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MDMA Induced Cardio-toxicity and Pathological Myocardial Effects: A Systematic Review of Experimental Data and Autopsy Findings

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Abstract
3,4-Methylenedioxymethamphetamine (MDMA), more commonly known as "ecstasy," is a semi-synthetic entactogenic phenylethylamine. In recent years it has gained popularity as a recreational drug whose use has registered an upward trend especially among adolescents and young adults. Despite its unwarranted reputation of being a "safe" drug, the actual scientific data denote that it actually leaves a trail of cardio-toxicity, above and beyond its neurotoxicity and other somatic effects. Both experimental and clinical data, in fact, indicate that ecstasy can alter cardiac function leading to rhythm disturbances, myocardial infarction, and even sudden cardiac death. We reviewed and summarized the bio-medical literature on the cardiovascular response to MDMA both in humans and laboratory animals. The aim was to elucidate the various pathophysiological mechanisms involved, as well as the clinical, autoptic, and experimental findings underlying MDMA-induced cardio-toxicity. Finally, an illustrative case report of ecstasy-induced adolescent death due to acute cardio-toxicity was described so as to highlight some key features.

Keywords 3,4-Methylenedioxymethamphetamine · Myocardial damage · Cardio-toxicity · MDMA-related deaths

Introduction

3,4-Methylenedioxymethamphetamine (MDMA), popularly known as "ecstasy," is a semi-synthetic entactogenic phenylethylamine [1]. Its recreational use as a "party" drug is a facet of "rave culture" and somewhat of a mainstay of frequently unauthorized all-night dance parties with high-volume electronic music [2]. MDMA has unique psycho-active properties interpolated between those of typical stimulants (such as amphetamines) and hallucinogens (mescaline, LSD) [3, 4]. MDMA has gained popularity in recent decades due to its ease of availability and low cost, but above all because of the widespread misconception as to its low toxicity [5]. The desired effects include a sense of euphoria and a surge in energy or activity level, altered sensations, and sexual arousal. In addition, it also has entactogenic effects, such as emotional closeness and empathy with other users, purportedly enhancing "inner awareness" [4, 6–8]. Unfortunately, MDMA may elicit undesirable symptoms such as appetite loss, trismus and bruxism, nausea, muscle aches, fatigue, excessive perspiration, and ataxia [9, 10]. Of greater concern, however, are adverse events like psychosis or acute cardiac, hepatic, renal, and cerebral toxicity [11]. In fact, a host of serious complications of acute MDMA-induced toxicity have been reported. These include hyperthermia, convulsions, cardiac arrhythmia, rhabdomyolysis, disseminated intravasal coagulation, hyponatraemia, hepatotoxicity, aplastic anemia, pneumo-mediastinum, stroke cerebral hemorrhage, and death [9, 12–14]. Fatalities from MDMA overdose usually occur as a complication of malignant hyperthermia, heat stroke, or acute liver failure [15–19].

Once in the gastrointestinal tract MDMA is readily absorbed. Peak serum/plasma levels occur after 1–3 h, whereas its elimination half-life is approx. 7 h [20, 21]. Onset of action occurs within 30–60 min after ingestion and lasts for 4–6 h [8]. It is both metabolized in the liver and

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excreted in the urine. The drug is metabolized by hepatic microsomal cytochrome P450 (CYP) enzymes (especially CYP2D6). Its principal metabolite 3,4 methylenedioxyamphetamine (MDA) is pharmacologically active; however, approx. 65% is excreted unchanged [8, 10, 22]. Establishing the toxic dose of MDMA proves elusive, given the variability in individual susceptibility and tolerability. Also, all the more some adverse effects are not dose-dependent [8, 23]. In most reported deaths from ecstasy overdose, measured serum/plasma levels were in the 0.5–10 mg/L range [24]. However, death may occur at a lower dose range in so-called 'poor metabolizers', i.e., subjects with a deficiency of CYP2D6, an inherited autosomal recessive trait affecting 5–9% of Caucasians and 1% of Asians [8].

