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Case Report

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4-Fluoromethylphenidate: Fatal Intoxication Involving a Previously Unreported Novel Psychoactive Substance in the USA

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Abstract

The (±)-*threo*-4-fluoromethylphenidate (4F-MPH) is a fluorinated analog of the prescription central nervous system stimulant medication, methylphenidate. This novel psychoactive substance was first detected in drug paraphernalia at the Miami-Dade County Medical Examiner Department Toxicology Laboratory in 2016 but was not detected in a biological specimen until 2018. Limited literature is available on 4F-MPH, with predominate literature being published out of Europe, and no known toxicities reported in the USA. Post-mortem specimens were screened using both gas chromatography mass spectrometry and liquid chromatography ion trap mass spectrometry (LC–Ion Trap-MS^n). In addition, a validated method for the quantification of 4F-MPH was developed using liquid chromatography–tandem mass spectrometry (LC–MS-MS), with a linear range of 0.01–0.500 mg/L and acceptable validation criteria including precision, bias, carry-over, linearity and endogenous/exogenous interferences. In addition to the detection of 4F-MPH, 3-methoxy-PCP, amphetamine, methamphetamine, 6-monoacetylmorphine, morphine, codeine and tetrahydrocannabinol were also identified in the decedent. A single source of blood was collected (femoral vein) and quantified in all blood tubes used for collection, with concentrations varying from 0.012 to 0.05 mg/L. Additional specimens available for screening included gastric contents and urine. An additional peak having the same targeted ions and transitions as 4F-MPH was identified in both the LC–Ion Trap-MS^n screening procedure and the LC–MS-MS quantitative procedure. This peak suggests the presence of a structural isomer, possibly (±)-*erythro*-4-fluoromethylphenidate, which cannot be confirmed due to there being no available certified reference material. This case report presents the first time that 4F-MPH was detected in a decedent, as well as the first time 4F-MPH has been listed in the official cause of death of a decedent in Florida.

Key words: 4-fluoromethylphenidate, LC–MS-MS, post-mortem toxicology, NPS

Introduction

Since the emergence of synthetic cathinones in 2012, post-mortem toxicological casework in Miami-Dade County, Florida has been rampant with the presence of novel psychoactive substances (NPSs). These compounds, including synthetic cathinones, synthetic cannabinoids, designer hallucinogens and synthetic opioids, consistently evolve to evade restrictions from both foreign and domestic drug enforcement agencies. As the number of NPS increase, so does the

demand for accurate and reliable identifications of these compounds in complex biological matrices. Recently, a new class of NPS similar in structure to methylphenidate (MPH) was identified in a case received from Collier County, Florida. The substance identified and confirmed by the laboratory was (±)-*threo*-4-fluoromethylphenidate (4F-MPH).

MPH is a schedule IIN controlled substance (1) that acts as a central nervous system (CNS) stimulant. It was first synthesized in 1944 (2) and structurally resembles both benzylpiperidine and phenethylamine—two compounds that are commonly used as structural backbones for the synthesis of stimulant-like substances (3). MPH is available by prescription only for the treatment of attention deficit hyperactivity disorder (1) and is currently sold in the USA under the trade names, Concerta® and Ritalin®. The primary mechanism of action of MPH is to inhibit the re-uptake of dopamine and norepinephrine in the CNS (4). MPH contains two chiral centers (5), with the potential for four separate isomeric compounds.

MPH analogs have been reported in Europe in the past several years (6), with the most popular analog, ethylphenidate, contributing to fatal intoxications (7–9). Other analogs not associated with reported fatalities include 3,4-dichloromethylphenidate, propylphenidate and methylnapthidate (HDMP-28), which are controlled to various degrees throughout Europe (10). Like most NPS, these compounds can be acquired online, and while the literature is scarce in reference to human exposure, there are several self-reporting users that describe MPH analogs as having a higher potential for both stimulatory and euphoric effects (11). While the prevalence of these compounds is noted in Europe, evidence and reporting of MPH analogs is almost non-existent in the USA. Currently, no MPH analogs are officially listed as scheduled substances in the USA, except for in the state of Alabama where 4-F-MPH is a Schedule I controlled substance (12).

