Death by "Legal" Psychedelic Piperidines and Phenethylamines: Postmortem Tissue Distribution of Desoxypipradrol (2-DPMP) and 4-chloro-2,5-dimethoxyamphetamin (DOC)

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Abstract

▪After attending this presentation, attendees will have a better understanding of the piperidine and amphetamine class designer drugs **desoxypipradrol (2-DPMP)** and **4-chloro-2,5-dimethoxy-amphetamine (DOC)** and their concentrations in postmortem matrices.

▪This presentation will impact the forensic community by informing forensic professionals on new abuse trends for amphetamines and designer drugs, particularly in our youth. It adds to the relatively sparsely published data concerning the potential toxicity of these stimulant drugs and provides a comprehensive approach to extraction, detection, and quantification of these substances.

▪These type of compounds have recently achieved "epidemic" status for abuse by young people. 2-DPMP exhibits a cocaine-like binding profile while DOC is a long-acting agonist of serotonin receptors; the fluoroamphetamines stimulate release and prevent reuptake of dopamine, serotonin and norepinephrine.

▪Toxicities observed are similar to amphetamine toxicity: tachycardia, nausea, hypertension (vasoconstriction), insomnia, hyperthermia, mydriasis, panic attack, and seizures with the added predominant neuropsychiatric features of: hallucinations, paranoia and agitation.

▪An autopsy was performed at the **Cuyahoga County Medical Examiner's Office.** Autopsy findings included dilated cardiomyopathy with a 460-gram heart, cerebral edema and edematous lungs. Heart and femoral blood, vitreous humor, bile, liver, brain (medulla) and gastric were submitted for a comprehensive toxicology analysis.

▪The heart blood was positive for amphetamine 0.058 mg/L, methamphetamine 0.170 mg/L, fentanyl 2.0 ng/mL; norfentanyl 0.44 ng/mL, acetaminophen, atropine, caffeine, cotinine, lidocaine and nicotine. The femoral blood was not sufficient in volume for analysis. No antemortem admission blood samples were available for analysis.

▪Because of the decedent's drug history further testing was performed to determine the presence of other possible phenethylamine and amphetamine class drugs. Samples were extracted at a basic pH into ethyl acetate. 2-DPMP, DOC and the fluoroamphetamines were separated and detected by an Agilent GC/MS-EI in full scan mode with a Restek-DB5 capillary column.

▪Further confirmatory testing was performed at **AIT Laboratories**, Indianapolis, IN for the 2-DPMP, DOC and fluoroamphetamines. Specimens were extracted at a basic pH into n-butyl chloride. Separation and detection was completed by a Waters Acquity UPLC coupled to a Waters LCT Premier XE TOF mass spectrometer as well as a Waters Acquity UPLC coupled to a Waters tandem quadrupole detector (TQD). The analytical column for both analyses was a Waters BEH C18, 2.1 x 100 mm, 1.7 µm particle size.

▪The concentrations for the subsequent testing are as follows: desoxypipradrol (2-DPMP) concentrations (mg/L) were 0.271, heart blood; 0.236, vitreous humor; 1.98 mg/kg, liver; 0.838 mg/kg, brain (medulla); >1.0, bile, and negative, in the gastric.

▪4-chloro-2,5-dimethoxy amphetamine (DOC) concentrations (mg/L) were 0.466, heart blood; 0.380, vitreous humor; 1.40 mg/kg, liver; 1.09 mg/kg, brain (medulla); and 2.04 in the bile. 2-DPMP and DOC was found to be distributed among multiple matrices with values ranging from 0.236 to >1.0 mg/L for 2-DPMP and 0.380 to 2.04 mg/L for DOC. Tissues responsible for detoxification and excretion had higher concentrations of the drugs. 2-DPMP, DOC and the fluoroamphetamines were present in all tissues analyzed except gastric.

▪Drug Chemistry results from submitted drug and drug paraphernalia exhibits were found to contain the following: 2-fluoro-meth-amphetamine, alprazolam, 2-(1-pyrrolidinyl)-(4-methylphenyl)-1-propanone (MPPP), methamphetamine, dimethyltryptamine (DMT), psilocin, cannabis, fluoromethamphetamine, 4-chloro-2,5-dimethoxyamphetamine (DOC), phencyclidine and lysergic acid.

