Minireview

Heart disease, methamphetamine and AIDS

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Abstract

Methamphetamine (MA) not only affects the nervous system but also has cardiac toxicity and immunosuppressive properties. This manuscript will provide support that there is a relationship between MA use and heart disease as well as immune dysfunction. The cardiovascular manifestations of acute MA use include tachycardia, atrioventricular arrhythmias, myocardial ischemia, myocardial ischemia and hypertension, resulting in cardiac lesions. Chronic use of MA causes cardiomyopathy including cellular infiltration, myocardial hypertrophy, myocardium rupture and fibrosis. The increased catecholamine levels are responsible for the cardiac lesions induced by MA. The additional problem with MA use is its potential to disrupt the immune system function leading to suppression of mitogen-stimulated lymphocyte, a reduction in circulating lymphocyte numbers and alternation T-lymphocyte cytokine secretion as well as B cell proinflammatory cytokine secretion. Concomitant MA use and Human Immunodeficiency Virus (HIV) infection not only enhances immunosuppression associated with HIV but also increases the heart disease occurrence with a coincidentally complication of AIDS or AIDS medications.

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Introduction

Methamphetamine (MA) also known as speed, crank, go, crystal, meth, ICE or poor man’s cocaine, is a derivative of amphetamine. Amphetamine including MA has a similar structure to a natural extract, ephedrine, a sympathomimetic amine used as a stimulant and possessing appetite suppression and
bronchodilation properties. (MacKenzie and Heischober, 1997) MA was first synthesized by a German chemist in 1887, studied extensively, and used in the clinic until 1930s. (Anglin et al., 2000) Subsequently, MA was widely available for users and caused abuse epidemic that occurred rapidly. In the 1960s, the United States government realized that MA has significant potential of tolerance and physiologic dependence. Therefore in 1970, MA was restricted as a controlled substance by government law. MA is easily made in clandestine home laboratories by reduction of ephedrine or by the condensation of the phenylacetone and methylamine. MA is less expensive compared to cocaine and has become the most common illicit abused amine drug, resulting in rapidly increased users number. In 1996, about 2.3% of the population had used MA at least once in the United States and this epidemic also greatly spread world-widely such as Asian countries. (The National Institute on Drug Abuse, 2002; NIDA Research Report, 2002).

MA as a sympathomimetic stimulant affects the central nervous system (CNS). MA use leads to rapid rise in blood levels generating a quick and long lasting high resulting in intense euphoria and addictive potential. (Centers for Disease Control and Prevention, 1995) MA can be taken orally, snorted, smoked or injected, in approximately increasing order of immediacy of onset. Duration is subjective, but is probably on the order of 4–8 hours. Delayed absorption (for example, due to oral ingestion) can prolong the effects relative to time of administration. Of course, larger doses last longer due to the fact that it is removed from the blood at a finite rate. The serious side effects of MA use include neurologic, obstetric, gastrointestinal, renal, endocrine complications, with possible long-term damage and cardiovascular disease, which is the most common complaint by MA users. (Derlet and Horowitz, 1995) MA abuse is also a social problem related to crime, traffic and non-traffic accidents, physical and psychological hazards. In California, MA-related hospital admissions increased 49% in 1994 compared to 1993. In Iowa, MA use accounted for 65% drug arrests, even more than alcohol arrests. (US Department of Justice-Drug Enforcement Administration, 1996) In 1999, the American Association of Poison Control Centers’ (AAPCC) Toxic Exposure Surveillance System did not categorize specific methamphetamine exposures; these exposures were included in the amphetamine category. A total of 16,684 exposures were reported, with 4593 in those younger than 6 years and 4614 in those older than 19 years. During 1999, a total of 18 deaths associated with amphetamine exposures were reported to the AAPCC. Frequently, many local coroners’ offices have more reliable data on fatalities associated with street-drug abuse. More seriously, MA acute overdose or chronic use has high death rate. A 5-year retrospective investigation in Japan revealed that 2.32% victims of drug use were MA-related in the drug-related death cases. (Zhu et al., 2000) In Greece, until 1997, only one MA-related fatality case was reported, while from 1997 to 2002, there were 7 out 1500 fatalities. (Raikos et al., 2002) MA use is also highly related to HIV infection and AIDS development. (Rotheram-Borus et al., 1994; Molitor et al., 1998).

