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Cathinone Neurotoxicity ("The "3Ms")

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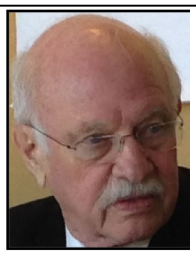

Steven B. Karch

Abstract: Synthetic cathinones are designer drugs of the phenethylamine class, structurally and pharmacologically similar to amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), cathinone and other related substances. New analogues, legal at least, until formally banned (a time consuming process), are introduced almost daily The United Nations estimates nearly 250 new drug analogues are produced per year. Various combinations of these drugs are sold under the name of "bath salts." They can be ingested by any route and some appear capable of causing great harm, mostly behavioral. One drug in particular, MDVP, appears to frequently cause symptoms indistinguishable from the classic findings in Excited Delirium Syndrome (ExDS). Little is known about the pathology or clinical toxicology of these drugs but their molecular mechanism of action seems to be identical with that of cocaine. This mini-review examines what little is known on the subject and explains the suspected mechanisms of excited delirium syndrome.

Keywords: "Bath salts", cathinones, methedrone, methelone, MDMA, MDVP.

INTRODUCTION

Synthetic cathinones are designer drugs, belonging to the phenethylamine class. They are similar to amphetamine, 3,4-methylenedioxymethamphetamine (Ecstasy, MDMA) and cathinone (the amphetamine found in khat) structurally and pharmacologically. All drugs in this category share certain common structural similarities, namely a beta-keto substituent to phenethylamine. This addition yields a group of substances with cathinone as their core structure. Three particular synthetic cathinones – methedrone, methylone, and MDVP (the "3Ms") seem to be particularly widespread and problematic. The three molecules are likely to be the active agents found in illicit products referred to as "bath salts" (now controlled drugs the U.S. and many of the EU countries). Structural analogues of cathinone did not appear on the United States' illicit drug market until 2010, but they have been popular drugs of abuse in Europe since 2003. This paper contains a brief review of the 3Ms. While there are countless other analogues that need attention, these three agents account for most police seizures, and the drugs themselves seem to be associated with the most toxicity [1].

The term '*synthetic cathinone products'* refers to synthetic cathinones packaged as authentic commercial products. These products include purported beauty and household goods such as "bath salt" products sold as Bliss, Blizzard, Blue Silk, Charge+, Hurricane Charlie, Ivory Snow, Ivory Wave, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Star Dust, Vanilla Sky, White Dove, White Knight, White Rush, and White Lightening. Synthetic cathinone products are also marketed as plant food/fertilizer, insect repellant, pond cleaner, and vacuum fresheners [2].

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Synthetic cathinones are commonly distributed in powder, crystal, and liquid forms, but they are also available and abusable in the tablet and capsule forms. Distributers have marketed some synthetic cathinone tablets and capsules as ecstasy, a practice that may account for many-reported case of toxicity. According to the U.S. Drug Enforcement Administration (DEA) databases, and reports from State forensic laboratories that analyze seized ecstasy tablets, these tablets contain synthetic cathinones, alone or in combination with other drugs. Generally these tablets and capsules are sold in retail outlets and on the Internet in conjunction with the more widely recognized "bath salts" [2]. Of course, legitimate drugs such as bupropion, diethylpropion and pyrovalerone would not only qualify, as bath salt like substances they are considered as legal medications.

There are other similarities among these drugs besides sales and packaging. Each of the 3M drugs has been linked to varying degrees of agitation, hyper arousal, confusional states, and various types of psychotic behavior, up to and including a syndrome indistinguishable from excited delirium syndrome. These symptoms are not different from those caused by cocaine. This state exists because some "bath salts" components share common molecular mechanisms of action with cocaine (see below on Excited Delirium Syndrome). Among the hundreds of cathinones that have been synthesized, or can be synthesized, three molecules in particular appear to account for the content of most products sold as "bath salts." These are discussed below.

IMPORTANT CATHINONES

Mephedrone

Mephedrone was initially synthesized in 1928 but did not become a recreational drug until in 2003. It had first gained notoriety in Europe, especially in the U.K., because of the

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remarkably high incidence of hospital admissions, even deaths, associated with its use. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) indicates that over the first quarter of 2010, mephedrone was detected in some 20 E.U. Member States [3]. Mephedrone is synthesized by the bromination of substituted propiophenone and subsequent reaction with the appropriate, amine or *via* reduction of the hydroxyl of the substituted ephedrine to form mephedrone [4].