▪This case was consistent with the suspicion that this was an acute drug exposure. The cause of death was ruled toxic metabolic encephalopathy due to mixed drug intoxication. The manner of death was ruled as accidental.

Key Words: Desoxypipradrol, Phenethylamines, Amphetamines.

Introduction

General Pharmacology:

▪ Stimulants with Empathogen/Entactogen (ecstasy MDMA-like) hallucinogenic properties are unique, similar to LSD or psilocybin (visual, auditory, olfactory, or physical).

▪ Produce different psychological effects than observed with methamphetamine and amphetamine. Ring-substitutions on the base molecule vary the psychoactive and hallucinogenic properties.

Introduction

Case History:

A 30-year-old male called a friend and advised him he had been snorting *"DOC"*, 4-chloro-2, 5-dimethoxy-amphetamine, and was "tripping" and needed assistance.

▪ EMS and police were called and found the individual lying face down, breathing, but unresponsive, convulsing, extremely warm to the touch and sweating heavily.

▪ He was conveyed to the hospital with an initial diagnosis of an acute drug overdose.

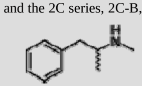
▪ All indications were that the overdose occurred within the last 3 hours. The individual died 42 hours after arriving at the hospital.

▪ A collection of paraphernalia was confiscated from the residence as evidence and later submitted for analysis.

Designer recreational drugs classes:

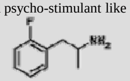
1) Phenethylamines 2) Piperazines, 3) Piperidines and 4) Tryptamines. Many are Schedule 1 drugs; others are listed under the Synthetic Drug Abuse Prevention Act of 2012.

▪ **Phenethylamines:** Methamphetamine, is the quintessential phenethylamine, a sympathomimetic stimulant. Other examples of phenethylamine class psychoactive drugs are MDA, MDMA, MDEA, MBDB, MDPV, (3,4-methylenedioxypyrovalerone) and the 2C series, 2C-B, 2C-I, 2C-T-7, and 2C-T-2.



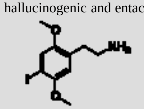
Methamphetamine: MW=149.23

▪ **Fluoroamphetamines** are new fluoro-methoxy-substituted analogues of the phenethylamine amphetamine, they stimulate release and prevent reuptake of dopamine, serotonin and norepinephrine. DUID cases exhibited sympathomimetic effects and psycho-stimulant like impairment.



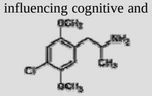
2- fluoroamphetamine: **2-FA**
MW=153.196

▪ **2, 5-dimethoxy-4-iodophenethylamine (2C-I)** is another psychedelic phenethylamine which was first synthesized by Alexander Shulgin. Used recreationally for its psychedelic/ hallucinogenic and entactogenic drug.



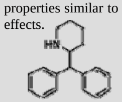
2, 5-dimethoxy-4-iodo-phenethylamine: **2C-I**
MW=307.13

▪ **2, 5-Dimethoxy-4-chloroamphetamine, (DOC)** is a long-acting agonist of serotonin receptors. It is a classic type psychedelic influencing cognitive and perception areas of the brain.



2, 5-Dimethoxy-4-chloro-amphetamine: **DOC**
MW=229.70

▪ **Piperidines: Desoxypipradrol, (2-DPMP)** is structurally similar to Ritalin. It is a psychostimulant with sympathomimetic properties similar to cocaine and can cause prolonged psychotic effects.



Desoxypipradrol: **2-DPMP**
MW= 251.36

Introduction

Clinical Side Effects:

Toxicities for these designer drugs are similar to **"**Amphetamine" toxicity: tachycardia, nausea, hypertension, vasoconstriction, chest pains, insomnia, hyperthermia, mydriasis, panic attack, seizures, vomiting, bruxism, muscle tension, fever, chills, sweating, agitation, paranoia, delusions, and suicidal ideations.[1-6]

▪ **2-DPMP:** Produces added prolonged neuropsychiatric symptoms features of hallucinations, paranoia, agitation, anxiety, and insomnia (up to 24-72 hours).[1]

▪ **DOC :** Limited published scientific literature on adverse effects, see http://www.erowid.org/experiences/exp.php?ID=73020, nausea, chest pain and vasoconstriction were noted.