Thus, understanding the mechanisms, pathogenesis and effects of MA use and HIV infection on heart disease will help define therapeutic targets and avenues of prevention for these MA users, AIDS and heart disease patients.

**Pharmacology**

MA Free Base is N, α-Dimethylbenzeneethanamine C\textsubscript{6}H\textsubscript{4}CH\textsubscript{2}CH(NHCH\textsubscript{3})CH\textsubscript{3}, molecular weight is 149.24. Its hydrochloride salt, which is strongly hydrophilic, is as easily smoked as cocaine. It is an N-methyle homologue of amphetamine. MA freebase is an oil and is uncommon on the street. MA is a white,
odorless, bitter, crystalline powder that can be soluble in water and alcohol. The purity of MA depends on the manufacture process. Ephedrine or pseudoephedrine is the basic MA precursors. Chloroephedrine is the intermediate of MA synthesis, which also affects the purity of MA. (Fig. 1) (Varner et al., 2001) Impure MA has an increased toxicity that causes additional medical complications. MA can be ingested, injected, smoked and snorted intranasally. (MacKenzie and Heischober, 1997) Immediately afterwards, the user experiences an intense rush or “flash” that lasts only a few minutes and is extremely pleasurable. As with similar stimulants, MA most often is used in a “binge and crash” pattern. When inhaled, MA vapors are rapidly absorbed across the large surface area of the alveolar membrane and are deposited in lungs. (Riviere et al., 2000) Redistribution happens after MA administration, first to the kidneys followed by the spleen, brain, liver, heart and finally to the serum. (Riviere et al., 2000).

MA has (+) and (−) enantiomer. The (+) enantiomer is five times as potent as the (−) enantiomer. (Cho, 1990) The chemical structure of MA is amphetamine with an addition of one methyl group. (Fig. 2) The methyl group makes the drug even more potent by facilitating its penetration into the central

Fig. 1. Clandestine methods for MA synthesis.

Fig. 2. The structure of MA.
nervous system. (Davis and Swalwell, 1994) MA’s actions are often compared to cocaine since MA and cocaine are both potent sympathomimetics. (Schindler et al., 1992) The average half-life of MA in the body is much longer than cocaine. (Schindler et al., 1995) Table 1 summarized short-term and long-term psychological and physical effects of MA use.

The cardiovascular complications and heart disease of MA

MA can cause a variety of cardiovascular problems, which include rapid heart rate, irregular heartbeat, increased blood pressure, and irreversible damage brain blood vessels, leading to stroke. (Varner et al., 2002) Intravenous administration of MA in rats caused a pressure response consisting of an initial rapid blood pressure increase and a biphasic heart rate change consisting of bradycardia followed by tachycardia. (Varner et al., 2002).

MA overdose induces tachycardia, atrioventricular arrhythmias, myocardial ischemia and acute hypertension. (Derlet and Horowitz, 1995) Chronic MA use results in inflammation of the heart lining and cardiomyopathy including cellular infiltration, myocardial hypertrophy, myocardium rupture and fibrosis. (Citron et al., 1970; Smith et al., 1976; Kalant and Kalant, 1975) The cardiotoxicity of MA is also evident in the autopsy investigations. In total 84 autopsies, 35 were found aortic dissection, among them, there were seven cases tested as MA positive. The aortic dissection was found in those MA users, which is most likely due to MA’s hypertensive effect. (Swalwell and Davis, 1999) MA was detected in another anatomic and toxicologic investigation of 413 deaths. Coronary artery disease with enlarged hearts, ranging from minimal to severe multivessel, was identified in 79 of the 413 MA users. 65% death