Mephedrone and its analogues exert extremely potent effects on serotonin and dopamine transporters. Some of the analogs are 10 times more potent blockers of serotonin than methcathinone [5]. Like all cathinones, mephedrone can be administered by almost any route, though it is most often used orally at doses between 100 to 200 mg. Pharmacokinetic studies are lacking, but peak effects are said to be observed roughly two hours after the drug has been taken. If the stomach is full, absorption is delayed and so is the onset of action. The effects of the drug last for 2–3 hours [6]. Nasal insufflation is said to require smaller doses of drug and produces quicker onset of action, usually in less than 30 minutes. Rectal use has been reported and is said to produce the quickest onset of action [7].

To a greater or lesser degree all 3Ms produce the effects generally associated with sympathetic excitation: anxiety, tachycardia, hypertension, sweating, and flushing, all as a consequence of the cathinone's ability to block norepinephrine reuptake. Unlike simple amphetamines, intensified sensory experiences may also occur, and even moderate sexual arousal has been reported, but explanations for these responses remain lacking. At higher doses, perceptual changes have been reported. Hospital admissions are relatively common, but when they occur, they are treated no differently than other hyperadrenergic states, namely with benzodiazepines and supportive care [8]. Individual case reports describing more severe toxicity (confusion, psychosis, chest pain) have been published [9-11], but these complications almost always occur in the setting of poly-drug abuse, making it impossible to attribute causation to any one drug [12].

In a case where mephedrone was the only drug detected, a 22-year-old man who took 0.2 g orally, followed by 3.8 g intramuscularly, required hospitalization. He developed all the signs and symptoms of a hyper sympathetic state, and finally delusional psychosis, but the psychosis persisted for only a few hours. His serum mephedrone concentration was 0.15 mg/L. Six hours later his vital signs returned to normal and he was discharged [8]. Since mephedrone was the only drug that he had used, this suggests a relative lack of toxicity, at least compared to the other 3Ms.

Higher blood levels of mephedrone are associated with increased mortality. In the U.K. over 45 cases of suspected deaths from mephedrone have been reported, most confirmed by toxicology testing; however the reports contain very few details, and most of those who died were poly-drug abusers [9]. One report describes a 36-year-old man arrested after having injured himself severely by smashing windows in a rage of fury. He died despite resuscitation attempts. At autopsy mild cerebral edema was evident, but otherwise no other obvious cause of death was apparent. Toxicologic analysis showed a high concentration of mephedrone in femoral blood (5.1 mg/L) and traces of cocaine, MDMA, and oxazepam [13]. Many of the symptoms displayed by this patient (particularly the glass-breaking behavior) resemble symptoms of excited delirium syndrome that, until recently, was a disease more or less confined to cocaine and methamphetamine abusers (see below).

In a second autopsied case, the anatomic findings were described as "irrelevant." The blood and urine concentrations were 1.33 mg/L and 144 mg/L respectively; cocaine and its metabolites were also present, and hair testing disclosed prior exposure to methadrone, ketamine, and MDMA. It is difficult to know what to make of such reports since a microscopic examination of the heart was not, so far as can be determined, performed. The possible presence of underlying heart disease, even at the molecular level (i.e. a channelopathy), makes it impossible to classify the cause of death with any certainty. However, the paper is not without value as it was the first to report mephedrone concentrations in the bile, lung, and brain (1.29, 0.79, and 0.89 mg/L (kg) respectively [14]. Too few cases have been autopsied to speak of specific findings.

METHYLONE

Methylone is the b-k analogue of MDMA (3,4-methylenedioxymethcathine). It first appeared in the Netherlands, mixed with mCCP (meta-chlorophenylpiperazine) as the main component of a designer drug called "Explosion" [15]. According to UN drug monitors, Methylenedioxypyrovalerone (MDPV) and methylone are among the most popular synthetic cathinones (United Nations Office of Drugs and Crime). MDMA and mCCP are both semi-synthetic derivatives methcathinone, like the 3Ms.

Methylone acts on the plasma membrane catecholamine transporter and has a weak effect on the vesicular monoamine transporter [16]. It is metabolized by *N*-demethylation, reduction of the keto group, and oxidation of the tolyl moiety [17]. If 4-Hydroxy-3-(HMMC) is also present, that would confirm the use of methylone, as HMMC is by far the most abundant of methylone's major metabolites. Almost all of methylone ingested is metabolized. *In vitro* studies suggest metabolism is mainly *via* CYP2D6 with minor contributions from CYP1A2, CYP2B6, and CYP2C19 [18]. Less than 3 percent of an administered dose is excreted in 24 hours [19]. Very little is known about methylone pharmacokinetics but there are unsettling reports that when methylone is co-ingested with MDVP, bizarre behavior, including a number of suicides, deaths, highly violent crimes and delirium have occurred [20].