4F-MPH is a halogenated analog of MPH that first appeared in Europe in 2015 (6). Like MPH (5), 4F-MPH has four separate isomeric compounds; two diastereomers, (±)-*threo*-4F-MPH and (±)-*erythro*-4F-MPH, which in turn each contain two enantiomers, (+)-*threo*-4F-MPH, (+)-*erythro*-4F-MPH, (-)-*threo*-4F-MPH and (-)-*erythro*-4F-MPH. Figure 1 a pharmacological study was conducted on 4F-MPH, identifying (+)-*threo*-4F-MPH as the most active stereoisomer, which is also the case for prescription MPH, (+)-*threo*-MPH (13). In addition, (±)-*threo*-4F-MPH was determined to be 2.5 and 3 times more potent than MPH at the norepinephrine and dopamine transporters, respectively (13). Also following suit with MPH, the (±)-*erythro*- stereoisomer was deemed inactive, yet can be found mixed with the (±)-*threo*- stereoisomer in both prescription preparations and in illicit materials (13). User reports for 4F-MPH tend to focus on the 'removal' of traditional side effects that are common with other MPH analogs, including anxiety, paranoia and re-dosing (14). However, some reports of dosing with this drug contradict those findings, focusing on the high potency of the compound. With that high potency comes high potential for anxiogenic effects. One user reported quickly losing the euphoric feeling of the drug, and feelings of non-stop anxiety ridden stimulation. Eventually, the user dosed themselves with etizolam, a common synthetic benzodiazepine, to come down from the high (15). Until recently, no reports regarding measured levels of 4F-MPH in humans have been reported. A recent case report highlighted a clinical manifestation of 4F-MPH in Italy with measured concentrations in both blood and urine specimens (16). To date, no known reports of post-mortem detection of 4F-MPH have been published, nor has any literature on 4F-MPH detection been reported in cases occurring from the USA.

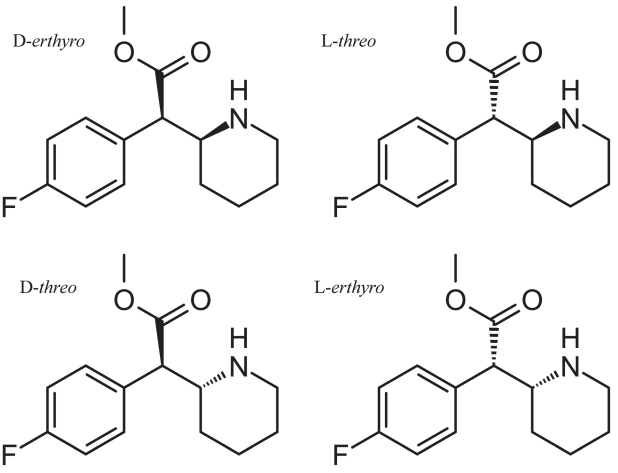

Figure 1. Chemical structures of enantiomers and diastereomers of 4-fluoromethylphenidate.

The Miami-Dade County Medical Examiner (MDME) Toxicology Laboratory first encountered 4F-MPH in 2016 in the form of drug paraphernalia. The case containing the drug paraphernalia was a delayed death due to a multiple drug toxicity, and among the several exhibits of paraphernalia that were collected at the scene, an orange round pill with an 'A' stamped onto one side was analyzed in the laboratory and positive for 4F-MPH (17). To confirm the presence of this new NPS, a reference standard was ordered and added to all in-house screening libraries. While 4F-MPH was confirmed in the paraphernalia, it was never detected in any biological specimens in the decedent. The following case study highlights the detection of 4F-MPH in a multiple drug toxicity case, as well as the development and validation of a quantitative procedure to establish a known concentration in select post-mortem biological specimens. To our knowledge, this report will be the first time 4F-MPH is reported in a post-mortem specimen as well as implicated in the official cause of death. In addition, this case report will also be the first time 4F-MPH concentrations are detected in a human in the USA.

