Reviews

Methamphetamine-Associated Cardiomyopathy

Address for correspondence:
Sekon Won, MD
Queens Heart
1301 Punchbowl Street
Honolulu, HI 96813
wsekon@yahoo.com

Sekon Won, MD; Robert A. Hong, MD; Ralph V. Shohet, MD; Todd B. Seto, MD, MPH; Nisha I. Parikh, MD, MPH
John A. Burns School of Medicine University of Hawaii at Manoa Honolulu, Hawaii

ABSTRACT

Methamphetamine and related compounds are now the second most commonly used illicit substance worldwide, after cannabis. Reports of methamphetamine-associated cardiomyopathy (MAC) are increasing, but MAC has not been well reviewed. This analysis of MAC will provide an overview of the pharmacology of methamphetamine, historical perspective and epidemiology, a review of case and clinical studies, and a summary of the proposed mechanisms for MAC. Clinically, many questions remain, including the appropriate therapeutic interventions for MAC, the incidence and prevalence of cardiac pathology in methamphetamine users, risk factors for developing MAC, and prognosis of these patients. In conclusion, recognition of the significance of MAC among physicians and other medical caregivers is important given the growing use of methamphetamine and related stimulants worldwide.

Introduction

After cannabis, methamphetamine and related compounds have become the most widely abused illicit drug worldwide.[1] A myriad of clinical complications have been associated with methamphetamine use. Although methamphetamine-associated cardiomyopathy (MAC) is increasingly being reported, this has not been well studied. In 2010, heart failure ranked as the third most common reason for hospitalization in the United States among adults,[2] and registry data have shown that >5% of patients hospitalized for heart failure reported abusing stimulants, including methamphetamine.[3] This article will review (1) the pharmacology of methamphetamine, (2) historical perspective and epidemiology, (3) case and clinical studies, (4) proposed mechanisms of MAC, and (5) treatment.

Pharmacology

Amphetamine is a synthetic derivative of phenethylamine, a natural amine that is biosynthesized from phenylalanine.[4] The addition of an extra methyl group to amphetamine yields methamphetamine (Figure 1), which has increased lipid solubility and crosses the blood–brain barrier more readily, thereby increasing the stimulant properties on the central nervous system.

There are 2 isomeric forms of methamphetamine, a dextro-isomer and a levo-isomer.[5] The dextro-isomer is the abused drug, as it is the central nervous system stimulant and is five times more biologically active, while the levo-isomer is used in over-the-counter nasal decongestants.[6] The most popular route of administration is smoking of crystal methamphetamine; injection and insufflation are other popular routes.[7]

Depending on route of administration and urine pH, methamphetamine is excreted primarily in urine, with approximately 30% to 50% of a dose excreted as the parent drug and up to 10% as dextroamphetamine.[8,9] The half-life of the drug is approximately 9 to 12 hours, and this appears to be independent of the route of administration.[4] Initial drug screening typically uses immunoassay to detect the presence of methamphetamine of amphetamine in urine. False positives can occur, and further testing can be obtained using techniques such as gas chromatography–mass spectrometry or chiral chromatography.[10]

Though structurally very similar to catecholamines (Figure 1), methamphetamine exerts its sympathomimetic effects indirectly by causing increased release of dopamine, norepinephrine, epinephrine, and serotonin into the synapse.[11] It does not have direct sympathomimetic properties. Various mechanisms have been described, such as methamphetamine entering the presynaptic neurons via both transporters and passive diffusion to cause release of catecholamines into the cytosol and eventually into the synapse.[11] Also, reuptake transporters for these neurotransmitters are blocked by methamphetamine, causing increased neuronal activity.

