Published in final edited form as:

Drug Test Anal. 2017 April ; 9(4): 657–659. doi:10.1002/dta.1988.

Acute Dilated Cardiomyopathy and Myocardial Injury after Combined 4-Fluoroamphetamine and Modafinil Ingestion

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Keywords

4-Fluoroamphetamine; Modafinil; Cardiomyopathy; Myocardial

Introduction

Ring-substituted amphetamines are commonly used and abused for their entactogen and hallucinogenic effects. Currently, these drugs are halogen substituted amphetamines. With the substitution of a fluorine molecule on the aromatic ring, fluoroamphetamine becomes more lipophilic than amphetamine and thus can more easily cross the blood-brain barrier. 4-Fluoroamphetamine is the most commonly detected halogen ring-substituted amphetamine, and its street name is “Molly Mosquito”. It has similar entactogen effects as MDMA (Molly)^[1] and is currently not scheduled by the US Drug Enforcement Agency.

An association between use of amphetamines or substituted derivatives and acute cardiomyopathy has previously been described.^[2–4] Two recent reviews of toxicity from pharmaceuticals used to treat attention-deficit hyperactivity disorder (ADHD) summarized the adverse effects but did not include acute cardiomyopathy as a sequelae.^[5, 6] Modafinil is a non-amphetamine drug that is not FDA approved for ADHD, but is occasionally prescribed to treat ADHD in both adults and children. Fluoroamphetamines are relatively novel substituted amphetamines with no medical use and are manufactured by clandestine laboratories. There are few data on fluoroamphetamines or modafinil causing acute cardiomyopathy other than single case reports.^[7, 8] We describe a patient who self-reported using 4-fluoroamphetamine, methylphenidate and modafinil recreationally who developed acute cardiomyopathy with cardiac injury. With innovative methods of laboratory

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

confirmation, the true exposure was revealed and likely etiology of the cardiomyopathy was delineated.

Case

An 18 year old female presented to the emergency department after drinking two capfuls of “Molly’s Mosquito cap,” which she believed was a “synthetic ecstasy.” She also reportedly insufflated 110 mg of methylphenidate and ingested 800 mg of modafinil. After the initial euphoric effects subsided, she experienced headache, nausea, vomiting, lightheadedness, and diaphoresis. On arrival to the ED, her only complaint was anxiety.

Initial vital signs were temperature 97.7 °F, heart rate range 110–124 bpm, and blood pressure 96/65 mmHg. Electrocardiogram revealed sinus tachycardia with QRS 82 ms, and QT/QTc 340/470 ms, with no evidence of ischemia or infarction. Initial laboratory results were sodium 141 mEq/L, potassium 4.4 mEq/L, chloride 104 mEq/L, bicarbonate 20 mEq/L, glucose 166 mg/dL, BUN 12 mg/dL, creatinine 0.7 mg/dL, AST 19 U/L, and ALT 34 U/L. Troponin I was initially 0.15 ng/mL and peaked four hours later at 5.4 ng/mL. Chest radiograph did not reveal acute abnormalities. An echocardiogram obtained on the day of admission approximately 36 hours after ingestion revealed an ejection fraction of 10–15% with mild left ventricular dilation and severe diffuse hypokinesis, normal right ventricular function, and mild mitral regurgitation. Computed tomography of the chest showed extensive ground glass opacities more prominent in the lower lobes and no evidence of pulmonary embolism. She continued to have some anxiety and tachycardia throughout her hospital course which was responsive to benzodiazepines. She did not develop clinically concerning hypotension. Initial drugs of abuse testing of the patient’s urine collected at time of admission by Syva enzyme immunoassay (Siemens Healthcare Diagnostics, Tarrytown, NY) yielded a positive result for amphetamines. A gas chromatography – mass spectrometry (GC/MS) qualitative full scan drug screen identified the presence of modafinil and an amphetamine derivative. Modafinil was later quantitated at 1.08 mg/L (1080 ng/mL), methylphenidate and ritalinic acid were both quantitated at < 0.10 mg/L (<100 ng/mL) in urine. Serum testing for ethanol, acetaminophen, and salicylates were negative, unfortunately this specimen was not forwarded to VCU Health for additional testing. Forty-eight hours after admission she had mild tachycardia to 111 bpm though her symptoms improved and she was discharged home.