In 2012, Cawrse described the tissue distribution in four fatalities [21]. All four cases had detectable levels of methylone; heart blood concentrations were mostly at or below 1 mg/L (0.118, 0.060, 0.740, and 1.12 mg/L). Analysis of several other tissue samples showed that methylone does not sequester in a particular tissue type after death. The average liver-to-blood ratio was 2.68. Two cases also had MDPV present, but insufficient data was collected to reach any conclusions [21].

In 2014, McIntyre reported the toxicology findings in a 19-year-old woman who had drowned. She was known as a regular methamphetamine and marijuana user. Concentrations of methylone found in the peripheral blood, central blood, vitreous, liver and gastric contents were measured at 3.4 mg/L 3.4 mg/L, 4.3mg/L, 11 mg/kg, and 1.7 mg, respectively. No other amphetamine-like compounds (including ecstasy) were detected. While this information may prove to be useful to death investigators, it is important not to forget that DNA resequencing was not performed, and the young woman might well have died from a previously undiagnosed channelopathy (Type L1 is prominently associated with drowning deaths) [22]. The same could be said of Carbone's report of sudden death in another otherwise healthy 19 year-old [23]. A thorough examination of the heart, indeed the entire autopsy, showed no significant abnormalities. The postmortem methylone blood concentration was 0.07 mg/L – an order of magnitude lower compared to earlier reported cases. In this case, attributing sudden death to methylone, without first seeking a channelopathy, may be premature.

Pearson described three deaths where the deceased exhibited seizure-like activity and elevated body temperatures (103.9°, 105.9° and 107°F). Two of the three cases also suffered from metabolic acidosis. One of the three individuals was hospitalized only to die of multisystem failure, metabolic acidosis, rhabdomyolysis, acute renal failure and disseminated intravascular coagulation. The laboratory results for this patient over the 24 hour period of hospitalization were significant for increased lactate, liver transaminases, creatinine, myoglobin, creatine kinase and clotting times, with decreased pH, glucose and calcium. Peripheral blood methylone concentrations in the three fatal cases were 0.84, 3.3 and 0.56 mg/L. In conclusion, it appears that peripheral blood methylone concentrations in excess of 0.5 mg/L may result in lethal toxicity, including hyperthermia and other sympathomimetic-like symptoms [24].

The pathophysiology of methylone-related deaths is also poorly understood, but some *in vitro* evidence is emerging, the results of which seem to explain the myriad of symptoms observed. Symptoms seem to fall on a scale somewhere between serotonin-syndrome [25] and excited delirium. Further more, the greater the methylone concentration, the greater the agitation produced. Both the psychological and physiological abnormalities appear to be dose related [26, 27]. *In vivo* animals studies show methylone has a high affinity for 5H(2A) receptors, comparable to that of MDMA [25]. If methylone inhibits dopamine uptake in the same fashion as MDMA, which it almost certainly does, that action may account for many of the observed psychological symptoms.

MDVP (METHYLENEDIOXYPYROVALERONE)

MDPV is a derivative of pyrovalerone, which is a psychoactive drug that was used to treat chronic lethargy and fatigue. MDPV differs from other synthetic cathinones because it contains a pyrrolidine ring, which makes the drug a potent uptake blocker at dopamine and norepinephrine transporters, in much the same fashion as methylone. Although MDPV, mephedone and methylone are now controlled drugs, a group of MDPV derivatives remains legal. The most frequently encountered are referred to as pyrrolidinophenones and alpha-pyrrolidinovalerophenone (alpha-PVP) is the one most frequently encountered. In studies using rat brain synaptosomes, alpha-PVP acts as a potent uptake blocker of dopamine and norepinephrine transporters, comparable in activity to MDPV, it is also a catecholamine transporter blocker [28], though not as potent as MPVD. This property may explain the hyperactivity that MDPV seems to induce. It may also explain why MDPV, and all of its analogs, induce typical stimulant effects at lower doses, but bizarre behaviors at higher doses [29].