The mechanism of action of MDMA involves central and peripheral pharmacological actions [25]. MDMA increases serotonin and, to a lesser extent, norepinephrine and dopamine levels, by blocking re-uptake in presynaptic nerve terminals or stimulating their release from synaptic vesicles [25–29]. Ecstasy also indirectly increases the levels of these neuro-transmitters by blocking their degradation by monoamine oxidase (MAO). The drug inhibits tryptophan hydroxylase activity, mostly due to its metabolites rather than by MDMA itself [30]. Ecstasy is also a 5HT2A-, alpha1-, and alpha2-adrenergic receptor agonist [31, 32].

The cardio-toxicity of MDMA has been hypothesized to depend on a sympathoadrenergic activation akin to that of cocaine [33]. However, the intricacies regards the mechanism of its effects on cardiomyocytes remain largely unknown [7–33]. Consequently, our investigation addressed the issue of MDMA-induced cardiac pathology so as to review and summarize the evidence regarding the molecular mechanisms of cardiotoxiciy described to date in the literature. In addition, an illustrative case of ecstasy-related adolescent death due to hyperthermia and acute cardiac toxicity is described herein.

Search Strategy

We conducted a comprehensive bio-medical literature search focusing on myocardial damage from ecstasy intoxication.

Specifically, we used PUBMED/MEDLINE (https://www.ncbi.nlm.nih.gov/pmc/) and SCOPUS (https://www.scopus.com) search engines to find indexed citations using the search terms: "MDMA", "Myocardial damage", "cardiotoxicity", and "MDMA-related deaths." To increase specificity, our keywords were combined with the descriptors Restrict to MeSH Major Topic [MAJR] and Main Heading [MH] (in title and/or abstract fields of citation records) for articles published in English in the preceding 30 years. The resulting citations were then vetted with reference to MDMA-induced cardio-toxicity. The full-text articles of all relevant citations were retrieved and reviewed.

Our Experience

A 16-year-old girl suddenly felt ill a few hours after taking 1 g of MDMA orally. Shortly after arriving at the emergency room she appeared comatose with generalized tremor. In addition, she was hypotensive (90/60 mmHg) and had bilaterally nonreactive dilated pupils with hyperpyrexia (41.7 °C). Her arterial blood gas showed metabolic acidosis with pH 7.243, pCO_2 36.6 mmHg and pO_2 22.5 mmHg. On physical examination she had an irregular rhythm. A 12-lead ECG showed junctional rhythm with frequent ventricular extrasystoles and diffuse ST-segment depression; moreover, there was an alternating pattern of narrow complex tachycardia (180 b/min) and junctional rhythm with bradyarrhythmia and absent pulses. A NG tube was placed and atropine, sodium bicarbonate, and magnesium sulfate were administered. However, after approx. 35 min the patient died despite the resuscitation efforts undertaken.

At autopsy, gross examination of the heart showed the coronary arteries to be pervious and elastic; weight 225 g. Diffuse subepicardial petechiae were widespread over the anterior and posterior aspects of the heart. A pale-whitish streak was visible on the posterior wall of the left ventricle (Fig. 1a, b). Histological examinations revealed myocardiocyte fragmentation, myocardial disarray with widespread eosinophilic contraction band necrosis, myofibrocellular "square" nuclei, and mild subendocardial fibrosis (Fig. 1c, d). The lungs were edematous with endoalveolar hemorrhage and congestion of alveolar capillaries. No noteworthy findings were present in other organ systems. Blood samples were taken during autopsy (stored at − 20 °C) as well as hair samples, whereas no urine was available for sampling. Postmortem toxicology analysis was performed via quantitative technique, i.e., liquid chromatography–mass spectrometry (LC–MS/MS). The results indicated a blood MDMA level of 2997 ng/ml (cutoff concentration 20 ng/ml). The toxicology analysis on blood samples was negative for alcohol, methadone, cocaine, opiates, THC, benzodiazepines, and barbiturates.

The postmortem toxicology tests on hair for the eventual presence of drugs within the 12 months prior to collection indicated habitual abuse of MDMA.

