg oral dose of methamphetamine in a 70 kg male would be expected to give a peak blood level of 0.03 μg/mL [4]. Hypertension was known to exist in two of our seven patients. In five of seven we found enlarged hearts, with weights that ranged from 375 to 610 g. Nevertheless, two of seven had neither cardiac hypertrophy nor clinical hypertension.

Discussion

The San Diego County Medical Examiner's office sees many deaths associated with methamphetamine intoxication; in the years 1987 to 1992 the office handled 541 such cases with manners of death that ranged from accident to suicide to homicide. (An earlier study showed that there is no significant difference between the tissue concentration of methamphetamine in cases of death due to homicide compared to cases of death due to accidental overdose [5].) In 125 cases death was attributed to accidental overdose by methamphetamine. The blood methamphetamine level in these cases of accidental overdose ranged from 0.0 to 27.6 μg/mL with a mean of 1.37 μg/mL (standard deviation 3.20).

If methamphetamine does contribute to the formation or rupture of cerebral aneurysms and aortic dissections, then what is the mechanism of the drug's contribution? Several hypotheses have been proposed in the literature. Some studies have reported vasculitic lesions associated with methamphetamine abuse [6,7]. Vasculitis was diagnosed by radiologic studies in some cases [6]; in others vasculitis was confirmed by tissue section at autopsy [7]. The autopsy cases showed a necrotizing angiitis similar to polyarteritis nodosa that affected both the brain and visceral organs. The authors of both of these papers suggest that this vasculitis may be due to a direct toxic effect of methamphetamine on arteries or a secondary effect from impurities in the street drug. In none of the cases in our study was there any vascular inflammation in either the brain or the viscera. Furthermore, cross polarization showed no birefringent foreign body material in the vessel walls.

Some have suggested that the vascular lesions seen in cases of methamphetamine abuse are sequelae of drug use itself [6,8]. For example, an aneurysm might develop following trauma to a vessel, or bacterial endocarditis might lead to the formation of a mycotic aneurysm. We found no evidence of this in our cases.

We believe the key to methamphetamine's mechanism of action in arterial rupture lies in the pharmacologic nature of the drug. Since methamphetamine is an adrenergic drug, it causes transient hypertension and tachycardia. Berry aneurysms are the result of degenerative

TABLE 1—*Deaths caused by arterial rupture associated with methamphetamine.*

Case	Age, Race, and Sex	Cause of Death[a]	Methamphetamine Level[b]	Other Drugs	Heart Weight	Evidence of Hypertension
1.	42 yo WM	BA	0.59 μg/mL	No	400 g	Yes
2.	52 yo WM	AD	0.62 μg/mL	Yes	480 g	Yes
3.	27 yo WF	BA	0.70 μg/mL	No	375 g	Yes
4.	42 yo BM	AD	0.24 μg/mL	No	610 g	Yes
5.	57 yo WM	BA	1.81 μg/mL	No	500 g	Yes
6.	28 yo WM	AD	0.66 μg/mL	No	350 g	No
7.	38 yo WF	BA	0.09 μg/mL	Yes	295 g	No

[a]BA, berry aneurysm; AD, aortic dissection.
[b]In whole blood.

changes at arterial branch points brought on by hemodynamic stress. These are associated with hypertension and have characteristic loss of the media, weakening the arterial wall [*9*]. The attenuated wall of the artery is prone to rupture with an acute increase in intracranial pressure [*10*]. Two factors underlie the formation and propagation of aortic dissections—medial degeneration and arterial hypertension [*11*]. When present, medial degeneration is the more important of the two, but dissection does occur in the presence of hypertension in which no medial degeneration is seen [*10*]. Medial degeneration and hypertension combine to form an intimal tear. Once the intimal tear has formed, the steepness of the pulse wave (that is, the change in pressure over the change in time [*dP/dt*]) and the increased peripheral blood pressure propagate the dissection. The greater the pulse wave and blood pressure, the greater the rate of propagation. Methamphetamine causes a sudden, sharp increase in both the pulse wave and the blood pressure by causing both tachycardia and hypertension.

Since the rupture of berry aneurysms and aortic dissections can be precipitated by a sudden increase in vascular pressure, we contend that the adrenergic effect of methamphetamine plays a role in the aggravation of both berry aneurysms and aortic dissections by causing transient hypertension and, in the case of aortic dissection, tachycardia. The possibility that pharmacologic increase of blood pressure and heart rate may contribute to vascular rupture has been discussed, to some extent, in conjunction with arterial rupture associated with acute cocaine intoxication [*12–14*]. If it is the increase in blood pressure and heart rate that precipitates vascular rupture, then death owing to rupture of a berry aneurysm or aortic dissection may be caused by abuse of any drug that, like either methamphetamine or cocaine, causes hypertension and tachycardia. Thus N-methylcathinone, an amphetamine of abuse that has recently become popular around the Great Lakes, is likely to contribute to some deaths caused by ruptured berry aneurysm or aortic dissection.

In summary, we have noted an association between methamphetamine use and sudden deaths due to ruptured cerebral aneurysm or ruptured aortic dissection. This association has previously been reported for cocaine [*12–14*] but not for methamphetamine. Methamphetamine, like cocaine, has hypertensive and tachycardic effects that would exacerbate, if not initiate, the formation of berry aneurysm or aortic dissection. Therefore, we recommend toxicologic analysis for methamphetamine, as well as cocaine, in all cases of ruptured berry aneurysm or aortic dissection and, when found, that the drug be noted on the death certificate as a contributor to the cause of death.

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