Case History

A 25-year-old white male was last seen by his mother acting paranoid and claiming to hear voices and that people were in his residence. The decedent's mother told him to go to bed because he had to wake up early in the morning for work, and the decedent complied. The next morning, the decedent was found unresponsive in his bed and was pronounced at the scene. The decedent was a known user of methamphetamine; however, no drug paraphernalia was reported to have been found at the scene. The autopsy and terminal event occurred in Collier County, Florida, and all biological specimens collected at autopsy were sent to the MDME Toxicology Laboratory for routine testing. At autopsy, the forensic pathologist noted marked lung congestion indicative of pulmonary edema, a distended bladder and a swollen brain.

Experimental

Post-mortem sample collection

At autopsy, femoral vein blood (four vials totaling ~50 mL), urine (40 mL), bile, ocular fluid and gastric contents (273 g) were collected and submitted for toxicological testing.

Table I. Analyte RTs and MRM Transitions

Target analyte	RT (min)	Precursor ion (*m/z*)	Product ion[a] (*m/z*)	Collision energy (V)	Pause time (msec)	Dwell time (msec)	Qualifier ion ratio limit
Methylphenidate-D_4	1.79	238.10	<u>88.20</u>	−45.0	3.0	25.0	
			56.10	−51.0	3.0	25.0	±20%
4-Fluoromethylphenidate	1.84	252.20	<u>84.20</u>	−48.0	3.0	25.0	
			56.10	−49.0	3.0	25.0	±20%
			109.20	−46.0	3.0	40.0	±30%

[a]Underlined product ions were used for quantification.

Initial toxicological analysis

Routine testing was conducted on post-mortem femoral blood and urine specimens. The femoral blood was initially analyzed for the presence of volatile compounds, including ethanol, methanol, isopropanol and acetone, utilizing dual-column headspace-gas chromatography (HS–GC) coupled to a flame ionization detector (FID). The post-mortem urine specimen was screened by enzyme multiplied immunoassay technique (EMIT) for the presence of amphetamines, benzoylecgonine, opiates, oxycodone, cannabinoids and benzodiazepines. A comprehensive drug screen utilizing basic and acid/neutral drug extracts was also conducted on the femoral blood using a GC coupled to a nitrogen phosphorus detector (NPD) and a mass spectrometer (MS). This provided both chromatographic separation, as well as full-scan spectral data that are matched to an in-house library and, select downloaded library databases. Any drugs that screened positive on either the EMIT or the blood drug screen were confirmed using various targeted quantitative procedures, in addition to a targeted liquid chromatography-ion trap mass spectrometry (LC–Ion Trap-MS^n) screening/confirmation method, which provided chromatographic separation, full-scan data and targeted MS^2 and MS^3 spectral detail that is matched to an in-house library (18).

Quantitation of 4F-MPH

Chemicals, reagents and standards

The (±)-*threo*-4-fluoromethylphenidate (*threo*-4F-MPH) calibrator and control reference standards were purchased from Cayman Chemical (Ann Arbor, MI, USA). The (±)-*threo*-Methylphenidate-D_4 deuterated internal standard (ISTD) certified reference standard was purchased from Cerilliant Corporation (Round Rock, TX, USA). Acetonitrile, water, sodium hydroxide, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, methanol, hexane, ethyl acetate, ammonium hydroxide, hydrochloric acid, glacial acetic acid and formic acid were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Dichloromethane and isopropanol were purchased from Honeywell (Morris Plains, NJ, USA). Deionized (DI) water was produced in-house using carbon and ion-exchange resin tanks provided by Evoqua Water Technologies (Pittsburgh, PA, USA). All solvents and reagents used in the extraction were Certified ACS Grade or higher. Mobile phase solvents and additives were LC/MS Grade. Defibrinated sheep blood was purchased from Hemostat Laboratories (Dixon, CA, USA) and confirmed negative for the target analyte by in-house analysis prior to use.

