

A case of fatal idiosyncratic reaction to the designer drug 3,4-methylenedioxypyrovalerone (MDPV) and review of the literature

Brigitte Desharnais^{a,b,*}, Yann Dazé^c, Laura M. Huppertz^d, Pascal Mireault^a,
Cameron D. Skinner^b

^a*Department of Toxicology, Laboratoire de sciences judiciaires et de médecine légale
1701 Parthenais Street, Montréal, Québec, Canada H2K 3S7*

^b*Department of Chemistry & Biochemistry, Concordia University
7141 Sherbrooke Street West, Montréal, Québec, Canada H4B 1R6*

^c*Department of Forensic Pathology, Laboratoire de sciences judiciaires et de médecine légale
1701 Parthenais Street, Montréal, Québec, Canada H2K 3S7*

^d*Institute of Forensic Medicine, Department of Forensic Toxicology, Medical Center,
Faculty of Medicine, University of Freiburg, Albertstrasse 9, 79104, Freiburg, Germany*

Abstract

The stimulant designer drug 3,4-methylenedioxypyrovalerone (MDPV) was first synthesized by Boehringer Ingelheim in 1969 and introduced on the black market in 2006. Only a small number of fatal intoxication cases have been reported in the literature, all with significant blood MDPV concentrations. In this report, we describe one fatality attributed to an idiosyncratic reaction to MDPV. The victim displayed agitation, violent behavior and delirium followed by cardiac arrest. Hyperthermia was observed at the hospital. The MDPV cardiac and femoral blood concentrations were 6 *ng/mL*. The presence of excited delirium syndrome and MDPV, a drug with a pharmacology similar to cocaine, leads to the conclusion that the victim suffered a fatal adverse reaction to MDPV. This is the first published case of idiosyncratic reaction to MDPV.

1. Introduction

In order to circumvent existing legislation on controlled substances, derivatives of known psychoactive substances began to appear on the black market as “designer drugs” in the mid-2000s [1, 2]. One popular family of designer drugs are the synthetic cathinones or “bath salts”. 3,4-methylenedioxypyrovalerone

* Author to whom correspondence should be addressed.

Email: brigitte.desharnais@msp.gouv.qc.ca

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(MDPV) is a member of this family: a β -keto phenylalkylamine, derivative of the natural alkaloid cathinone found in the plant *Catha edulis* (khat) [1, 3]. MDPV, initially synthesized by Boehringer Ingelheim in 1969 [1], was first detected in Japan in 2006, and subsequently was increasingly found throughout the world [4, 5]. In 2011, the Drug Enforcement Agency of the United States (DEA) scheduled MDPV on a temporary emergency basis [6, 7]. Since this time, the prevalence of MDPV in synthetic cathinones decreased in favor of unregulated compounds.

Synthetic cathinones are stimulants consumed for the effects of increased alertness and energy, euphoria, excitement, improved mood, sociability and intensification of sensory experience (mild empathogenic effects) [5]. Undesired cardiac and neurological effects include tachycardia, hypertension, cardiac arrest, agitation, aggressive and combative behavior, disorientation, confusion and paranoia [1, 5, 6, 7, 8, 9, 10].

The physical form of MDPV is a white, tan, gray, yellow or brown odorless powder [1, 6] and is often mixed with caffeine and lidocaine or benzocaine [5]. It is marketed as “bath salt” (in the US) or “plant feeder” (in Europe) and sold under 50 different known brand names on the Internet or in head shops, convenience stores, gas stations and tobacco shops [5, 6, 11, 12]. Its main modes of ingestion are oral, intravenous, insufflation (snorting) and inhalation (smoking) [1, 5, 6, 8, 13, 14, 15]. Doses of 5 to 30 *mg* in a single ingestion are typical [1, 5, 8], with effects lasting 1 to 3 h [10].

Although several clinical cases of consumption of, or intoxication by, MDPV have been reported [4, 9, 12, 13, 15, 16, 17, 18, 19, 20, 21], there are only a few fatal MDPV intoxication cases published with toxicology results [3, 6, 10, 14, 22, 23]. In all of these cases, the MDPV concentration was elevated (> 80 *ng/mL* in whole blood). We present here a case of fatal idiosyncratic reaction to MDPV, a radically different type of MDPV intoxication than what has been previously published.

2. Case history

2.1. Background

The victim was a 42 year old Native American male that had been incarcerated for several months prior to the event. In the early afternoon, the man was standing in front of his cell, talking incoherently. He then approached the guards' post and became hysterical and disorganized. Prison personnel attempted to

physically control him, but he fought them vigorously. He was eventually cuffed at the wrists and ankles and put into a padded cell, lying on his side. 27 minutes later, the man was in cardiorespiratory arrest and resuscitation maneuvers were started. Upon arrival at the hospital, 1h19 into the event, the victim's rectal temperature was 39.3 °C. His death was pronounced 1h40 after the beginning of the event. Since the victim was in cardiac arrest upon arrival at the hospital, no biochemistry or toxicology screen was performed.