Affirmative effects of Designer Drugs:

Euphoria, feeling, giddy or excited or increased alertness and awareness, increased wakefulness, increased energy and motivation, increased mental stimulation and concentration, increased sociability, sexual stimulation, decrease in the perceived need for food and sleep.[1-6]

Materials/Methods

▪ A "standard" post-mortem toxicological analysis for illicit and non-illicit drugs was performed at **CCMEO.** It consisted of the following tests: volatiles, bases, benzodiazepines, acidic-neutrals, blood and urine immunoassays which included opiates, oxycodone, methamphetamine, amphetamine, tricyclic anti-depressants, carisoprodol and meprobamate, fentanyl, cannabinoids, cocaine and metabolites, barbiturates, benzodiazepines, phencyclidine, methadone, GC/MS confirmations, acetaminophen, salicylate, and electrolytes.

Sympathomimetic Amine Extraction of fluids and tissues:

Analytes including 2-DPMP were extracted at a basic pH from biological matrices, into ethyl acetate. Appropriate calibrators and controls were utilized. Tissues were homogenized with dilutions. 2-DPMP was obtained from Cayman Chemical.

GC/MSD-EI Analysis:

An Agilent 6890/5975 (full scan), was used to identify analytes by their retention times and obtained spectra were compared to a spectral library or calibrator for match quality. Analytes were quantitated using a 5-point calibration curve.

▪ A Restek Rxi®-5ms capillary column was used (#13423, 30 m × 0.25-mm I.D., 0.25-µm film thickness) with helium as the carrier gas, flow rate was 1.2 ml/min. The ion source and quadrupole were, 230 °C and 150 °C, with a mass range m/z 40-500 amu, threshold 100, scan rate 14.02 scans/sec. Retention time window +/-2%.

Operating parameters:

The injection port was 250° C, oven temperature 70°C, hold time of 0.50 min., ramp 50.0 °C per minute, final temperature 300 °C, final hold of 6.90 min. Total run time 12 minutes. Splitless mode, 1µl injection.

Amphetamine and Methamphetamine:

Linearity: 0.05 - 2.33 and 0.033 -3.0 mg/L, respectively. LOQ/LOD was 0.05 and 0.033 mg/L, coefficient of determination > 0.995, % CV for intra-run precision was 6.7 % and 7.9 %, respectively.

Desoxypipradrol, 2-DPMP:

The 7-point calibration curve was linear from 0.01 to 1.2 mg/L. LOQ/LOD was 0.05 mg/L, coefficient of determination > 0.995.

▪ The result of 2-DPMP analysis from the reference lab was used as a control for validation of the 2-DPMP calibration curve.

Results & Discussion

Forensic Autopsy Findings:

▪ A complete autopsy was performed at the Cuyahoga County Medical Examiner's Office (CCMEO), Cleveland, Ohio.

▪ It consisted of: External and internal examination of the body, microscopic examination, toxicological examination and police investigation.

▪The body was that of a normally developed obese male. He was thirty years old 6' 0" tall and 250 lbs in weight.

▪Autopsy findings included dilated cardiomyopathy with a 460-gram heart, cerebral edema and edematous lungs.

▪External and internal examination showed no significant abnormality.

Initial Toxicology Results:

▪ The heart blood was positive for: Amphetamine, meth-amphetamine, fentanyl 2.0 ng/mL; norfentanyl 0.44 ng/mL, acetaminophen, atropine, caffeine, cotinine, lidocaine and nicotine.

▪ 2-DPMP, DOC and fluoroamphetamines, were spectrally identified by GC/MS.

▪Specimens were later sent to **AIT Laboratories** for confirmation and quantitation of 2-DPMP, DOC, 2C-I and the fluroamphetamines, these were performed by TOF mass spectrometer and UPLC/tandem quadrupole detector (TQD) analysis.