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<th>Model</th>
<th>Outcomes</th>
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<td>Myocytes</td>
<td>Cellular granulation, myocyte hypercontraction, broken membrane, increased cell size, injured cytoskeleton, cellular hypertrophy</td>
<td>(He, 1995; Maeno et al., 2000a,b)</td>
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<tr>
<td>Mouse</td>
<td>Hypotrophy, myolysis, edema, cellular infiltration, contraction band necrosis, disarrangement of myofibers, vasculature, fibrosis</td>
<td>(Matoba, 2001; Islam et al., 1995)</td>
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<tr>
<td>Rat</td>
<td>Myocytic degeneration, necrosis, myocytolysis, contraction bands, atrophied myocytes, fibrosis, myoglobin loss, myocardial mitochondrial dysfunction</td>
<td>(Kaiho and Ishiyama, 1989; He et al., 1996)</td>
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cases were due to MA toxicity. (Karch et al., 1999) Morphology and histopathology studies of MA’s cardiotoxicity in different model were summarized in Table 2.

MA also induces cardiomyopathy, leading to myocardial infarction (MI), dilated cardiomyopathy (DCM) in the moderate MA users. Table 3 summarized some complications and heart disease in MA users.

The cardiotoxicity seen with MA use is similar to that seen with the use of cocaine. However, MA does not cause the same degree of severity vasoconstriction as cocaine. (Derlet and Horowitz, 1995; Nahas et al., 1991; Pitts and Marwah, 1988) Small doses of topical, intranasal cocaine result in a significant reduction in epicardial coronary arterial diameters (6–9%) and coronary blood flow, despite the fact that myocardial oxygen demand increases. (Lange et al., 1989) The moderate vasoconstriction caused by MA may benefit heart conditions by preventing secondary damage from the vasoconstriction, which is very severe to the heart in cocaine use. (Benzaquen et al., 2001) However, because of the cardiotoxicity associated with MA, large doses cause congestive heart failure (CHF) and sudden death. (Derlet and Horowitz, 1995; Bailey and Shaw, 1989).

Chronic MA use alters the hemodynamic parameters in heart function. The pre-load and after-load independent contractile parameters that describe the left ventricular contractility including pre-load recruitable stroke work (PRSW) and LV end diastolic volume at the occurrence of maximum dP/dt (dP/dtmax vs. Ved) are significantly decreased in MA treated mice, the decreased LV contractility suggests LV enlargement even dysfunction. (Yu et al., 2002a,b) This information is consistent with the autopsy reports of MA use. (Swalwell and Davis, 1999).

It has been reported that detrimental effects of MA could be reversed upon cessation of use; however, this reversal takes time. After 12 weeks of MA treatment, the walls of the heart became thicker. There were also cellular disarray, infiltration, edema, myolysis, tissues granulation, fibrosis and vacuolization. However, these symptoms were reversed within 4 weeks after MA use was discontinued, with the exception of the fibrosis. (Islam et al., 1995) The irreversible fibrosis in long-term MA use makes it a severe consequence both on deteriorating the cardiac tissue and function. (Islam et al., 1995; Jacobs, 1989; Robinson and Becker, 1986).