Method for Detection and Quantification of 4-Fluoroamphetamine

Confirmation urine testing for specific amphetamines by GC/MS yielded a compound with a retention time similar to amphetamine; but had a mass spectrum with a molecular ion and tropylium fragmentation ions 18 amu higher than amphetamine. This indicated a ring fluorine substituted amphetamine derivative, not methylphenidate which has a much higher fragmentation ions. Unable to differentiate which of the three possible isomers were present in the patient’s urine; 2, 3, or 4-fluoroamphetamine, a GC/MS assay for the determination of fluorine ring substituted amphetamines in urine was developed, for the 2 & 4-fluoroamphetamines as the 3-fluoro isomer was not available at the time of analysis. Applying the assay, 4-fluoroamphetamine was identified in the patient’s urine at 37 mg/L

(37,000 ng/mL). In an intoxicated patient with life-threatening hyperpyrexia, a urine 4-fluoroamphetamine concentration of 285 mg/L (285,000 ng/mL) was observed.^[9]

Preparation of calibrators and quality control specimens

In-house certified drug-free urine provided the matrix for all prepared calibrators, and quality control (QC) specimens. Appropriate volumes of the working solution 2-fluoroamphetamine and 4-fluoroamphetamine (Cerilliant Corporation, Round Rock, TX) were added to pooled urine to obtain a seven point calibration curves with a range of 50 ng/mL to 5000 ng/mL, as the 3-fluoro isomer was not available at the time of analysis. Calibration curves were prepared in duplicate. The following quality control urine specimens for 2-fluoroamphetamine and 4-fluoroamphetamine were prepared and analyzed with the test specimen: limit of quantification quality control (LOQC), target concentration of 50 ng/mL; low control (LQC), target concentration of 150 ng/mL; medium control (MQC), target concentration of 300 ng/mL; high control (HQC), target concentration of 4000 ng/mL and a dilution control (DQC), target concentration of 10,000ng/mL. A drug free control (negative control) that did not contain 2-fluoroamphetamine or 4-fluoroamphetamine; but, did contain the 4-fluoroamphetamine-d₅ internal standard (ISTD), and a double negative control that did not contain 2-fluoroamphetamine, 4-fluoroamphetamine or ISTD were also run with each sample batch. All QC samples were stored at -20°C until analysis.

Specimen extraction

Fluoro-amphetamine derivatives were isolated from urine by liquid/liquid extraction with 4 mL n-butyl chloride as previously described for amphetamines and other phenylisopropylamines and their metabolites.^[10] Briefly, to 1mL of calibrators, control and test specimens (DQC and patient specimen were diluted times 10 for analysis with drug-free urine) 500 ng/mL ISTD was added followed by 100μL concentrated ammonium hydroxide and 2mL of n-butyl chloride. Samples were mixed by inversion for 2min and centrifuged for 5min at 3000rpm. The n-butyl chloride layer was transferred to a borosilicate test tube (75 × 12 ram) and 100uL of heptafluorobutyric anhydride (Sigma Aldrich, St. Louis, MO) was added and the tube was capped and heated at 70°C for 20 min. The n-butyl chloride was then evaporated under nitrogen at room temperature, and the residue was dissolved in 50 uL ethyl acetate. One microliter of the extract was injected into the GC/MS.

GCMS Analysis

2-fluoroamphetamine and 4-fluoroamphetamine was identified and quantified using a Shimadzu gas chromatograph-mass spectrometer QP-2010 system with EI ionization (Shimadzu Scientific Inc., Columbia, MD). Chromatographic separation was performed on an Rtx®-5 30m × 0.32mm, 0.5μm capillary column (Restek Bellefonte, PA) with an initial temperature of 70°C, hold time of 1min, 20°C/min ramp to 320°C and held for 0.5min. The injection port, ion source and interface temperatures were 250°C, 260°C, and 280°C, respectively. The total flow rate was 42.1mL/min with a column flow of 3.65mL/min. The following ions were monitored for: 2-fluoroamphetamine, *m/z* 240,136 and 109; 4-Fluoroamphetamine, *m/z* 240,136 and 109; and 4-Fluoroamphetamine-d₅, *m/z* 244 and 141. The retention times were: 2-fluoroamphetamine, 5.77 min; 4-fluoroamphetamine, 5.93 min

and 4-fluoroamphetamine-d₅, 5.91 min, Figure 1. Amphetamines, dimethoxyamphetamines, various other phenylisopropylamines and their metabolites did not interfere with the assay.