In particular, the following concentrations were recorded:

0–4 months prior to death: 44 ng/mg (0.2 ng/mg cutoff);
4–8 months prior to death: 40 ng/mg (0.2 ng/mg cutoff);
8–12 months prior to death: 104 ng/mg (0.2 ng/mg cutoff).

In contrast, hair analyses for methadone, cocaine, opiates, and THC were all negative.

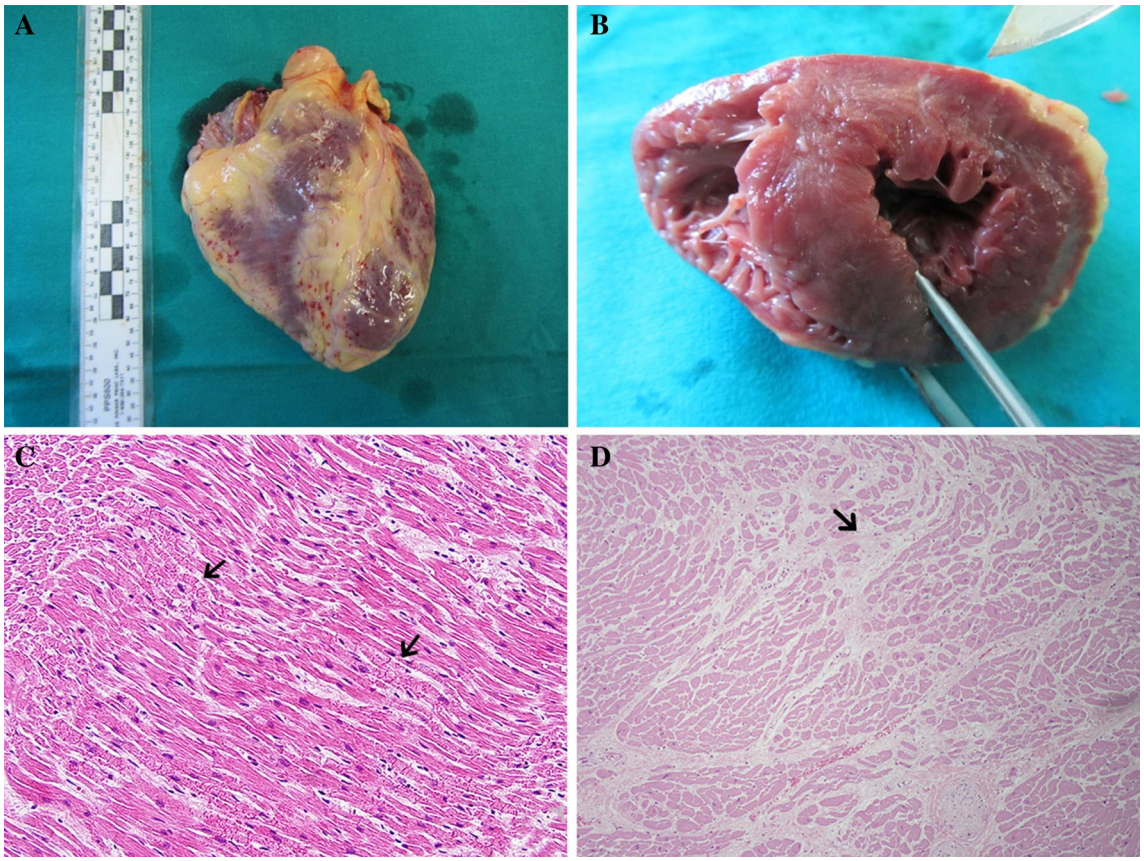

Fig. 1 Autopsy findings. **a** Diffuse subepicardial petechiae. **b** Pale-whitish streak on the posterior wall of the left ventricle. **c** Widespread eosinophilic contraction band necrosis. **d** Fibrosis of the myocardium

In conclusion, the toxicology findings were consistent with fatal MDMA-induced cardio-toxicity from acute exposure in the context of chronic abuse.

Discussion

Like other amphetamines, MDMA induces cardiotoxic effects that include arrhythmia, myocardial infarction, and even heart disease [34–38]. Whilst reports on cases of MDMA-induced cardio-toxicity remain rare, even a single dose has been known to cause serious cardiac complications, as reported in the literature [39].