Preparation of working stock solutions

Calibrator working stock solutions were prepared in methanol by serial dilution to represent a concentration range of 0.05–5 mg/L. Two positive control working stock solutions were prepared in methanol at low and high concentrations, 0.2 and 4 mg/L, respectively. The ISTD working stock solution was prepared in methanol at 0.8 mg/L. All working stock solutions were stored in amber glass vials at 4°C.

Preparation of calibrators and positive controls

Calibrator and positive control samples were prepared by adding 50 µL of the individual calibrator and positive control working stock solutions into 500 µL of defibrinated sheep blood and then vortexed.

Sample preparation and extraction

Blood specimens were analyzed utilizing matrix-matched calibrators and controls. In a silanized glass culture tube, 500 µL of blood were buffered with 4 mL of 0.1 M, pH 6 sodium phosphate, and 50 µL of the ISTD working stock solution was added. All samples were vortexed, allowed to sit for 15 min and then centrifuged for 10 min at 2,300 × *g*. Positive pressure solid phase extraction was performed using United Chemical Technologies (Bristol, PA, USA) Clean Screen® DAU mixed mode (reverse-phase and ion-exchange) columns. The columns were conditioned with 3 mL of methanol, 3 mL of DI water and 1 mL of 0.1 M, pH 6 sodium phosphate buffer. Each supernatant was slowly added to the columns, which were subsequently rinsed with 3 mL of DI water and 1 mL of 1 M acetic acid. The columns were dried for 5 min at 100 psi. Columns were further rinsed with 2 mL of hexane, 3 mL of hexane:ethyl acetate (50:50, *v/v*) and 3 mL of methanol and were dried for an additional 3 min at 100 psi. Analytes were eluted with the addition of 3 mL of dichloromethane:isopropanol:ammonium hydroxide (78:20:2, *v/v/v*) and were evaporated to ∼1 mL in a water bath at 40°C under a nitrogen stream at 5 psi. After the addition of 100 µL of 1% methanolic HCl, the samples were vortexed and evaporated to dryness. The samples were reconstituted with 500 µL of 0.1% formic acid in water, vortexed, transferred to amber autosampler vials with glass conical inserts and capped for analysis by ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS-MS).

Instrumentation and chromatographic conditions

A Shimadzu (Columbia, MD, USA) Nexera X2 UHPLC system coupled to a model 8060 MS-MS was used for quantitative analysis. The refrigerated autosampler was maintained at 15°C. The injection volume was 0.5 µL. Chromatographic separation was achieved using a Restek Corporation (Bellefonte, PA, USA) Raptor™ ARC-C18 column (50 mm × 2.1 mm × 2.7 µm) with a Restek Raptor™ ARC-C18 guard column (5 mm × 2.1 mm × 2.7 µm) maintained at 50°C in a column oven. The mobile phase consisted of 0.1% formic acid in water (A) and methanol (B) delivered at a constant flow rate of 0.75 mL/min. A gradient elution was used with the following

Table II. Quantitative Values of Analytes in Case Specimens

Analyte	Gray top #1	Gray top #2	Red top	Purple top	Gastric
6-MAM	—	1.835 ng/mL	—	—	—
Codeine	—	0.022 mg/L	—	—	—
Morphine	—	0.268 mg/L	—	—	—
Amphetamine	0.135 mg/L	—	—	—	—
Methamphetamine	0.850 mg/L	—	—	—	—
threo-4F-MPH	0.017 mg/L	0.019 mg/L	0.012 mg/L	0.049 mg/L	0.795 mg total

pump program: 10% B maintained for 0.50 min and increased to 55% B over 2.00 min, then increased to 95% B over 0.25 min and maintained for 0.50 min, then decreased to 10% over 0.10 min and maintained for 0.90 min for column re-equilibration. The total run time was 4.25 min. Mass spectral data were acquired using positive electrospray ionization (ESI) in multiple reaction monitoring (MRM) mode. ESI source and MS settings are as follows: nebulizing gas flow (N_2) = 3 L/min, heating gas flow (N_2) = 10 L/min, drying gas flow (N_2) = 10 L/min, interface temperature = 300°C, desolvation line temperature = 250°C, heat block temperature = 400°C and CID gas pressure (Ar) = 270 kPa. Target analyte retention times (RTs) and MRM transitions are shown in Table I.

