PAPER

TOXICOLOGY

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Forty-Three Fatalities Involving the Synthetic Cannabinoid, 5-Fluoro-ADB: Forensic Pathology and Toxicology Implications

ABSTRACT: Forty-three fatalities involving the potent synthetic cannabinoid, 5-Fluoro-ADB, are summarized. For each case, a description of the terminal event, autopsy findings, cause of death, qualitative identification of 5-Fluoro-ADB and its ester hydrolysis metabolite, 5-Fluoro-ADB metabolite 7, in urine, and the quantitative values obtained in the blood specimens are outlined. Central blood concentrations ranged from 0.010 to 2.2 ng/mL for 5-Fluoro-ADB and 2.0 to 166 ng/mL for 5-Fluoro-ADB metabolite 7. Peripheral blood concentrations ranged from 0.010 to 0.77 ng/mL and 2.0 to 110 ng/mL for 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7, respectively. The majority of cases resulted in central to peripheral blood concentration ratios greater than 1 for 5-Fluoro-ADB (58%) and 5-Fluoro-ADB metabolite 7 (71%) suggesting that postmortem redistribution occurs to some extent. Combining the increased cardiac weight and/or gastric volume and toxicology data identifying 5-Fluoro-ADB, it is hypothesized that abuse of this substance may precipitate a dysrhythmia and cause sudden death.

KEYWORDS: forensic science, forensic pathology, forensic toxicology, synthetic cannabinoids, 5-Fluoro-ADB, postmortem redistribution

5-Fluoro-ADB, also known as 5-Fluoro MDMB-PINACA, shown in Fig. 1, is an indazole-based synthetic cannabinoid receptor agonist with the chemical name, methyl 2-{[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate. Its name is derived from its structural features: a fluoro moiety at position 5 of the pentyl chain (5F), a dimethyl methyl butanoate linked group (MDMB), a pentyl tail (P), and indazole core (INA) and a carboxamide linker (CA) (1). 5-Fluoro-ADB has become an increasingly popular drug of abuse as evidenced by the magnitude of confiscations reported in Europe and the increase in the number of acute intoxications and fatalities reported worldwide (2). Law enforcement reports suggest that 5-Fluoro-ADB is generally a white solid usually sold in powder form or as herbal material in sealed foil packages, marketed as "legal high" products. It has also been detected in liquids for use in e-cigarette vapes and on blotter paper for sublingual use (1,2). As with other reported synthetic cannabinoids, 5-Fluoro-ADB is typically inhaled via a pipe or rolled into a cigarette and smoked. (3). Although several synthetic cannabinoids are classified as scheduled controlled substances in a few countries, many are still available for purchase on internet web stores or in specialized smoke shops and gas stations. Their popularity is a direct result of their desirable effects in combination with their ease of accessibility and nondetectability in drug screens.

5-Fluoro-ADB is functionally similar to Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive constituent of cannabis. The psychological and behavioral effects of 5-Fluoro-ADB share similarities with cannabis, including relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalization, hallucinations, paranoia, dry mouth, bloodshot eyes, tachycardia, nausea, vomiting, and impaired motor function. Aggressive behavior, violence, and psychotic episodes have also been reported, suggesting that the effects are much more severe when compared to cannabis (1). Banister et al. supported these findings when evaluating the pharmacological properties of synthetic cannabinoids and concluded that 5-Fluoro-ADB is a highly potent agonist of human cannabinoid receptor type-1 (CB_1) and is more than 290 times the potency of Δ^9-THC (4). A postmortem study by Hasegawa et al. concluded that a sufficient concentration of 5-Fluoro-ADB enters the brain after inhalation causing symptoms similar to serotonin syndrome (agitation, seizure, muscle rigidity, elevated body temperature, and tachycardia) suggesting that 5-Fluoro-ADB affects brain endocannabinoid systems (5). An additional study by Asaoka et al. suggested that 5-Fluoro-ADB activates local CB_1 receptors and potentiates midbrain dopaminergic systems, but, in contrast to Hasegawa et al., concluded that 5-Fluoro-ADB does not have a direct effect on midbrain serotonergic systems (6).