2.2. Autopsy findings

The deceased was 182 *cm* tall and weighed 156 *kg*. The external exam revealed the presence of linear abrasions and light bruises at the wrists and ankles, most likely due to the cuffs placed on the victim. Also, numerous bruises were observed on the four limbs, which could have resulted from confinement of the victim by the prison personnel or have been auto-inflicted. A linear abrasion on the shoulder blade and abrasions on the knees were also observed. No other significant traumatic lesions were apparent on external examination.

The internal exam revealed the presence of left pleural adhesions. The heart weighed 520 *g* and revealed a slight left ventricle hypertrophy, without any congenital anomaly, valvular or coronary disease. The lungs (right 820 *g*, left 870 *g*) were heavy and congested, which was confirmed through histological analysis. The liver weighed 1780 *g* and was affected by steatosis without associated cirrhosis, which was also confirmed by the histological exam. The urinary bladder contained 80 *mL* of urine. The full length of the gastro-intestinal tract was opened and no intra-luminal body was found. Gastric contents (60 *mL*) were a brownish liquid with beige, black and green particles. Rib fractures attributed to CPR were observed. No cranial, spine, hip or limb fractures were seen. No other anatomic lesions were observed.

2.3. Toxicological analysis

Peripheral blood from the femoral vein, cardiac blood (pooled from both ventricles), urine, gastric contents and vitreous humor were recovered for toxicological analyses. Toxicology included cyanide screening, ethanol and volatile compound determination, immunological screening (cocaine, opiates, PCP, amphetamines, cannabinoids, barbiturates, salicylates, benzodiazepines, acetaminophen, paracetamol and methadone) as well as gas-chromatography-mass spectrometry (GC-MS-NPD) screening and liquid chromatography-tandem mass spectrometry (LC-MS/MS) quantification. All of these methods (unpublished) are validated, and the quantitative methods are accredited under ISO 17025/CAN-P

1578 standards. To carry out the LC-MS/MS analysis, all matrices were extracted with a protein precipitation protocol using a mixture of acetonitrile and acetone as the precipitating agent. Results of the toxicological investigation are shown in Table 1.

Table 1: Postmortem toxicological analysis results

Biological Matrix	Concentration (ng/mL)					
	MDPV	Mirtazapine	THC	THC-OH	THC-COOH	7-amino-clonazepam
Femoral Blood	6	17	4	4	27	2
Cardiac Blood	6	26	1	2	38	3
Urine	166	290	ND	1	290	5
Gastric Contents	19	180	273	61	64	ND
Vitreous Humour	5	2	ND	ND	1	ND

ND: not detected

Also detected in cardiac blood, femoral blood and urine were the metabolites demethylenyl-methyl-MDPV, N-desmethyilmirtazapine and THC-COOH glucuronide. According to medical records, the victim had a prescription for mirtazapine and clonazepam, explaining the presence of these two compounds in the toxicology results.

By taking into account circumstances surrounding death (agitation, violent behavior, hyperthermia) and toxicology results, the cause of death was ruled to be complications of an adverse reaction to consumption of MDPV by the victim. It was also noted that the pre-existing medical condition of the victim (obesity, slight cardiac hypertrophy) may have contributed to death.

Subsequent toxicological screening by liquid chromatography-time of flight mass spectrometry (LC-QToF) initially suggested the presence of 4-acetoxy-DMT (4-AcO-DMT) in cardiac blood and urine via a library hit. 4-acetoxy-DMT (also known as psilacetin and O-acetylpsilocin) is a synthetic pro-drug of the hallucinogenic compound psilocin [24]. However, further analysis using reference material confirmed this as a false positive, since retention time did not match and specific fragments were absent.

3. Discussion

A certain number of MDPV intoxication cases have already been published in the literature (see Table 2). In all published reports, the MDPV concentration in blood is more elevated than what was observed in the case presented here. Indeed, all but one case show MDPV concentrations at least 10 times higher than the 6 *ng/mL* found in the cardiac and femoral blood of the victim. Although an MDPV overdose (in the strictest sense of the term) seems unlikely here, an adverse reaction to MDPV is a probable mechanism of death.

MDPV is a dopamine and norepinephrine reuptake inhibitor acting as a stimulant [1, 7, 9, 22]. *In vitro* transporter assays performed on brain synaptosomes show that MDPV functions as a monoamine uptake pure blocker (like cocaine) and not as a monoamine transporter substrate (like amphetamine) [25]. The pharmacology of MDPV is thus closer to cocaine than MDMA, as was previously thought.

It is well known that there is no “safe” concentration for cocaine, since virtually any concentration can trigger an adverse reaction and ultimately death [26]. Given the similarity between the pharmacology of MDPV and cocaine, it would seem logical that a similar potential for adverse reactions exists with MDPV.

