Case Report of a Death Involving Designer Opioid MT-45 Raises the Spectre of Synthetic Opioids in Forensic Casework

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NPS Movement

• NPS: Novel Psychoactive Substances

• Started in late 2000s

• Primarily started with synthetic cannabinoids and cathinones
  • Ex. JWH-073, AM-2201, XLR-11
  • Ex. Methylone, MDPV, Alpha PVP

• Market has expanded to include designer benzodiazepines and opioids
Designer Opioids vs. Morphine

AH-7921

Acetyl Fentanyl

Mitragynine

Morphine
Designer Opioids

- **AH-7921**

- **Acetyl fentanyl**

- **MT-45**
MT-45

- 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, I-C6

- Invented in 1970s by Dainippon Pharmaceutical Co

- Shared analgesic and CNS depressant properties similar to that of morphine

- Not controlled in the United States

Formula: $C_{24}H_{32}N_2$
Mol. Mass: 348.523 g/mol
Recreational abuse of MT-45

- Typically sold as dihydrochloride salt
- Oral, intranasal, or IV routes of administration
- Doses vary between 15 - 75 mg
- Sometimes found mixed with other substances
Adverse side effects (n=7)

- Somnolence
- Unconsciousness
- Tachycardia
- Decreased respiratory rate
- Hypoxia
- Cyanosis
- Hypotension
- Hypokalemic
- Vomiting
Case Series of MT-45 Hospitalizations

- Patients admitted to hospitals in Sweden from Nov 2013 - Feb 2014 for NPS use
- All patients male, 17-32 y/o
- 9 cases with toxicology testing
  - MT-45 only (n=4): 6 - 157 ng/mL in blood
  - MT-45 + other (n=5): 19 - 102 ng/mL in blood
- 3 patients complained of bilateral hearing loss

MT-45 Mass Spectrum

Identification of two new-type designer drugs, piperazine derivative MT-45 (I-C6) and synthetic peptide Noopept (GVS-111), with synthetic cannabinoid A-834735, cathinone derivative 4-methoxy-α-PVP, and phenethylamine derivative 4-methylbuphedrine from illegal products. Forensic Toxicology, January 2014, 32(1):9-18
Case Report

- 35 year old male found deceased by his roommate
- Known history of drug use
- Found collapsed next to the couch
- Scale, spoon, lighter, and two packets of white powder found nearby
- One bag tested positive for MT-45; the other tested positive for Etizolam
Case Report

- One pink punctate mark on dorsum of right foot (possible injection site)
- Cerebral edema and lung congestion
- Specimens collected for toxicology: Femoral and heart blood, urine, vitreous
- Microscopic examination of major organs was performed
- No anatomical cause of death; toxicology requested
Toxicology

- Routine toxicology performed first with few positive findings
- After identification of materials as MT-45 and etizolam, targeted analyses were developed and samples analyzed
  - Extraction
  - Method parameters
  - Quantitative results
    - Standard addition
LC-MS/MS Analysis

- Liquid-liquid extraction using NH$_4$OH and n-butyl chloride/acetonitrile (4:1, v/v)
- ISTD = acetyl fentanyl - d5
- Positive electrospray, MRM
- BEH C18, 2.1 x 5.0 mm column for separation
- Mobile phases of 0.1% formic acid in methanol and 0.1% formic acid in diH$_2$O
## Analyte Characteristics

<table>
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<th>Analyte</th>
<th>Quant Ion</th>
<th>Qual Ion</th>
<th>RT (min)</th>
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<tr>
<td>Acetyl Fentanyl d5</td>
<td>328.3 &gt; 105.1</td>
<td>328.3 &gt; 188.1</td>
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<tr>
<td>MT-45</td>
<td>349.3 &gt; 181.1</td>
<td>349.3 &gt; 169.2</td>
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</table>

**Acetyl Fentanyl d5**

**MT-45**
MT-45 Calibration Curve

- Calibration curve handspikes of 1.0-100 ng/mL
- Run in triplicate
  - Slope = 0.999
  - Bias = 0.05%

Compound name: MT-45 Quant
Coefficient of Determination: $R^2 = 0.999795$
Calibration curve: $0.00804825 \times x^2 + 29.456 \times x + 0.768522$
Response type: Internal Std (Ref 1), Area * (IS Conc. / IS Area)
Curve type: 2nd Order, Origin: Exclude, Weighting: 1/x, Axis trans: None
## Precision & Accuracy (n=15)

<table>
<thead>
<tr>
<th>Level</th>
<th>Concentration (ng/mL)</th>
<th>Precision (%CV)</th>
<th>Accuracy (%Difference)</th>
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<tr>
<td></td>
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<td>Total</td>
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<td>High QC</td>
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<td>3.8</td>
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</table>
Toxicology Results

- NMS Expanded Postmortem Toxicology Panel was positive for Diphenhydramine (220 ng/mL) in femoral blood
- Urine presumptively positive for cannabinoids and benzodiazepines
- Targeted analyses in femoral blood
  - MT-45: 520 ng/mL
  - Etizolam: 35 ng/mL
Neither drug is prescribed in the U.S.
  - Etizolam – a benzodiazepine derivative with hypnotic and sedative properties
  - Prescribed in certain Asian and European countries

Investigation found that decedent had purchased both drugs online from a Canadian company, and had been doing so monthly for some time

Cause of death – combined toxicity of MT-45 and Etizolam

Manner of death – accidental
Interpretation of Results

• **Etizolam concentration of 35 ng/mL consistent with therapeutic levels**

• **MT-45 linked to adverse events and fatalities in Sweden**
  • From 21 reported fatalities; 6-1900 ng/g
  • In 6 PM cases attributed to MT-45 intoxication; 200-1900 ng/g

Discussion

• Opiates/opioids are frequently encountered in toxic deaths

• Designer opioids, like MT-45, are starting to hit the market; intoxications by these compounds may look like other opiates/opioids

• MT-45 currently not included in most routine forensic drug screening panels

• MT-45 commonly found in combination with other drugs
Disclaimer

• Work completed on behalf of the Center for Forensic Science Research and Education
Questions?