### Mechanisms of MA in heart disease

As a psychological stimulant, MA produces intoxication through the increased stimulation of dopamine and norepinephrine receptors in the brain. The alertness, euphoria and sense of well being results from the use of MA. MA potentiates the presynaptic neural terminal’s release of catecholamine neurotransmitters, norepinephrine, and dopamine, causing stimulation of the postsynaptic receptor. MA inhibits the uptake of

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<th>Complications</th>
<th>Outcomes</th>
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<td>MA intoxication, suicidal intention, vomiting, myalgias, paresthesias, headache, and orthostasis</td>
<td>Cardiac tamponade, Ventricular outflow laceration, pulmonary edema, DCM, diffuse, vasospasm, myocardial infarction, idiopathic congestive cardiomyopathy, septic shock, disseminated intravascular coagulation, rhabdomyolysis with myoglobinuria, azotemia</td>
<td>(Horiguchi et al., 1999; Hong et al., 1991; Jacobs, 1989; Kendrick et al., 1977; Meeker and Reynolds, 1990; Rajs and Falconer, 1979; Farnsworth et al., 1997; Furst et al., 1990)</td>
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these neurotransmitters and prevents their degradation by inhibiting monoamine oxidase. (Ruth et al., 1978; Wagner et al., 1980) MA does not stimulate postsynaptic catecholamine receptors directly. Because the effect of the drug depends on endogenous catecholamine stores, continued use leads to depletion, and a clinical binge-crash cycle occurs. This action on endogenous catecholamines also explains the rapid development of tachyphylaxis. These effects are stereoselective, with the d-form being approximately five times as active as L-form. Evidence also suggests that permanent damage may occur to the synaptic “complexes” in chronic users of MA. Such damage has been documented in experimental animals given prolonged high doses of MA, possibly due to formation of free radicals or the interaction of an excitatory amino acid.

Increased catecholamine levels are responsible for cardiotoxicity by coronary vasoconstriction, calcium overload, and the production of oxygen-free radicals by either the auto-oxidation of catecholamines or their degradation by monoamine oxidase. (Wagner et al., 1980) Abnormal catecholamine levels also have some other detrimental effects on the heart, such as inducing hypertrophy, myocardial ischemia and reperfusion, fibrosis, infarction, and cardiomyopathy. (Maeno et al., 2000a,b; Islam et al., 1995; Furst et al., 1990; Simpson et al., 1982; Uchima et al., 1983; Tang et al., 1987) The chronic norepinephrine (NE) treatment in rats causes left ventricle (LV) remodeling and fibrosis. The matrix metalloproteinase 2 (MMP-2) activity associated with hypertrophy was also enhanced in these rats. (Briest et al., 2001) Additionally, dysfunction of the heart causes increased cardiac workload which increases the risk of a sudden release of an asymptomatic atherosclerotic plaque. These factors put subjects at an increased risk for myocardial infarction. Thus, increased catecholamine levels due to MA use are a significant factor that leads to heart disease.

MA can directly affect cardiomyocytes by increasing the intracellular Ca\(^{2+}\) concentration. The increased Ca\(^{2+}\) markedly inhibits synthesis of myosin, therefore inhibits development of cardiomyocytes as well as damages the microtubular and actin structure of cardiomyocytes. (Salomon, 1978; Guo et al., 1986; Keith et al., 1983; Schliwa et al., 1981).

The signaling pathways of MA to the cardiac responses are MA-dose dependent and mediated via \(\alpha_1\)- and \(\beta_1\)-adrenoceptors by regulation of G-protein coupled PKA and IP3 casacade signaling pathways. (Schindler et al., 1992).

MA also affects vascular system by increasing the sensitivity to the pressor actions, while the sensitivity to the depressor actions decreases. MA administration also can have the far-reaching consequences of aneurysms and even aortic dissection. (Harrington et al., 1983) Increased blood pressure and tachycardia increase the workload on the heart and its accompanying vessels, focused on arterial branch points. This increased pressure can lead to aneurysms. Added stress of chronic MA use causes small intimal tears and in some cases vasculitic (Schindler et al., 1992; Citron et al., 1970; Harrington et al., 1983) and myocardial lesions. (Kobayashi, 1986; Call et al., 1982; Nogi et al., 1988) These small tears can eventually lead to gross aortic dissection, resulting in death with prolonged MA use. It has been shown that binge use of MA results in significant cardiac pathology, including focal monotypic inflammatory infiltrates and foci of necrosis in the hearts of rats. (Wagner et al., 1980).