Clinically desirable effects of methamphetamine use may include increased alertness, euphoria, energy, and decreased appetite.[12] Dopamine appears to be the major neurotransmitter affected by methamphetamine abuse,

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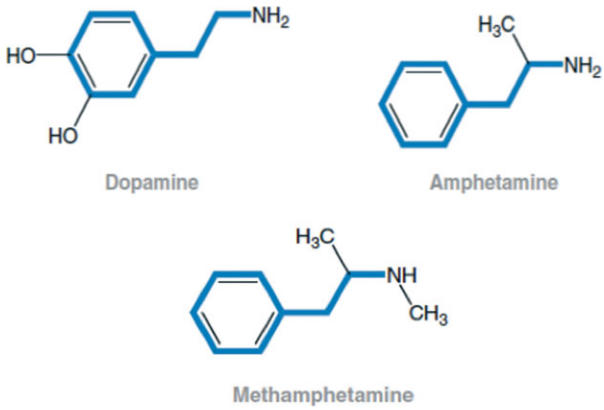

Figure 1. Chemical structures of methamphetamine and related compounds.[11]

with dopaminergic neurons involved in the mesolimbic and mesocortical pathways playing a key role in reward, pleasure, and mood.[13]

Methamphetamine is more potent and longer lasting than cocaine, which only blocks the reuptake of catecholamines.[5] When smoked, the sense of euphoria can last for hours as opposed to minutes with cocaine. Also, because it is less expensive, methamphetamine is becoming a progressively more attractive drug for abuse.

Historical Perspective

Nagai Nagayoshi first isolated ephedrine from the Chinese shrub *Ephedra distachya* in 1885.[14] Ephedra is a genus with several species, including *E. sinica* (ma huang), which has been used in Chinese traditional medicine for thousands of years for treatment of asthma and hay fever.[15] Nagayoshi then synthesized methamphetamine from ephedrine in 1893.[14]

Methamphetamine has been prescribed for a variety of clinical conditions. The US Food and Drug Administration approved methamphetamine for treatment of narcolepsy, depression, alcoholism, and hay fever in 1944 and for the treatment of obesity in 1947.[16] Methamphetamine was widely used by both Allied and Axis forces in World War II as a stimulant to decrease fatigue and heighten alertness.[14,16] In the United States in 1967, methamphetamine reached a peak of 31 million prescriptions. Currently it is approved for obesity and attention deficit hyperactivity disorder.[17]

Epidemiology of Methamphetamine Abuse

According to the 2011 National Survey on Drug Use and Health, illicit-drug use had risen to nearly its highest level in 10 years in the United States, with 8.7% of Americans age ≥12 years, or approximately 22.5 million people, saying they had used illicit substances in the month prior to the survey.[18] The number of current methamphetamine users rose to 439,000. Historically, methamphetamine abuse was most common in Hawaii and on the West Coast, but there has been a clear spread eastward (Figure 2).[19] The mean age at first use in 2011 was only 17.8 years.[18]

Methamphetamine and Cardiac Pathology

Methamphetamine has been linked to various cardiac pathologies. Hypertension and tachycardia appear to increase with increasing doses of methamphetamine due to adrenergic stimulation.[20] Other pathologies described include arrhythmias; vasospasm; accelerated atherosclerosis; acute coronary syndrome; sudden cardiac death; coronary, carotid, and aortic dissections; and circulatory collapse, as well as cardiomyopathy.

Case Reports and Clinical Studies

Reports of death related to centrally stimulating amines such as amphetamine were noted as early as the 1940s.[21] Kalant et al described the linkage between methamphetamine abuse and death from left ventricular (LV) failure in 2 persons in 1975.[22] In 1979, Rajs described the pathologic findings of cardiac-chamber enlargement, LV hypertrophy, hemorrhage, fibrosis, and contraction-band necrosis in 14 subjects who had used centrally acting amines such as amphetamine or methamphetamine.[23]

Multiple case reports from postmortem studies then followed, and in 1989, Jacobs was the first to describe an association of methamphetamine use with dilated cardiomyopathy in a living patient.[24] A 48-year-old woman was hospitalized for pulmonary edema. Her echocardiogram showed a dilated, poorly contracting left ventricle, and subsequent cardiac catheterization revealed global LV hypokinesis with a left ventricular ejection fraction (LVEF) of 35% and normal coronary arteries. The patient had abused methamphetamine pills for weight loss; after discontinuation of this drug, her LV systolic dysfunction resolved. Also in 1989, Nestor described a case of a 28-year-old woman hospitalized with pulmonary edema and dilated cardiomyopathy who admitted to smoking crystal methamphetamine. This was the first association between smokable methamphetamine and cardiac dysfunction. The patient was documented to have no cardiac ischemia or infarct on a thallium treadmill stress test. Numerous cases of MAC have since been reported.