Among the 3Ms, MDPV seems to be the one most likely to induce severe behavioral abnormities. A Hungarian study published in 2013 described heterogeneous symptoms in five MDPV abusers; delusional behavior was frequent. Some of these patients had psychiatric history but others did not; the majority were chronic intravenous drug abusers [30]. It appears that at least some of the behavioral abnormalities induced by MDPV may require a pre-existing substrate, such as chronic poly-drug abuse.

Though nothing can be concluded from a solitary case report, it appears that MDPV may, in some respects, behave more like an amphetamine than the other two cathinones discussed here. A 2013, case report described a 27 year-old male, with no past medical history. He was brought to an emergency room because of increasing agitation and admitted he had been injecting and inhaling "bath salts." The salts were found to contain a combination of mephedrone and methylenedioxypyrovalerone (MDPV). On presentation, he was tachycardic, hypotensive and febrile. His initial lab tests showed an elevated white count, and increased levels of creatinine and creatinine phosphokinase. EKG showed a persistent sinus tachycardia and an echocardiogram was performed. The study disclosed a dilated cardiomyopathy with an ejection fraction (EF) of 15-20% and global hypokinesia. A left heart catheterization was done and was negative for coronary artery disease. At a 20-week follow up, the patient stated that he had stopped abusing bath salts and was asymptomatic. A repeat echocardiogram showed an EF of 52% [31]. Additional cases have not been report with the 3Ms, but reversible cardiomyopathy is commonly seen in methamphetamine abusers [32].

Marinetti and Antonides (2013) studied the postmortem toxicology results in 23 cases [33]. The concentration range for blood methylenedioxypyrovalerone was 10–640 ng/mL, with an average value of 109 ng/mL. When peripheral and heart blood values were available, the average heart-to-peripheral blood ratio was 1.48, with a range of 1.3 to 1.7. The highest MDPV concentration occurred in a suicide by hanging and the highest methylone concentration was in a driver killed in a collision. After reviewing the results, it appeared to the authors that blood concentration does not predict either fatalities or impairment. Others have come to the same conclusion [34].

EXCITED DELIRIUM SYNDROME (ExDS)

ExDS seems to occur more frequently in MDPV users than with others 3M drugs. The difference is probably a consequence of slightly different affinities for dopamine

receptors. Cocaine, methamphetamine and synthetic cathinones all bind to the dopamine transporter (DAT), a membrane spanning protein that pumps dopamine out of the synapse back into presynaptic terminal where it is stored and later released. Dopamine reuptake *via* DAT is the primary mechanism that clears dopamine from synapses. MDPV is a very high potency DAT reuptake inhibitor, even more powerful than cocaine [35].

Dopaminergic pathways originate in the midbrain and provide input into the cortical and subcortical regions of the brain. Abnormally high dopaminergic transmission is known to cause psychosis and schizophrenia. The finding that stimulant drugs increase dopamine levels by more than tenfold is probably the mechanism by which these cathinone derivatives cause temporary psychosis, though it is not the mechanism that causes full blown excited delirium (ExDS) [36].

In order for excited delirium to occur, a substrate is required. Chronic psychostimulant abuse is probably the most common substrate of all [37]. This notion is supported by experimental data showing that mephedrone does not, itself, damage striatal nerve endings, but enhances the neurotoxicity of methamphetamine and amphetamine. Given that 3M users are often poly-drug abusers [38], neurotoxicity would seem likely. Another substrate could be extreme environmental stressors that also act to prevent dopamine reuptake [39, 40]. When reuptake of dopamine is blocked, dopamine remains trapped in the synapse, leading to a hyperdopaminergic state, which can cause violent behavior, delirium, agitation and sudden death if, and when, the neurocardiac axis is activated. This sequence has been repeatedly demonstrated in the murine models using various cathinone derivatives [41, 42]. This particular mechanism might explain the unexpected deaths of drug users when they are being taken into custody, but the hypothesis has yet to be tested.

CONCLUSION

Epidemiologic studies by many different agencies have detected the increasing use, and proliferating variety of new synthetic psychoactive drugs. Today, the three most commonly encountered are mephedrone, methylone, and MDPV ("bath salts"). Toxicity, most often manifested as psychosis or even fatal excited delirium, seems to be dose related, and more likely to occur in chronic drug abusers. No unique pathologic lesions have been identified, and the clinical toxicology of these drugs is poorly characterized. The underlying molecular disorder, however, closely resembles chronic cocaine toxicity and, in cases of ExDS may be well identical.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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