Acute MDMA administration in humans induces increases in blood pressure and heart rate with effects lasting last up to several hours [15, 22, 40–42]. Dowling et al. [15] reported that cardiac arrhythmia occurred in four out of five fatal cases. In three of these cases the subjects had pre-existing cardiac pathologies while in the remaining case MDMA appeared to be the sole cause of arrhythmia.

Cases of myocardial infarction were less common. Some reports presented cases of myocardial ischemia in subjects devoid of coronary artery disease [38, 43]. In these cases the mechanism was deemed to be sympathoadrenergic activation leading to coronary vasospasm.

Mizia-Stec et al. [33] reported a case of severe dilated cardiomyopathy in a subject regularly using MDMA twice a week in the two previous years. The subject also had mitral and tricuspid regurgitation, but there was no demonstrable myocardial inflammation. Furthermore, MDMA has also been associated with restrictive valvular regurgitation [44] likely to be related to activation of 5HT2B receptors on valvular interstitial cells.

In a retrospective study, cardiac hypertrophy was found to be statistically more prevalent at autopsy among MDMA users than in non-users [36]. However, it is not clear whether these differences are determined by a direct MDMA-induced effect on the heart, or the end result of functional alterations.

One animal study in an experimental murine model showed that repeated administration of ecstasy causes left-ventricle (LV) dilatation and systolic dysfunction [45].

In a review [46] on MDMA-induced deaths from 2000 to 2005 in Australia, cardiovascular complications were considered the primary cause of death in 10% of drug toxicity cases. Several studies [19, 25, 47] have highlighted the hurdles to understanding the scope of MDMA-induced

cardio-toxicity. In fact, there is generally a lack of critical information regarding factors such as the frequency of use, associated multi-drug use and the history of cardiac pathologies, especially in adult subjects. On the other hand, another confounding factor is the presence of adulterants or substitutes that may be present in the "ecstasy" illicitly sold in powder/crystal form, under a variety of street names [24].

The mechanisms underlying the drug's cardiac effects are complex (Fig. 2), but appear to be related to its ability to boost synaptic levels of monoamine neuro-transmitters in the peripheral sympathetic system, activate alpha adrenergic and serotonergic receptors, and increase central sympathetic responses [24, 47]. On the other hand, experimental studies [48] have suggested that repeated administration of MDMA to mice may activate a vasovagal reflex that acts on the heart, subsequently causing bradycardia and hypotension. Brody et al. investigated resting heart rate variability (HRV) and heart rate response to the Valsalva maneuver (Valsalva ratio) in MDMA users. In many of these individuals there was a total absence of post-Valsalva release bradycardia [49]. Based on these findings, these authors concluded that the drug impacts parasympathetic cardiac tone and contributes to autonomic dysregulation.

As to the pathophysiology of serotonin, it appears capable of causing myocardial injury and subsequent hypertrophy of the LV. The purported mechanism, which is independent of receptor stimulation, envisages serotonin uptake into cardiomyocytes followed by its enzymatic degradation via mitochondrial MOA, in turn leading to ROS production [50].

In the literature [1, 12, 45, 51] the classic histopathological alterations of fatal cardio-toxicity from MDMA manifest as contraction band necrosis (CBN), coagulative necrosis, myocyte hypereosinophilia, and inflammatory neutrophil and macrophage infiltrates. In animal experiments, the administration of repeated doses of MDMA to rats has been shown to produce myocarditis with inflammation and necrosis [48]. Leukocyte infiltration, per se, is an adaptive response to the death of cardiomyocytes and a marker of advanced contraction bands necrosis [52].

Neri et al. [53] measured significant increases, in rats, of (cardioinhibitory) inflammatory cytokines at 3 and 6 h after a single dose of MDMA. Maximum levels of TNF-alpha, IL-6, IL-8, IL-10, IL-1beta, and MCP-1 were reached after 24 h. According to the authors, these cytokines are expressed as an adaptive inflammatory response triggered by myocardial damage from MDMA. Furthermore, they directly affect cardiomyocytes and down-regulate sarcoplasmic reticulum proteins [53–56]. However, IL-8 and MCP-1 recruit neutrophils and mononuclear cells [57], whereas IL-10 reduces inflammatory infiltrates as well as the expression of pro-inflammatory cytokines. Thus, the net biological effect of cardio-inhibitory cytokines depends on the extent and duration of their expression. While moderate and short-lived elevations tend to be protective, disproportionate increases ultimately induce irreversible cardiac damage [53].