Stimulant drug use, particularly cocaine, is a known trigger of excited delirium syndrome (ExDS), even at recreational dosages [27]. Excited delirium syndrome is characterized by an excited or agitated state, delirium, sometimes complemented by tachycardia and hyperthermia followed by cardiac arrest [3, 27]. The behavior reported by prison personnel as well as the hyperthermia highlighted at the hospital both fit the ExDS profile. The exact mechanism of this potentially lethal side effect is unknown. The observed hyperthermia is thought to result from dysregulation of the dopaminergic pathways in the hypothalamus [3] and has been reported in an elevated number of MDPV intoxications and adverse reactions [3, 4, 6, 9, 16, 17, 23]. The presence of ExDS adds to the profile of an adverse reaction to a stimulant. It is worth noting that the presence of mirtazapine, even at therapeutic concentrations, might have contributed to the elevation of serotonin levels and thus the reported agitation of the victim.

Table 2: Previously published MDPV fatal intoxications

<p>Namera et al. [22]</p> <p>35 year old female, declared dead at the hospital.</p> <p>MDPV concentration(s): 200 ng/mL (cardiac blood), positive (hair).</p> <p>Other toxicological results: α-PBP (positive)</p> <p>Cause of death: MDPV intoxication.</p>
<p>Kesha et al. [6]</p> <p>39 year old male, seen talking to himself in front of his residence, delusional. Brought to the hospital; agitated, tachycardic, 41.72°C. Died 12 h post admission.</p> <p>MDPV concentration(s): 700 ng/mL (cardiac blood), 1000 ng/mL (femoral blood)</p> <p>Other toxicological results: Cardiac blood: diphenhydramine (100 ng/mL) promethazine (200 ng/mL), nordiazepam (100 ng/mL)</p> <p>Cause of death: MDPV intoxication. Manner of death: accident.</p>
<p>Murray et al. [2]</p> <p>40 year old male, aggressive, uncontrollable, delusional, tachycardic, underwent cardiac arrest. Temperature post-resuscitation: 40.7°C. Subsequent development of coagulopathy, rhabdomyolysis, renal failure, anoxic brain injury and death.</p> <p>MDPV concentration(s): 82 ng/mL (serum), 670 ng/mL (urine)</p> <p>Other toxicological results: Serum: trimethoprim (2.2 mcg/mL). Urine: trimethoprim (12 mcg/mL).</p> <p>Cause of death: MDPV intoxication.</p>

<p>Wyman et al. [14]</p> <p>39 year old male found unresponsive at home.</p> <p>MDPV concentration(s): 500 ng/mL (cardiac blood), 440 ng/mL (femoral blood), >5000 ng/mL (urine), >2000 ng/mL (gastric content). (Other matrices available.)</p> <p>Other toxicological results: also identified in matrices: caffeine, fluoxetine, lamotrigine, risperidone, hydroxyrisperidone, ibuprofen, nicotine/cotinine, pseudoephedrine, benzotropine.</p> <p>Cause of death: MDPV intoxication.</p>
<p>Marinetti et al. [10]</p> <p>39 year old male, known user of bath salts, known to become manic when used. Found dead at home.</p> <p>MDPV concentration(s): 91 ng/mL (femoral blood), >200 ng/mL (urine)</p> <p>Other toxicological results: Femoral blood: lidocaine (100 ng/mL)</p> <p>Cause of death: MDPV intoxication. Manner of death: accident.</p>
<p>Marinetti et al. [10]</p> <p>33 year old female, drug abuser found two days after death.</p> <p>MDPV concentration(s): >4 800 ng/g (liver)</p> <p>Other toxicological results: Liver: trazodone (presumptive identification) and beta-phenethylamine (positive).</p> <p>Cause of death: MDPV intoxication. Manner of death: accident.</p>
<p>Young et al. [23]</p> <p>48 year old female, ingested bath salts and was found unresponsive. At the hospital, sinus tachycardia, 37.0°C (evolved later to 39.4°C). Developed disseminated intravascular coagulation and died.</p> <p>MDPV concentration(s): 29 ng/mL (ante-mortem blood; time of collection unknown).</p>

Demethylenyl-methyl-MDPV (also called methyl cathecol pyrovalerone [2]) has been previously identified in studies of *in vitro* human liver microsomes and *in vivo* rat MDPV metabolism [2, 28]. It is hypothesized to result from the methylation of the initial demethylenyl-MDPV metabolite produced by CYP 1A2, CYP 2C19 and CYP 2D6 [28] enzymes. The lack of additional metabolite standards limited LC-MS/MS analysis for identification and quantification of other metabolites besides demethylenyl-methyl-MDPV in the matrices.

In the case reported here, several elements point towards a case of fatal idiosyncratic reaction to the stimulant designer drug MDPV, such as excited delirium syndrome with hyperthermia, low concentrations of MDPV in blood and the similarity of the pharmacology of MDPV with cocaine. This is a category of MDPV intoxication previously unreported in the literature.

4. Key points

1. 3,4-methylenedioxypropylvalerone (MDPV) is a stimulant designer drug with a pharmacology similar to cocaine.
2. Excited delirium syndrome (ExDS) is characterized by agitation, delirium, tachycardia and hyperthermia. A common trigger is stimulant drug consumption.
3. Presence of ExDS with recreational MDPV concentrations should be considered as indications of a potential adverse reaction to MDPV.

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6. Compliance with ethical standards

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6.2. Conflict of interest

The authors declare that they have no conflict of interest.

6.3. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Consent to publish this case report was obtained from the coroner.

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