Case Report

Flashback phenomenon and residual neurological deficits after the use of "bath salt" 3, 4-methylenedioxypyrovalerone

Aaron R. Mangold¹, Thomas P Bravo², Stephen J. Traub³, Steven A. Maher³, Christopher A. Lipinski^{3,4}

¹ Department of Dermatology, Mayo Clinic, Phoenix, Arizona, USA

² Department of Neurology, Mayo Clinic, Phoenix, Arizona, USA

³ Department of Emergency Medicine, Mayo Clinic Hospital, Phoenix, Arizona, USA

⁴ Department of Pharmacology, Mayo Clinic, Phoenix, Arizona, USA

Corresponding Author: Christopher A. Lipinski, Email: Lipinski.christopher@mayo.edu

BACKGROUND: The use and abuse of designer drugs has been recognized for decades; however there are many derivatives of compounds that make their way into the community. Abuse of compound(s) known on the street as "bath salt" is on the rise.

METHODS: We report the case of a 33-year-old man who complained of "flashbacks" and right arm shaking that followed a night of "bath salt" snorting. The active compound methylenedioxypyrovalerone methamphetamine (MDPV) was confirmed; however, analysis of three different "bath salt" products showed difference in their active components.

RESULTS: The patient's symptoms remained stable and he was discharged home after observation in the emergency department with instructions to return for any symptom progression.

CONCLUSION: Practitioners should be aware of the abuse of the compounds and that not all "bath salt" products contain MDPV.

KEY WORDS: Residual neurological deficits; Methylenedioxypyrovalerone methamphetamine; Emergency Department

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INTRODUCTION

Designer drugs are chemical substances generally used for recreational purposes, but have no legitimate medicinal assignment.^[1] The term "designer" signifies that the chemical compound represents a derivative of a controlled substance, one that is illicit, or sometimes to subvert a legal ban.^[2] The 1980s saw the parallel emergence of designer derivatives of the opiate class (e.g. alpha-methylfentanyl, or "China white") and mescaline/phenethylamine class (e.g. methamphetamine, methylenedioxypyrovalerone methamphetamine [MDMA, or "ecstasy"]). The phenethylamine derivatives differ in the neuropharmacological effects they induce.^[3] Amphetamine

and methamphetamine are primarily potent central nervous system stimulants; whereas those compounds more chemically reminiscent of mescaline, such as MDMA, produce "entactogenic" effects. An entactogen (or empathogen) is a compound that induces feelings of "empathy" in the user.^[4] Owing to their structural conservation to amphetamine, these molecules also have potent stimulant properties that make them useful as "party" or "rave" drugs of abuse. Current understanding of the mechanism of action of phenethylamines suggests that they alter primarily the dopaminergic/norepinephrine and serotonergic circuitry of the central nervous system by altering the neuronal cytoplasmic distribution

(indirectly increasing synaptic concentrations) in the case of dopamine and norepinephrine^[5] and activate the serotonergic 5-HT_{2A} and 5-HT_{2C} receptors.^[6] Whether MDPV shares similar pharmacological activities is not yet known.

MDPV is the methylenedioxy ring substituted analog of the FDA schedule V drug pyrovalerone (Centron, Thymergix) used infrequently in a medicinal capacity for the treatment of chronic fatigue or lethargy. MDPV was first synthesized and patented in 1969 by Boehringer Ingelheim and was found to act as a norepinephrine (NE) and dopamine (DA) reuptake inhibitor.^[7] The drug was originally used for the treatment of lethargy and chronic fatigue in the 1970s but was taken off of the market secondary to issues with abuse and dependence.^[8] The recreational abuse of MDPV first started appearing in drug forums and chat rooms in 2005, and was later identified and seized by German customs officials in Saxony, Germany (2007) from a shipment originating from China. MDPV was first discovered by U.S. Customs agents in 2008.

In recent years, "bath salt" abuse in the United States has risen dramatically and various case reports show the dangers of chronic consumption and acute intoxication.^[9-11] Users of these compounds experience symptoms of sympathetic arousal, delirium, and psychosis in acute intoxication. However, the long-term sequelae remain speculative. Moreover, the assumption is that products sold as "bath salts" contain as their active ingredient MDPV. To date, no cases have reported post intoxication neurological impairment or episodic recurrence, "flashbacks", of the previously intoxicated state. Here we describe a 33-year-old male patient presenting subacutely who claimed to have snorted a MDPV-containing "bath salt" called "Eight Ballz", obtained from a local "head shop". We briefly review the pertinent chemistry, pharmacology, and management of patients abusing MDPV.

CASE REPORT

A 33-year-old man with a history of polysubstance abuse, seizures secondary to traumatic brain injury, and hormonal transgender therapy presented to the emergency department (ED). He complained of episodes described as "spacing out" one day following intoxication with "bath salts". The patient reported snorting lines of a "bath salt" product called 8 Ballz every two-to-three hours, for a total of twelve hours. He stopped taking the drug approximately 36 hours prior to ED presentation.

The patient was found to be tachycardic, diaphoretic, and euphoric during the period of intoxication. He denied any hallucinations. These symptoms lasted for one-to-two hours requiring repeat doses of the drug to maintain this "high" sensation. Within hours of the last dose, the patient felt disoriented, mildly depressed, and had difficulty in sleeping. Beginning approximately 12 hours after intoxication, the patient began to have two distinct sequelae. First, he had an episode with blurred vision, tachycardia, diaphoresis, confusion, and recurrence of depressive symptoms. Second, he complained of "flashback" episodes every one-to-two hours prior to presentation to the ED. He described the flashbacks as reliving of the snorting of the drug, as though he was "back there". Beginning after the "flashbacks", the patient had episodes of spasticity beginning in the left hand and progressing to the left and right legs. This spasticity would last approximately 5 or 10 minutes and did not occur in conjunction with the "flashback" symptoms. During both types of episodes, the patient had no loss of consciousness, tongue biting, or visual disturbances. Upon arrival to the ED, the patient was complaining of word finding difficulty. He had a history of polysubstance abuse, including cannabis, GHB, ecstasy, methamphetamines, and cocaine. However, this is the first time the patient had used "bath salts." The patient denied concomitant use of any other illicit drugs in the last several months. He had seizures secondary to head trauma 4 years before, but was not on anti-epileptic medications.