As to our case report, the histopathological analysis showed findings consistent with toxicity from acute and chronic abuse. Specifically, subendocardial fibrosis can be explained by cardio-toxicity from past MDMA abuse. The postmortem toxicology tests on hair samples attest to exposure for at least a year, with maximum exposure dating 8–12 months prior to death. As with cocaine abuse,

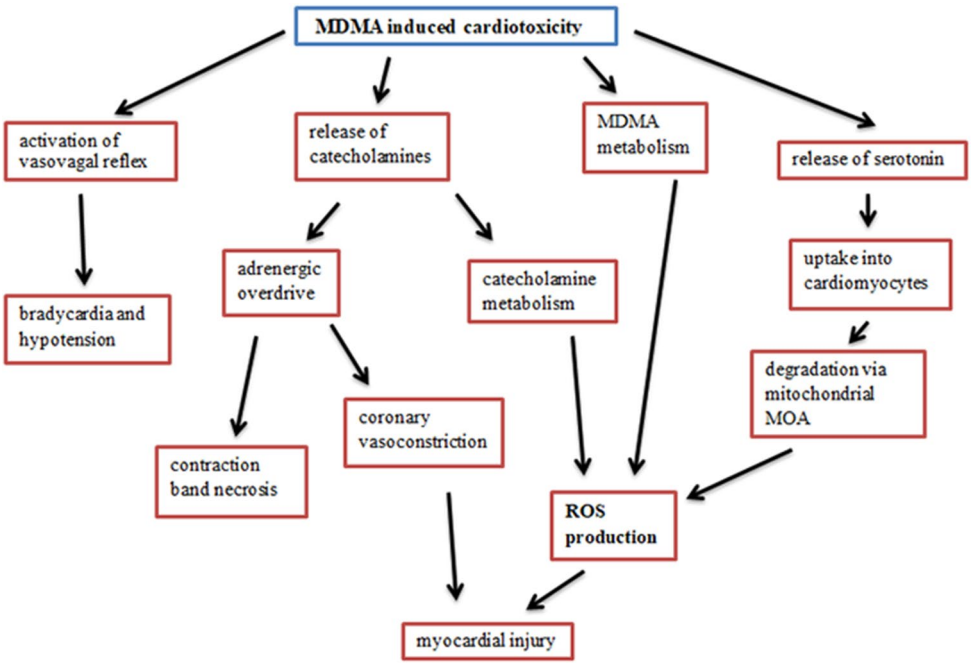

Fig. 2 Mode of action of MDMA (toxicity) on the heart

replacement fibrosis in response to damaged CBN myocytes occurs within weeks or months [36]. On the other hand, the presence of square nuclei indicated an initial hypertrophy of some myocytes [36] even in the absence of an increased overall weight of the heart. These findings are usually an expression of cardiac adaptation and remodeling that take place in adulthood, but are quite exceptional in adolescents [58]. In light of the fact that the subject was a 16-year-old girl with no cardiovascular risk factors, cardiac and/or coronary heart disease, the fibrosis and initial cellular hypertrophy may only be attributed to the cardiotoxic effects of MDMA.

With the fatal acute poisoning, the elevated serum levels determined severe cardio-toxicity. The ECG performed shortly before exitus showed signs of ischemia and myocardial death (diffuse ST-segment depression) and an impressive arrhythmic alteration (junctional rhythm with ventricular extrasystoles and alternating tachyarrhythmia/bradyarrhythmia). Histologically, there was widespread contraction band necrosis (of all LV and RV walls) with myofiber disarray and fragmented myocardiocytes.