Minimum identification criteria included a Gaussian chromatographic peak shape, elution at a known RT with a ±5% deviation allowance and the presence of two qualifier ions with acceptable ratios (Table I).

Method Validation

A limited fit-for-purpose method validation was performed in accordance with laboratory standard operating procedures, which included the following validation criteria: calibration model, limit of detection (LOD), limit of quantitation (LOQ), bias, intra- and inter-day precision, carry-over and selectivity. Spiked recovery of the case specimen was performed to counteract possible matrix effects or ionization suppression or enhancement.

Five calibration curves, each consisting of seven non-zero concentrations spanning the desired calibration range (0.005–0.5 mg/L) were extracted in single over five separate days and analyzed. Linear regression was performed on the calibration curves and the accuracy of each calculated calibration point was obtained. The working calibration range was determined to be 0.01–0.5 mg/L, and a linear fit with a $1/x^2$ weight was chosen. Each calibration curve had a coefficient of determination (r^2) of ≥0.990. The LOD and LOQ were 0.005 mg/L and 0.01 mg/L, respectively. Three sets of low and high positive controls were extracted with a calibration curve over five separate days (n = 15) and analyzed to assess bias and intra- and inter-day precision. The method demonstrated acceptable bias within ±6% and intra- and inter-day precision ≤5% at each control concentration. The absence of carry-over was determined by pentaplicate analysis. Blank blood was extracted and analyzed immediately following an extracted sample prepared at twice the concentration of the highest calibration standard. There was no observable carry-over up to 1 mg/L. Solvents are analyzed between all sets of case samples and reviewed if carry-over is suspected. The selectivity of the method was determined by conducting an interference study using 4 drug mixes, each containing 14 drugs commonly encountered at the MDME, added into negative blood and into blood fortified with the low control working stock solution and ISTD. The drug mixes included amphetamines, non-fentanyl opioid analgesics, cocaine and its primary metabolites, benzodiazepines, antidepressants, antipsychotics, barbiturates, over-the-counter medications and drugs generally administered in an emergency setting. All analytes were analyzed at 1 mg/L. No interferences from 56 commonly identified drugs were observed for any of the MRM transitions for *threo*-4F-MPH or its ISTD.