Case series have also been published on MAC. Wijetunga et al performed a retrospective analysis on patients discharged from a tertiary-care hospital with the diagnosis of cardiomyopathy over a 4-year time period.[25] More than 1600 patients were identified, of whom 120 had a diagnosis of substance abuse as well. After excluding those with coronary artery disease, alcohol or cocaine abuse, or other potential etiologies of cardiomyopathy, 21 subjects remained who were methamphetamine users. Nineteen underwent echocardiography, which revealed dilated LV chamber size with globally depressed LV systolic function to varying degrees in most patients.

Yeo et al performed a case–control study looking at patients age <45 years who were discharged from a tertiary-care hospital with diagnosis of either congestive heart failure or cardiomyopathy.[26] Controls were age-matched, hospitalized patients who had an echocardiogram with normal LVEF of ≥55% and no wall-motion abnormalities. Methamphetamine users had a 3.7-fold increased odds ratio of congestive heart failure or cardiomyopathy as compared with controls.

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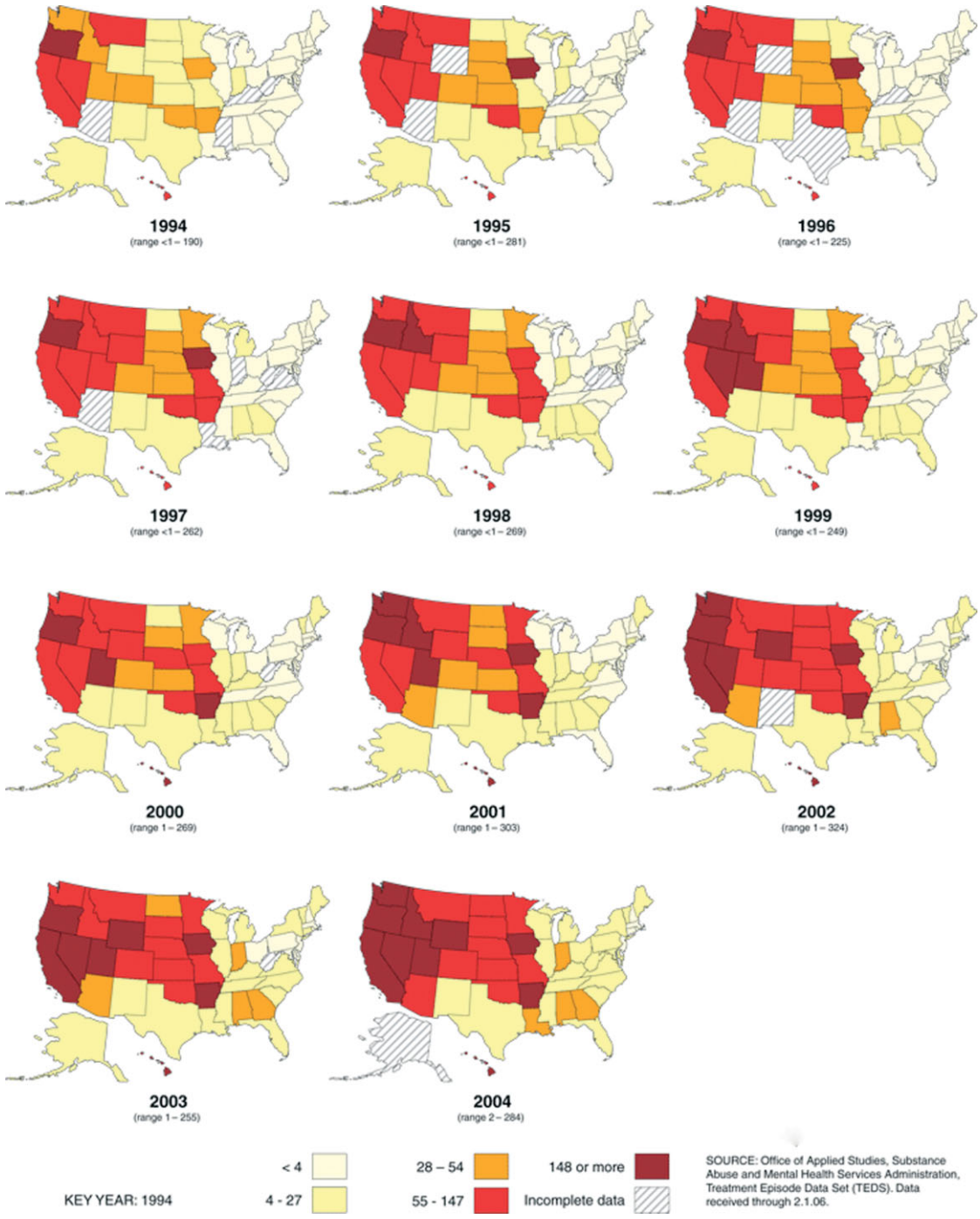