Coagulative necrosis may be interpreted as a histological hallmark of adrenergic overdrive with malignant arrhythmia and ventricular fibrillation [51]. In general, contraction band necrosis is quite common in stimulant abusers [37] and usually has an ominous potential.

As with amphetamines, excessive catecholamine discharge is among the likely explanations for myocardial necrosis [51]. This discharge can produce myocardial damage through a variety of actions such as ischemia from coronary vasoconstriction or the production of ROS during catecholamine metabolism by MAO. MDMA can also directly damage cardiomyocytes by inducing apoptosis [48].

Even a single dose of ecstasy is capable of altering cellular antioxidant responses and induces oxidative stress [1]. One of the mechanisms that attempt to explain this induced oxidative stress stems from the observation that MDMA and MDA are converted to *N*-methyl-alpha-methyldopamine and alpha-methyldpomanine. These catecholamines undergo several oxidative steps with the production of orthoquinones and aminochromes [59]. The assumption is that with high blood concentrations of MDMA there is an overabundance of metabolites which fuels the generation of ROS and reactive nitrogen species (RNS), in turn leading to lipoperoxidation and oxidative stress. The downstream effects would be a depression of the sarcolemmal Ca^{2+} pump ATPase, Na^{+}-K^{+} ATPase and inhibition of the sarcoplasmic reticulum Ca^{2+}ATPase (SERCA) pump [60]. The consequent intracellular free calcium ion overload [48] would induce cell damage. Furthermore, the production of ROS [1, 59, 61] directly damages mitochondrial DNA with ensuing cell death.

Therefore, MDMA may exert its cardiotoxic effects via its ability to activate a myocardial NF-kappaB response, disrupt cytosolic calcium and mitochondrial homeostasis, as well as by altering gene transcription [62].

In vitro, Carvalho et al. [61] proved that myocardial cells exposed to MDMA undergo cytotoxic effects with corresponding morphological alterations and depletion of the ROS scavenging systems. In another study, Shenouda et al. [63] reported that the MDMA-induced increases in ROS cause alterations in LV contractility in murine models. By proteomic analysis they also revealed that ecstasy increased nitration of contractile proteins (tropomyosin alpha-1 chain, troponin-T, myosin light polypeptide, and myosin regulatory light chain), mitochondrial proteins (Ub-cytochrome-C reductase and ATP synthase), and SERCA.

In experimental samples, Perrine et al. [7] documented that serotonin levels, but not norepinephrine, were decreased significantly and in a dose-dependent manner after administering MDMA, demonstrating the impact of the drug on cardiac serotonergic tone. The same study showed an increase in cardiac carnitine levels, which has a protective role in compromised heart muscle, preventing mitochondrial damage from oxidative stress [7, 64, 65]. L-Carnitine, an acyl carrier that stimulates fatty acid metabolism, is correlated to a compensatory action to re-establish balance in energy regulation, allow the heart to deal with an increased workload and act as an antiradical agent [66].

Also of note, the peripheral actions of catecholamines trigger muscular contractions via release of calcium from the sarcoplasmic reticulum. This cascade increases cell metabolism and oxygen demand, hence anaerobic respiration. The results are lactic acid and heat production, (potentially myolithic) hyperthermia, and metabolic acidosis. The latter damages cell membranes, in turn leading to hyperkalemia that lowers the threshold for the onset of fatal arrhythmias [67].

In conclusion, the present review illustrates the marked and potentially fatal cardio-toxicity linked to MDMA use. The evidence highlights its cardio-toxicity both with isolated and habitual use. Even when not fatal, repeated use can lead to progressive damage to myocardial tissue (triggering myocardial fibrosis) and cellular hypertrophy, thus increasing the risk of serious heart disease. On the other hand, even a single dose can cause extensive contraction band necrosis and ventricular arrhythmias. The case described also attests to the severity of this cardio-toxicity even in adolescents with no history of cardiac pathologies or cardiovascular risk factors.

The cardiotoxic mechanism, albeit multifactorial, mainly points to oxidative stress. However, despite the bulk of research, the pathophysiology underlying myocardial damage needs further elucidation [25]. Deeper inquiry into these mechanisms is deemed crucial in order to protect MDMA users from its toxic effects.

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