The immunomodulation of MA

Limited studies about the effects of MA or its related amphetamines on immune function revealed that MA has immunomodulation properties. MA injected rats at 25 mg/Kg dose induced both thymic and
splenic lymphocytes death via apoptosis. (Iwasa et al., 1996) The in vitro study showed MA Exposure resulted in a decreased IL-2 production by T-lymphocytes, while B-lymphocyte proliferation was suppressed by MA. Also NK cell function was enhanced by MA exposure. (House et al., 1994) The in vivo study of MA showed that MA treatment significantly suppressed the cytokines IL-2 and INF-γ expression while no significant effects on cytokines IL-4 and IL-6 in normal mice. However, TNF-α was significantly enhanced by MA treatment. (Yu et al., 2002a,b) Lee et al. recently reported that MA induces significantly increase in DNA binding activities of redox responsive transcription factors, AP-1 and NF-κB, which are known to regulate gene expression of the TNF-α. The increased AP-1 and NF-κB cause MA-mediated increased lipid peroxides, in addition of the upregulated TNF-α gene expression may also be responsible for MA-induced heart disease. (Lee et al., 2001) This result further supports our conclusion that MA has immunomodulation activity, which is also responsible for heart disease.

MA derivatives also were showed the immunomodulation functions. In vitro, high concentration of amphetamines including MA affects immune function with a significant suppression of IL-2, but not IL-4 by T-lymphocytes, as well as a suppression of B-lymphocyte proliferation. (Zule and Desmond, 1999) The MA derivatives such as 3,4-methylenedioxymethamphetamine (MADA) cause lymphocytes death and decreases lymphocyte’s response to concanavalin A (Con A) stimulation, reduced leukocyte numbers and an increase in plasma corticosteroid levels, which suppresses T cells. (Briensven et al., 2001) Acute MDMA administration also was found to impair IL-1β and TNF-α secretion following an in vivo LPS challenge, and that TNF-α is more sensitive to the suppressive effects of MDMA than IL-1β is. (Connor et al. 2000) Freire-Garabal et al. investigated the immune effects of chronically amphetamine (0.4 mg/kg/day) injection. They found a reduction in thymus and spleen cellularity, and in peripheral T lymphocyte population. (Freire-Garabal et al., 1991) Those results suggest that MA and its derivatives have immuno-toxicity, cause immune dysfunction, exist some extent of interaction between MA and HIV, as well as increase the susceptibility of cardiovascular disease.

MA and HIV infection

Numerous epidemiology studies showed that there is a higher risk rate of HIV infection in drug users. (Estrada, 2002; Sterk, 2002; Bell et al., 2002) In the Russian Federation, between 1998 and 1999 over 90 per cent of all new HIV infections were found among injecting drug users. In 1999, the number of countries reporting injecting drug use was 136, up from 80 countries in 1992. Of these 136 countries, 93 also identified HIV among drug injectors. In nearly one-third of the Americans infected with HIV, intravenous drug use is a major risk factor of HIV transmission, making drug abuse the fastest growing vector for the spread of HIV in the nation. (NIDA Research Report, 2002) Increased HIV transmission is a likely consequence of increased MA abuse, particularly in individuals who use the drug intravenously with shared needles and syringes, which is a common route of HIV exposure. In near future, those men have sex partners via the internet will increase the risk of HIV infection prevalence. (Benotsch et al., 2002) A recent survey in Thailand found that the prevalence of HIV infection is 2.44% in MA users which is significantly higher than common people. (Vongsheere et al., 2001) MA gives a high and enhances individual’s libido, which may lead to multi-sexual relationships and unsafe sexual behaviors, (Zule and Desmond, 1999; Briensven et al., 2001) which is also a very important HIV exposure route. MA was reported as a widely used recreational drug in homosexual, bisexual and commercial sex workers, who have an alarming HIV infection rate. (Shoptaw et al., 2002; Gorman et al., 1997).
HIV-infected patients remain asymptomatic for years prior to the development of AIDS. However, the immune function in HIV-infected individuals will gradually deteriorate and eventually culminate in immune incompetence. Medications given to AIDS patients, infections with opportunistic pathogens and drug abuse may contribute to the immunosuppressive effect of HIV. A number of opportunistic pathogens, such as coxackievirus, will cause heart disease in the immune compromised AIDS patients. HIV is also neurotoxic and introduces oxidative stress, which may exacerbate the vulnerability of the CNS and accelerate the disease progression. (Nath et al., 2001) The retrospective studies revealed that about 50% of reported AIDS cases showed cardiac abnormalities. (DeCastro et al., 1992; Fong et al., 1993) Symptomatic and asymptomatic cardiac involvement in AIDS patients ranges between 28% and 73%. (Lewis, 2000) The first cardiac involvement in AIDS patients was reported in 1983, (Autran et al., 1983) describing myocardial Kaposi’s sarcoma at autopsy. The cardiac diseases in AIDS patients mainly include myocarditis, dilated cardiomyopathy, pericardial effusion, non-bacterial endocarditis, pulmonary hypertension, cardiac neoplasm and medication-induced cardiotoxicity.