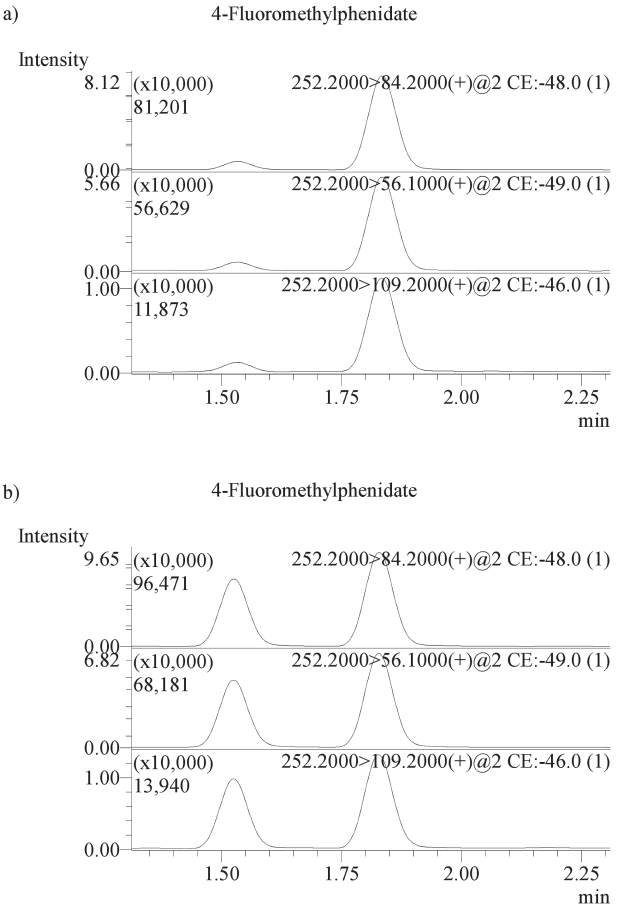

Figure 2. Comparison of (a) CAL L1 (0.010 mg/L) and (b) case specimen on LC–MS-MS.

Results and Discussion

Routine toxicological findings

The femoral blood screened negative by HS–GC–FID for volatile compounds, while the urine screened positive by immunoassay for amphetamines, cannabinoids and opiates. Confirmation of cannabi-

