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Selected Topics: Toxicology

METHAMPHETAMINE-RELATED STROKE: FOUR CASES

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□ **Abstract—Amphetamine use in certain parts of the United States has risen dramatically. Methamphetamine, the most-common illicitly abused type of amphetamine, can be inhaled, injected intravenously, or smoked. It is a potent sympathomimetic that may lead to vascular events including myocardial infarction and stroke. Because of the demographics of drug use, these potentially devastating events usually occur in relatively young patients. The pathophysiology of stroke related to amphetamine use is multifactorial. Elevation in blood pressure, vasculitis, or other vascular toxicity are postulated as major mechanisms. Four cases of stroke associated with the use of methamphetamine, all occurring in patients ranging in age from 29–45 years, are described. Methamphetamine use appears to be a risk factor for the development of stroke. The rise in methamphetamine use will undoubtedly result in increased Emergency Department admissions with clinical presentations very similar to those of cocaine intoxication. © 1999 Elsevier Science Inc.**

□ **Keywords—methamphetamine; amphetamine; stroke; vasculitis; drug abuse; intracerebral hemorrhage**

INTRODUCTION

The illicit use of amphetamine in certain parts of the United States has risen to increasingly epidemic proportions. From 1991–1994, the number of amphetamine-related annual deaths rose significantly from 63 to 134 in Los Angeles and from 8 to 76 in Phoenix (1). During this same period, Emergency Department (ED) episodes increased from 506 to 1,418 in Los Angeles and from to 164 to 770 in Phoenix annually (1). During 1990–1994, cocaine-related episodes rose by 78%, a comparatively small increase compared with methamphetamine (2). Methamphetamine, the most-common illicit amphetamine abused, is structurally related to amphetamine and has been used at least once by an estimated 4 million Americans (1).

Methamphetamine is particularly dangerous as it may be "snorted" (inhaled), injected intravenously, or smoked, leading to a rapid rise in blood levels resulting in intense euphoria and addictive potential. The metabolites of methamphetamine may be detected in the urine through drug screening assays. Because of their structural similarity, various types of amphetamines may be detected, making the test not specific for methamphetamine. Sympathomimetic effects of methamphetamine include an elevation of pulse rate and blood pressure, an increased level of alertness, decreased fatigue, and suppression of appetite (3). Adverse events occurring as a result of vascular effects include myocardial infarction and stroke. These manifestations of methamphetamine abuse are especially devastating as they occur largely in patients younger than age 45 and result in substantial disability or death (4,5). Strokes resulting from methamphetamine use may be ischemic or hemorrhagic and are

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of uncertain pathogenesis. One possible mechanism for both types of methamphetamine-related stroke involves a well-described associated cerebral vasculitis (6). In the present report, four cases of amphetamine-related cerebrovascular accidents occurring in younger patients are presented.

CASE REPORTS

Case 1

A 29-year-old female with a 20-week gestation was seen at home by paramedics summoned when the patient complained to her husband of weakness. She presented to the ED with labored respirations and unresponsiveness. Pregnancy-induced hypertension had been diagnosed 3 years before. Initial blood pressure recorded by paramedics at the patient's home was 250/160 mmHg. The patient was treated with intravenous (i.v.) diazepam and magnesium sulfate. In the ED, blood pressure was 184/114 mmHg. Computed tomography (CT) scan of the head revealed a large cerebellar and brainstem hemorrhage with obstructive hydrocephalus. The patient was a chronic user of methamphetamine. The timing of the last episode of use could not be confirmed. Urine microparticle enzyme immunoassay (Axsym System, Abbot, Abbot Park, IL) was positive for amphetamines but negative for cocaine. Brain death and fetal death were documented within 24 h after admission. Life support was discontinued, and the patient expired.

Case 2

A 36-year-old male presented with dysarthria, right upper extremity weakness, and right facial droop of approximately 24-h duration. The patient used approximately one-quarter gram daily of inhaled methamphetamine. He presented with a blood pressure of 199/140 mmHg. There was a history of poor compliance for treatment of hypertension, and also of tobacco use. Blood pressure decreased to 169/115 mmHg in response to nifedipine and labetolol. Urine toxicology testing was not performed. The patient had last used methamphetamine on the day he developed the symptoms. A head CT scan revealed a radiolucency in the left basal ganglia consistent with an ischemic infarct. Evaluation for the etiology of stroke including Doppler studies of the carotid arteries was negative. The patient was discharged with residual right upper extremity weakness but improvement in other symptoms. At follow-up a few weeks later, symptoms were completely resolved.