Figure 2. Primary methamphetamine/amphetamine admission rates by state,1994–2004 (per 100 000 population age ≥12).[19]

Ito et al looked retrospectively at patients age <45 years who were hospitalized for either cardiomyopathy or heart failure.[27] After exclusion of coronary artery disease or valvular heart disease, patients were divided into 2 groups, one that used methamphetamine and another that did not. The group that used methamphetamine had, on echocardiography, higher LV volumes and lower LVEFs than nonusers.

As previously reported, MAC appears to be potentially reversible upon cessation of methamphetamine use. Anecdotal experiences have also noted remarkable improvement in cardiac function in patients with MAC who have discontinued drug use. In one case report, cardiac magnetic resonance imaging was performed in a patient with severe MAC, demonstrating no delayed gadolinium enhancement to suggest any significant fibrosis.[28] The patient discontinued methamphetamine use and was placed on medical therapy, including a β-blocker and angiotensin-converting enzyme inhibitor. Her LVEF improved from 37% to 64% after 6 months. The timing of recovery of LV systolic function,

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and when meaningful recovery is no longer possible, remain unknown, however.

Proposed Mechanisms of Methamphetamine-Associated Cardiomyopathy

The mechanisms underlying cardiomyopathy in methamphetamine use are most likely multifactorial. Proposed etiologies for cardiac injury include catecholamine excess, coronary vasospasm and ischemia, increases in reactive oxygen species (ROS), mitochondrial injury, changes in myocardial metabolism, and direct toxic effects.[29,30] Pathologically, ventricular hypertrophy and dilation, fibrosis, and contraction-band necrosis commonly have been found.[29]

Catecholamine excess with associated coronary vasospasm has been postulated to be a cause of MAC. Chen reported on a case of a 19-year-old male who abused methamphetamine presenting with chest pain and was found to have inferolateral ST elevations on electrocardiogram.[31] He underwent emergent cardiac catheterization, which revealed no evidence of significant epicardial coronary stenosis; however, there was Thrombolysis In Myocardial Infarction grade 1 flow in all major epicardial vessels with myocardial blush grade of 0, suggestive of global coronary microvascular vasospasm. Hong et al described a patient who abused methamphetamine and died of cardiogenic shock.[32] Postmortem examination revealed diffuse transmural myocardial ischemia and focal areas of infarction. The coronary arteries, however, were free of obstructive lesions.

MAC also has been ascribed to increases in ROS. Rats treated with methamphetamine injections were found to have both increased ROS and LV dilation with systolic dysfunction.[30] Mitochondrial injury has been proposed to be another, and perhaps not mutually exclusive, mechanism for MAC. Kaiho demonstrated mitochondrial changes and myoglobin loss in rats undergoing intraperitoneal injection of methamphetamine.[33] The loss of myoglobin was demonstrated in the rat ventricle, and myocardial cells with myoglobin loss demonstrated marked mitochondrial swelling. Disruption of oxidative phosphorylation associated with myoglobin loss was proposed as a cause of cardiomyopathy with methamphetamine use.