▪ The femoral blood was not sufficient in volume for analysis.

▪ No ante-mortem admission blood samples were available for subsequent analysis.

▪ The inter-laboratory results from CCME and AIT Laboratories for the 2-DPMP in the cardiac blood, vitreous humor, liver, and brain (medulla) were within 4.05%, 15.1%, 0.1% and 20.6% respectively.

Drug Chemistry Results:

Testing from the submitted paraphernalia exhibits were performed by the State of Ohio Bureau of Criminal Investigation (BCI) and corroborated the post-mortem results.

Specimen (conc. mg/L) Unless noted	Drug distribution among multiple matrices					
	Heart Blood	*Vitreous Humor*	*Liver*	*Brain (Medulla)*	*Bile*	*Gastric*
Amphetamine	0.58	0.059	0.393 mg/kg	None detected	>1000 ng/mL	Not Tested
Methamphetamine	0.17	0.259	0.750 mg/kg	0.518 mg/kg	>1000 ng/mL	Not Tested
Desoxypipradrol (2-DPMP)	0.271	0.236	1,980 ng/g	0.838 mg/kg	>1.0 mg/L	Negative
4-chloro-2,5-dimethoxy amphetamine (DOC)	0.466	0.380	1,405 ng/g	1,098 ng/g	2,042 ng/mL	Not Tested
2-Fluro-amphetamine (2-FA)	19.2 ng/mL	< 5 ng/mL	21.9 ng/g	< 15 ng/g	166 ng/mL	Not Tested
2-Flurometh-amphetamine (2-FMA)	92.0 ng/mL	< 5 ng/mL	74.4 ng/g	107 ng/g	1518 ng/mL	Not Tested
2,5-dimethoxy-4-iodophenethyl-amine (2C-I)	None Detected	< 5 ng/mL	None Detected	579 ng/g	None Detected	Not Tested

Conclusions

• **2-DPMP** and **DOC** was found to be distributed among multiple matrices with values ranging from:

▪ 0.236 to >1.0 mg/L for 2-DPMP

▪ 0.380 to 2.04 mg/L for DOC

▪ Tissues responsible for detoxification/excretion had higher concentrations of the drugs.

▪These new designer sympathomimetic drugs produce "Amphetamine" like toxicity and added prolonged psychotic effects in the case of 2-DPMP.

▪ This case was consistent with the suspicion that this was an acute drug exposure. **The cause of death was ruled toxic metabolic encephalopathy due to mixed drug intoxication. The manner of death was ruled as accidental**.

Reported Toxicity Data from the Literature		
(conc. mg/L)	**Toxic (DUID)**	**Lethal**
Amphetamine [7-8]	0.2-3.0	0.5-41 (8.6)
Methamphetamine [7-8]	0.12-5.0	0.09-64
Desoxypipradrol (2-DPMP) [1-6]	106 (DUID) cases: **Median: 0.073 mg/L** **Range:0.006 - 0.890 mg/L**	Post-mortem cases: ▪ **1.6 mg/L,** femoral, COD: "unascertained". ▪ **0.79 mg/L,** blood, COD: "open" verdict. ▪ **0.025 mg/L,** after ~ 2 days, COD: overdose. ▪ In 5 autopsied cases, 2 of the 5 COD's reported as "Contributory".
(D2PM) [6]	Acute ingestion (survived) **0.22 & 0.17 mg/L**	No reported toxicity data.
(DOC) [9]	DOC not quantitated	No reported toxicity data.
(2-FA) and (2-FMA) [10]	3 Cases (DUID): **0.028, 0.041, 0.37 mg/kg**	No reported toxicity data.
(4-FA) [11-12]	▪ **DUID cases, n=106** ▪**Range: 0.006 - 0.58 mg/kg,** ▪ **2 cases: 350 & 475 ng/mL**	▪ 1 case: COD "Combined intoxication", value not reported.
(2C-I) [13-15]	No reported toxicity data.	The drug has been "linked" in several deaths in the United States.

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