Each calibrator concentration of the duplicate curves was determined to be within $\pm 15\%$ of the expected value. The linear regression correlation coefficients (r^2) for the 2-fluoroamphetamine and 4-fluoroamphetamine calibration curves yielded means r^2 of 0.998 or better. The lower limit of quantification (LOQ) and the lower limit of detection (LOD) for 2-fluoroamphetamine and 4-fluoroamphetamine were administratively set at 50 ng/mL. The LOD of both drugs had a response at least ten times the signal to noise ratio of the response to drug free pooled urine. The accuracy/bias of the assay for 2-fluoroamphetamine and 4-fluoroamphetamine at the LOQ (50 ng/mL) ranged from 95% to 108%, at the LQC (150 ng/mL) from 94% to 104%, at the MQC (300 ng/mL) from 96% to 115%, at the HQC (4000 ng/mL) from 92% to 94% and the DQC (10,000 ng/mL) diluted 1/10 ranged from 93.8% to 94.2%. The intra-day precision for 2-fluoroamphetamine and 4-fluoroamphetamine for the five QC specimens ranged between 5 to 13% and 5 to 14%, respectively with coefficient of variation (CV) of $<15\%$. The percent absolute recovery of the assay at 500 ng/mL for 2-fluoroamphetamine and 4-fluoroamphetamine and ISTD were: $87\pm 1\%$; $108\pm 5\%$ and $102\pm 18\%$, respectively. Sample carryover was evaluated using two different procedures. For the carryover study, the high calibrator containing 5000 ng/mL of 2-fluoroamphetamine and 4-fluoroamphetamine was followed a drug-free urine injection. 2-fluoroamphetamine and 4-fluoroamphetamine were not detected in the injected drug-free urine sample. An additional procedure to evaluate possible 2-fluoroamphetamine or 4-fluoroamphetamine carryover during analysis was assessed by injecting an extracted HQC (4000 ng/mL) immediately followed by an injection of LQC (50 ng/mL). Lack of carryover was confirmed as 2-fluoroamphetamine and 4-fluoroamphetamine did not demonstrate a significant quantified bias.

Discussion

In the presented case, the exact timing of symptoms related to the cardiovascular effects, which could have been masked by the euphoric effects, is not known. Mild hypotension, persistent tachycardia, lightheadedness, diaphoresis, nausea and vomiting could be manifestations of both sympathomimetic effects and cardiomyopathy. Markedly depressed ejection fraction in this case did not require hemodynamic support with pharmaceuticals or mechanical assistance as described in single case reports of cardiomyopathy from modafinil or 4-fluoroamphetamine.^[7,8]

Modafinil is not a phenylethylamine. The mechanism of toxicity has not been clearly defined, but it appears to increase extracellular serotonin, norepinephrine and dopamine in the neocortex, as well as decreasing GABA and increases glutamate release.^[5] In animal models 4-fluoroamphetamine increases synaptic dopamine, norepinephrine, and serotonin by decreasing re-uptake and increasing release^[1]. The most potent action of 4-fluoroamphetamine is from increased synaptic dopamine and serotonin concentrations.^[1,11]

The use of both drugs has been associated with cardiomyopathy. The cardiomyopathies described with modafinil were related to takotsubo cardiomyopathy (sudden weakening of

the heart) and acute eosinophilic cardiomyopathy.^[5,12] Whereas, the cardiomyopathy described with 4-fluoroamphetamine was similar to dilated cardiomyopathies (enlarged heart which causes the heart to not pump blood efficiently) described with other ring-substituted amphetamines.^[2,3,7,13] However, Al-Abri reported that their patient's echocardiogram suggested reverse takotsubo cardiomyopathy.^[7] The cardiomyopathy in our patient is consistent with amphetamine induced cardiomyopathy, which correlates to the significantly higher 4-fluoroamphetamine concentration in the urine. The surge in catecholamines caused by the modafinil may have caused peripheral vasoconstriction that compensated for the poor cardiac output, and maintained perfusion.

In the presented case, the patient had a small increase in troponin I most likely related to demand ischemia. Troponin I is one of the most specific and sensitive laboratory markers of myocardial cell injury. Mildly elevated cardiac troponin has been reported in up to ~80% of cases with a diagnosis of Takotsubo cardiomyopathy.^[14] She did not receive a cardiac catheterization to determine if coronary artery occlusion had occurred. However, considering her age and an echocardiogram that revealed global hypokinesis of the left ventricle and normal right ventricle, the procedure was unnecessary.

Conclusion

This case demonstrates the importance of confirmatory testing of toxicant exposure. The actual contents of drugs of abuse are frequently unknown to the user and the clinician, as street names can be misleading. The history relayed ingestion of "synthetic ecstasy" and insufflation of methylphenidate, which were not detected on initial testing. As in this case, drug testing results were not clinically relevant and did not affect management. However, the accurate identification of usual intoxicants such as 4-fluoroamphetamine clarifies the history of drug use preventing false assumptions and adds significantly to the understanding of the effects of specific intoxicants.

Acknowledgments

The study was funded in part by the National Institute of Health grant P30DA033934 (JP, AP).

Funding

This work was supported in part by the National Institutes of Health grant P30DA033934.

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Figure 1.