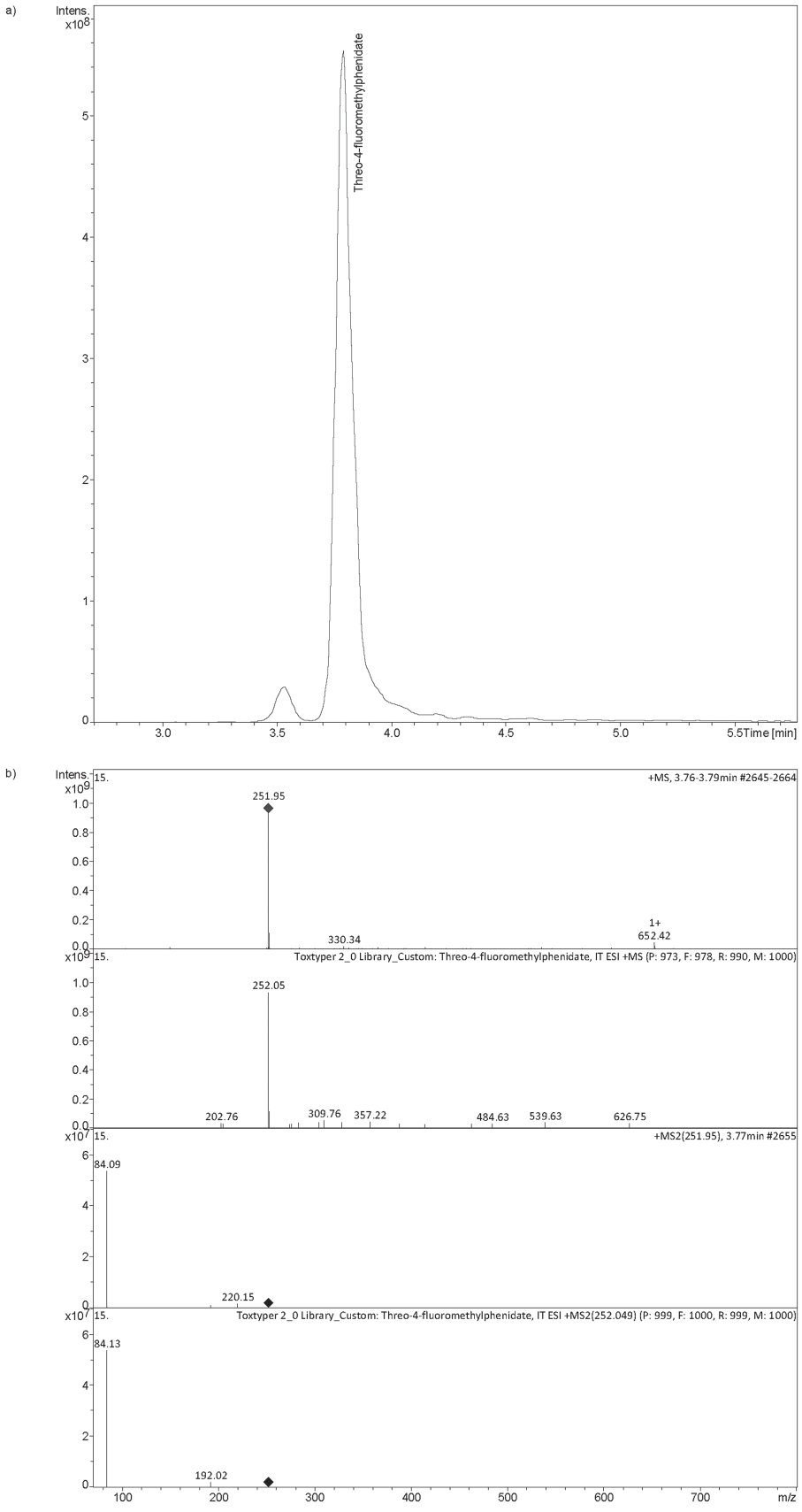

Figure 3. (a) EIC of molecular ion 252 m/z and (b) MS and MS^2 spectra for 4-fluoromethylphenidate on LC–Ion Trap-MS^n in the case specimen.

noids was conducted on GC-MS, detecting 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol and -Δ^9-tetrahydrocannabinol. Compounds detected in the blood drug screen using GC–NPD–MS included methamphetamine, codeine, morphine, papaverine, *threo*-4F-MPH and diphenhydramine. Gastric contents and urine were also screened by GC–NPD–MS, with the identification of methamphetamine, amphetamine, 6-monoacetylmorphine (6-MAM), codeine, acetylcodeine, naproxen, diphenhydramine and *threo*-4F-MPH in the gastric contents and identification of methamphetamine, amphetamine, morphine, 6-MAM, codeine, norcodeine, naproxen, diphenhydramine and 3-methoxyphencyclidine (3-MeO-PCP) in the urine. Based on the results from the GC–NPD–MS screen, additional testing was conducted to confirm designer stimulants and opiate-related compounds using LC–Ion Trap-MS^n. The presence of *threo*-4F-MPH, methamphetamine, amphetamine, 3-MeO-PCP, 6-MAM, morphine and codeine were confirmed in the femoral blood specimen. Quantitative procedures were conducted on the femoral blood contained in the grey top vials (sodium fluoride/potassium oxylate) utilizing UHPLC–MS-MS for amphetamine, methamphetamine, morphine, codeine and 6-MAM. All quantitative results can be found in Table II.

Threo-4F-MPH toxicological findings

The quantification of *threo*-4F-MPH was conducted on all available blood specimens as well as the gastric contents. Three out of the four blood vials, two gray top tubes and one red top tube, which were submitted for testing contained the preservatives sodium fluoride and potassium oxalate, while the fourth blood vial, a purple top tube, contained ethylenediaminetetraacetic acid (EDTA). Since femoral vein blood was the only source blood collected, differences in concentration among the blood vials was not expected. The average concentration of *threo*-4F-MPH in the three femoral blood samples that were preserved with sodium fluoride and potassium oxalate was 0.017 mg/L ($n = 6$), while the average blood concentration of the femoral blood sample preserved with EDTA was 0.049 mg/L ($n = 2$). This marked difference in concentration cannot be explained by the literature, especially since mean concentration of some stimulant drugs preserved in EDTA are noted to decrease over time versus being preserved in sodium fluoride and potassium oxalate (19). The gastric contents were quantified using method of standard addition and were initially diluted 1:9 with DI water before extraction. The same sample preparation procedure described above was also applied to this sample. The total drug content in the gastric was calculated to be 0.795 mg total.