Impairment of cardiac function with methamphetamine use may also be related to a hyperadrenergic state and a reversible stress-induced cardiomyopathy. Srikanth et al described a 42-year-old methamphetamine user who was found to have transient LV dysfunction and wall-motion abnormalities consistent with a stress-induced cardiomyopathy.[34] An index ventriculogram showed apical ballooning consistent with a takotsubo process. An echocardiogram performed 3 days later demonstrated significant improvement in LV function. Catecholamine excess, in this case produced by methamphetamine, has been postulated to be the cause for stress-induced cardiomyopathy. Patients with a hyperadrenergic state such as from pheochromocytoma causing a reversible cardiomyopathy have been well described.[35] Also, Abraham et al reported 9 patients who developed transient stress-induced cardiomyopathy after intravenous administration of catecholamines such as epinephrine or dobutamine.[36] Another link between methamphetamine use, catecholamine surge, and stress is the resultant cardiac-contraction band necrosis that can be seen in all 3 settings.[37]

MAC may be confounded by polysubstance abuse, particularly alcohol and cocaine use. Mendelson et al showed that the concurrent administration of alcohol with methamphetamine increased the rate-pressure product as compared with methamphetamine use alone.[38] This increase in workload may have a synergistic deleterious effect on the process of cardiomyopathy. Scant data exist on the concomitant use of cocaine and methamphetamine.[39] One study did find that patients who by survey abused methamphetamine alone, without history of alcohol or cocaine abuse, did have dilated cardiomyopathy.[40] Fleury et al studied predictors of cardiovascular response such as increased heart rate and blood pressure to methamphetamine administration.[41] Recent alcohol use was found to be a predictor, as was route of administration. Intravenous drug use had higher peak changes in diastolic blood pressure vs those who smoked methamphetamine. Also, female methamphetamine abusers were found to have lower diastolic and systolic pressures at baseline than males, which may have a protective effect.

Treatment

With withdrawal of adrenergic stress, resolution of LV systolic dysfunction may be seen as noted in patients with stress-induced cardiomyopathies, pheochromocytomas, and MAC. The potential for early reversibility of MAC has significant medical and social implications. Theoretically, as methamphetamine use induces a hyperadrenergic state, there may be potential preferential cardiac remodeling with β-blockers compared with other standard therapies; but this remains to be established, and caution should be used with respect to β-blocker therapy in active methamphetamine use.[42] Blockade of the renin-angiotensin system is also recommended for patients with reduced LV systolic function.[43]

Anti-methamphetamine monoclonal antibodies have been used in rats with reduction in methamphetamine-induced locomotor activity as well as hypertension and tachycardia.[44] Also, aripiprazole, a partial dopamine and serotonin agonist, in humans appeared to attenuate some of the stimulant effects of methamphetamine, both in the central nervous and cardiovascular systems.[45]

Conclusion

Methamphetamine and related substances are now among the most abused drugs worldwide. There is a growing body of evidence that methamphetamine abuse is associated with cardiomyopathy, although the mechanism for cardiac dysfunction is still unclear. Evidence points toward contributions from drug-induced vasospasm and ischemia, direct toxicity of methamphetamine, as well as deleterious effects of excess catecholamines on cardiomyocytes.

Clinically, many uncertainties remain, including the appropriate therapeutic interventions not only for MAC itself, but also for methamphetamine abuse in general. There appears to be an unclear window during which reversibility of cardiac dysfunction can occur with cessation of methamphetamine. Important areas for future research

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include finding the incidence and prevalence of cardiac pathology in methamphetamine abusers and risk factors for and prognosis of MAC. Future studies will need to adjust for concomitant drug use, including cocaine and alcohol. Recognition of MAC among medical caregivers is important given the growing use of methamphetamine and related stimulants.

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