MA and HIV-1 are both immunomodulators, which lead to immune dysfunction. Yet the understanding of the potential effects that simultaneous exposure to MA and HIV have on disease progression is extremely limited. Studying the interactions between MA and HIV disease progression is very important and essential. (Phillips et al., 2000) Whether MA use will potentiate HIV activity on immune dysfunction or heart disease remains unclear. A study investigated the co-activity of lentivirus infection and MA use in brain, they found that lentiviral replication was related to proviral copy number, suggesting the effect of MA is at the viral entry or integration into host genome levels, but not at the translational level. Thus, lentiviral infection of the brain in the presence of the psychostimulant MA may result in enhanced astrocyte viral replication, producing a more rapid and increased brain viral load. (Gavrilin et al., 2002) Another study tried to investigate the effect of MA use exacerbates LP-BM5 retrovirus induced murine AIDS. It was shown that MA did not further suppress the secretion of Th1 cytokines already reduced by murine AIDS, however, TNF-α secretion and lipid peroxidation were further enhanced in LP-BM5 murine leukemia virus infected mice by MA treatment. The increased TNF-α levels as well as lipid peroxides suggest that MA has the potential to exacerbate heart function and increase stress-responsive oxidation. (Yu et al., 2002a,b).

Conclusion

MA is a complex drug with dangerous cardiac side effects. The rise in MA abuse has resulted in an increase in MA-related health risks such as heart disease, HIV infection and mortality. The possibility of MA cardiotoxicity including tachycardia, atrioventricular arrhythmias, myocardial ischemia and hypertension should be seriously considered before using MA. Mechanisms of heart disease include increases in the level of catecholamines and secondary problems associated with increased vasoconstriction, vasospasm, hypertension and tachycardia. Cardiac hypertrophy, atrophy and destruction of the microtubular and actin structures also lead to heart disease.

MA and its derivatives also have immunomodulatory activity. It alters immune function by inhibiting T-lymphocytes, changing cytokine production, as well as, increasing oxidative stress. Particularly, enhanced TNF-α due to MA use is a very important factor related to both immune dysfunction and heart disease. Sharing of needles, syringes and inappropriate sexual behavior in MA users put them at higher
risk of HIV infection. Although the exact interaction of MA and HIV is not clear, both are CNS toxicants and have immunosuppressive effects, which accelerate AIDS progression.

Despite the current knowledge of MA use, heart disease and HIV infection, additional research is needed to pinpoint the remaining unknown pathways and mechanisms of action among them. This knowledge would lead to better treatment and prevention programs for HIV infection and heart disease caused by MA use.

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