Case 3

A 45-year-old male with a history of hypertension, chronic renal insufficiency, tobacco use, and i.v. methamphetamine use developed a sudden right temporal headache with left hemiparesis. The patient's brother confirmed use of methamphetamine by the patient before the event. Initial blood pressure recorded by paramedics was 250/150 mmHg. On presentation, agitation treated with sedation decreased the blood pressure to 193/118 mmHg. The patient was speaking incomprehensibly and became progressively lethargic. Urine microparticle enzyme immunoassay (MEIA) was positive for amphetamines and for opiates, which the patient had received in the ED before the test. Cocaine urine toxicology was negative. A head CT scan revealed a large temporal and parietal hemorrhage involving the internal capsule and associated with midline shift. Urgent evacuation of the hematoma was done, but rebleeding resulted in a second craniotomy. Postoperatively, the patient's neurologic deficit did not improve, and he became progressively less responsive. The hospital course was complicated by pneumonia, exacerbation of renal failure, and fever. Six weeks after admission, the patient was transferred to a chronic care facility with no significant neurologic recovery.

Case 4

A 29-year-old female who had resumed use of i.v. methamphetamine shortly after the birth of her child 2 weeks previously presented to the ED 36 h after her boyfriend noted the patient veering slightly to the left while walking. There was no history of preeclampsia. On initial examination, blood pressure was 112/71 mm Hg with a dense right hemiplegia and aphasia. The time of last use of methamphetamine could not be confirmed. The patient smoked cigarettes and also used cocaine and marijuana. Drug use apparently had been interrupted during pregnancy and was negative on admission for delivery. During the present admission, urine toxicology was positive for amphetamines but negative for cocaine and other drugs. Laboratory data included a hemoglobin of 8.0 g/dL, hematocrit 24%, and platelet count of 995×10^3/cc (3), the latter attributed to iron deficiency anemia. A CT scan of the head revealed a left middle cerebral artery distribution infarct with intraluminal echoes suggesting visible thrombus. Because 36 h had passed, thrombolysis was not considered. A transthoracic echocardiogram was unremarkable. Carotid Doppler ultrasound suggested thrombus in the left internal carotid artery extending to the carotid bulb and into the common carotid artery. Angiogram was not performed. Activity of protein C and S was normal as was antithrombin III. The patient was discharged to a rehabilitation facility after 2 weeks of hospi-

talization with no improvement in neurologic deficits. Eight months after hospitalization, aphasia remained, but motor strength on the right side had markedly improved.

DISCUSSION

The occurrence of stroke in young patients is a devastating event. While stroke in this group accounts for only a small percentage of the total, the associated morbidity and mortality are considerable. Kaku et al. found that cardiac disorders, drug abuse, diabetes mellitus, and hypertension (in that order) are associated with the highest risk ratio for stroke in a young population (5). This study more specifically examined the role of drug abuse as a risk factor in the development of stroke in a population aged 15–45 and found 21 cases of amphetamine-related stroke over a 10-year period. Coabuse of other drugs associated with stroke is possible, but the urine toxicology detected only amphetamine in our patients. Urine toxicology is not specific for amphetamines. Other sympathomimetic amines may crossreact with amphetamine to give a positive result, including methamphetamine. In Kaku's study, 47% of patients under the age of 35 were found to have used illicit drugs before the event, with 30% using more than one drug. In this study, virtually all strokes occurred within 6 h after use of cocaine or amphetamines. Amphetamines were identified as the second-most-common cause (after cocaine) of stroke occurring acutely after drug abuse, with the i.v. route being the most common route of administration. While cocaine has been the drug most associated with stroke in the literature, ED admissions for methamphetamine use in the United States rose from 4,887 in 1991 to 17,397 in 1994 (1).

The pathophysiology of stroke secondary to amphetamines may involve several mechanisms (7). These strokes may be either hemorrhagic or ischemic. Elevated blood pressure has been noted in approximately 50% of cases and was noted in three of our four patients (5). The patient in whom it was not detected presented 24 h after her last use of the drug. While three of our four patients had been diagnosed with hypertension before the event, it is likely that methamphetamine use resulted in significant elevations in blood pressure. In hemorrhagic strokes, these acute elevations in blood pressure may lead to wall stress, which leads to vessel rupture. The vasoconstrictive effect of amphetamine may also lead to the development of ischemic stroke.

Another very important pathophysiologic mechanism appears to be amphetamine-induced cerebral vasculitis, which has occurred mostly with hemorrhagic but also with ischemic stroke (7,8). The lesion is described as a necrotizing angiitis closely resembling periarteritis nodosa, consisting of hemorrhages, infarctions, microaneurysms, and perivascular cuffing occurring in small-to-medium-sized arteries (7). Treatment with steroids and cyclophosphamide has improved neurologic symptoms in some patients (6). Direct vascular toxicity, hypersensitivity reaction, impurities in the drug, or a response to simultaneously abused drugs have all been postulated as etiologic factors. The fact that cerebral vasculitis has been reported with oral and nasal and not just i.v. use may link amphetamine itself more closely with vasculitis (9,10). Vasculitis may not be associated with arteriographic findings (10). The dramatic increase in the illicit use of amphetamine in the United States may lead to an increase in devastating vascular complications, many of which are similar to those associated with cocaine intoxication.

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