All samples that were analyzed with the validated quantitative procedure, including the LC–Ion Trap-MS^n targeted screening procedure, contained an additional peak in the MRM window (Figure 2) and extracted ion chromatogram (EIC; Figure 3), respectively. This peak was fully resolved on both methods from the targeted *threo*-4F-MPH peak, with an average elution time of 0.3 min before the targeted compound. Both LC methods differ in not only their gradient, but also their mobile phase composition and run time. However, both methods are able to resolve the two diastereomers using C18 columns. As noted in both the recently published case report out of Europe (16) as well as the above-mentioned pharmacological study conducted by McLaughlin *et al*., the diastereomer, (±)-*erythro*-4F-MPH, is commonly found together with the (±)-*threo*-4F-MPH in seized drug material. As reported, the (±)-*erythro*-4F-MPH isomer is pharmacologically inactive, as are other (±)-*erythro*- isomers of MPH and MPH analogs. In addition, during the validation process, a peak at the same RT, but in a small presumed quantity, was detected in the reference material of (±)-*threo*-4F-MPH and is present in all quality control samples prepared for the method. A comparison between the reference material and the case sample MRM windows is presented in Figure 2. Based on the literature, it is likely that this additional peak is the (±)-*erythro*-4F-MPH diastereomer of (±)-*threo*-4F-MPH; however, a definitive identification could not be made due to the lack of available reference materials for (±)-*erythro*-4F-MPH. Thus, quantitative values were strictly from the targeted, known (±)-*threo*-4F-MPH. The only reported concentration of *threo*-4F-MPH in a human is a clinical manifestation at a concentration of 32 ng/mL in blood. Due to the detection of other analytes in the decedent with known toxic ranges and potencies, the contribution of the measured quantity of *threo*-4F-MPH is unknown, and no definitive conclusions can be drawn, especially in a post-mortem presentation.

The presence of 3-MeO-PCP in the screening results is only the third confirmed case seen at the MDME Toxicology Laboratory. 3-MeO-PCP is also considered a newly identified NPS in South Florida; however, both clinical and post-mortem manifestations and toxicities have been reported in the literature (20). It is likely that the observed behavior of the decedent in this case, specifically the overt paranoia and audio/visual hallucinations, can be attributed to the combination of methamphetamine, 3-MeO-PCP and *threo*-4F-MPH that the individual consumed. Whether this was an intentional drug mixture are details that the post-mortem toxicology community struggles with identifying.

To our knowledge, this is the first reported case of a fatality involving the presence of *threo*-4F-MPH. The final ruling from the forensic pathologist on the manner and cause of death was an accident due to a multiple drug toxicity of methamphetamine, heroin and *threo*-4F-MPH. This ruling also marks the first time 4F-MPH has been listed in the cause of death in an individual in the state of Florida, as well as in the USA.

Conclusion

This case report describes the sudden death of a 25-year-old male who consumed multiple drugs including 4F-MPH. Based on the toxicology and medical examiner's findings, the decedent likely succumbed to an acute overdose of heroin; however, the effects of methamphetamine, 3-MeO-PCP, codeine and 4F-MPH cannot be overlooked as contributing to death. The identification of 4F-MPH and its inclusion in the cause of death illustrates the necessity for an expanded scope of testing that includes the ability to detect new outlier analogs that have surfaced in death investigations in recent years. The majority of fatal cases investigated by the MDME that involve NPS are poly-drug intoxications, where one or more of the drugs present in the decedent contribute solely to the cause of death; however, in many other cases the multiple drugs present in combination contributed to the death. Consequently, understanding the toxicological significance of a single new NPS is difficult at best; however, the contributions of these NPS compounds cannot be ignored.

The flood of newly synthesized drugs over the past 6 years has covered a broad range of substances that have included stimulants, depressants and hallucinogens. Many of the most common substances have stemmed from the structural foundations of cathinones, cannabinoids, benzodiazepines and fentanyl. However, more fringe substances have emerged that are not common such as 4F-MPH. As a result, it is likely that additional NPS will become available furthering the need for laboratories to increase their scope of testing.

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