His vital signs were blood pressure 129/93 mmHg, pulse 83 beats per minute, respiratory rate 16 breaths/minute, temperature 37.0 °C (98.6 °F), and oxygen saturation 97% on room air. He was in no acute distress. Cardiac, respiratory, abdominal, ear, nose, and throat examinations were normal. The score of the Kokmen mental status examination was 30/38, missing one point for calculation, three for construction, and four for recall. Cranial nerve examination revealed weakness in an abduction of the right eye and a decreased upward deviation of the right eye. Neither processes induced diplopia. The motor portion of the neurological examination was normal. Reflexes were normal in the upper extremities and brisk without clonus at the patella bilaterally, but produced a painful "shock" sensation. Sensation, gait, cerebellar tasks, and plantar responses were normal.

Laboratory studies including a complete blood count, comprehensive metabolic panel, coagulation studies, urinalysis, and creatinine kinase were all unremarkable.

Importantly, urine screening for substances of abuse was negative for cannabinoids, cocaine metabolite, amphetamines, tricyclic antidepressants, opiates, phencyclidine, and benzodiazepines. Magnetic resonance imaging (MRI) of the brain with and without contrast was unremarkable, except for a 1 cm pineal cyst. The patient was discharged home with extensive counseling regarding the dangers of "bath salts" and drug abuse. We purchased a 500 mg vial of "Eight Ballz" from the head shop that the patient reported purchasing the "Eight Ballz" from that he nasally insufflated. GC-MS analysis (Mayo Clinic, Rochester, MN) identified the sample as containing MDPV and benzocaine.

DISCUSSION

This case of "bath salt" intoxication represents a "variation on the theme" of designer drug abuse presentations. On the street, the assumption is that these products contain MDPV, which also goes by peevee, magic, or super coke. MDPV is a phenethylamine whose use is most commonly associated with hallucinatory delirium, psychiatric disturbances, and dysphoria.^[9–11,16,17] Figure 1 illustrates the similarities between phenethylamine compounds that confer some similar pharmacology, but clearly some mechanistic differences must exist that account for varying "highs".^[14] Users of MDPV report that the stimulant effects of the molecule are the most prevalent and similar to methylphenidate at dose ranges of 100–200 mg and cocaine at higher doses. These dose ranges may not however be usable for the "seasoned" consumer as the actual active compound, percentage composition of the active, and additional active components likely vary substantially between products and preparations. Three different "bath salts" products

(Eight Ballz, Rave On, and Crazy Train) were analyzed by GC-MS and found that two contained MDPV and the third contained 4-fluoroamphetamine ("Flux"). Additionally, caffeine and benzocaine were also found in some of these products, but not all.

Our patient reportedly ingested 2/3 of the 500 mg vial of "Eight-Ballz", or approximately 333 mg total, over 12 hours with each administration approximately 80 mg. However since we have not determined the MDPV percentage by weight in this product, the actual pharmacological dosage is suspected. He described "cocaine-like" effects, but suggested that the effects were much longer than he had experience with cocaine. It is likely that the addition of benzocaine to these products simulates the topical anesthetic properties found with nasal insufflation of cocaine. The drug induced "flashback" phenomena, which could have occurred either from the drug or from partial seizures (reported episodes of "hand shaking"). An MRI of the brain was essentially normal and ruled out a structural correlate for palsy of the right abducens nerve and postulated that this resulted from his previous traumatic injury to the brain.

The toxicological similarities exist between various phenethylamine/mescaline designer drugs, including methamphetamine, MDMA, and MDPV. Patients often present with features of adrenergic overstimulation including tachycardia, hypertension, agitation, hyperpyrexia, diaphoresis, mydriasis, and muscle rigidity. Treatment of the acutely intoxicated patient is mainly supportive with expected toxicity lasting in the range of hours. Hypertensive emergencies are best managed with benzodiazepines, followed if necessary, by vasodilators such as nitroglycerine, nitroprusside, or an alpha-adrenergic blocking agent such as phentolamine. A report by Gay and Brown suggests that the mixed alpha-beta receptor blocker labetalol might also be effective, however many physicians avoid any beta-adrenergic blocking agent in such patients.^[12] A recent report suggested that labetalol was superior to diltiazem in managing hypertensive crisis related to ingestion of adrenergic stimulant designer drugs.^[13] Seizures and/or agitation are best managed with benzodiazepines (lorazepam). It has been suggested that protracted delusions or hallucinations can be managed with benzodiazepines, and can also be managed with perphenazine (Trilafon), clonidine, or roboxetine (Edronax). All patients presenting after recreational use of MDPV should be evaluated for rhabdomyolysis, but practitioners should realize that not all "bath salts" necessarily contain their advertized or implied active ingredient.^[15]

Figure 1. Chemical structures of several phenethylamines. The methylenedioxy-group phenyl-adduct of MDMA (B) and MDPV (D) renders these compounds structurally similar to mescaline (A). The phenethylamine backbone of MDMA and MDPV shares homology with amphetamine (C) as does 4-fluoroamphetamine (E).

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