Although the mechanism of toxicity remains unclear, intoxications, both acute and fatal, have been reported (5,7–10). Acute

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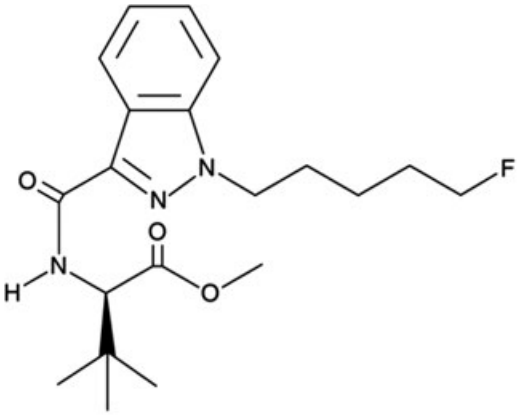

Molecular formula: $C_{20}H_{28}FN_3O_3$
Molecular mass: 377.46

5-Fluoro-ADB, or 5F-MDMB-PINACA

FIG. 1—*Molecular structure, formula, and mass of 5-Fluoro-ADB, or 5F-MDMB-PINACA.*

intoxications accompanied by psychomotor agitation, confusion, anxiety, psychosis, and tachycardia were reported in five patients subsequent to smoking a herbal mixture containing 5-Fluoro-ADB and MMB-2201 (7). Human performance effects were also reported in 24 impaired drivers involved in motor vehicle collisions. Approximately 50% of the drivers reported vomiting, loss of consciousness, and retrograde amnesia. All cases involving drivers under the influence of 5-Fluoro-ADB did not result in fatalities possibly due to loss of consciousness almost immediately postsmoking thus rendering the subjects unable to properly accelerate and operate the motor vehicle (8). Reidy et al. reported two human performance cases involving motor vehicle collisions with drivers in possession of drug paraphernalia. One driver was reportedly dazed, confused, and disoriented, while the other driver was complaining of psychological disturbances. Paraphernalia confiscated from both drivers tested positive for 5-Fluoro-ADB and MMB-FUBINACA (9).

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 28 deaths with confirmed exposure to 5-Fluoro-ADB were reported, with 20 deaths listing 5-Fluoro-ADB as the cause of death or contributing to the death. Postmortem blood concentrations from 13 cases of those cases ranged from <0.1 to 1.2 ng/mL (1). Six additional fatal intoxications involving 5-Fluoro-ADB have been reported in the literature from various forensic institutions in Japan. (5,10). Hasegawa et al. described a fatality in which the cause of death was asphyxia due to aspiration of stomach contents into the trachea. Multiple specimens were submitted for analysis of 5-Fluoro-ADB, including femoral vein blood, right heart blood, left heart blood, urine, stomach contents, and nine solid tissues. 5-Fluoro-ADB was not detected in the urine or blood specimens (limit of detection, 0.1 ng/mL); however, the range of 5-Fluoro-ADB in the solid tissues was 1.17–7.95 ng/g, with the highest concentration reported in the adipose tissue (5). Usui et al. were able to identify 5-Fluoro-ADB in the whole blood of four fatal cases at concentrations between 0.11 and 1.92 ng/mL. The autopsy findings, toxicology findings, and terminal event circumstances indicated that inhalation of 5-Fluoro-ADB might have contributed to the deaths, however, due to the lack of pharmacokinetic, pharmacodynamic, or toxicological data on 5-Fluoro-ADB, the cause of death in all cases was listed as acute circulatory failure after drug inhalation (10). Additional data, not well-studied with regard to blood concentrations of synthetic cannabinoids in death investigations, is postmortem redistribution (PMR). PMR is the process in which certain drugs can diffuse from the tissues into nearby blood compartments during the interval between death and blood sampling. For some drugs, there are significant concentration differences between blood samples from different sampling sites, therefore the importance of testing a known blood source as well as understanding whether a drug undergoes PMR is imperative. (11,12).

Kusanao et al. recognized the importance of identifying urinary metabolites when investigating a fatal intoxication of 5-Fluoro-ADB and diphenidine. The primary metabolic pathway of 5-Fluoro-ADB was determined to involve enzymatic hydrolysis of the ester group by carboxylesterase to 5-Fluoro-ADB metabolite 7, shown in Fig. 2 (13). The proposed primary pathway is consistent with previous reports on the metabolism of synthetic cannabimimetic agents using human liver microsomes (14). Nontargeted screening of urinary metabolites by high-performance liquid chromatography (HPLC) time-of-flight (TOF) mass spectrometry (MS) led to quantitation of 5-Fluoro-ADB in postmortem blood using a targeted HPLC-MS/MS procedure. The concentration of 5-Fluoro-ADB was quantified by standard addition to be 0.19 ± 0.04 ng/mL (13). Most recently, Reidy et al. reported a series of nine postmortem cases in which 5-Fluoro-ADB and/or 5-Fluoro-ADB metabolite 7 were identified in blood and/or urine using HPLC-MS/MS. The correlation between the observed behavior and the presence of 5-Fluoro-ADB was described (9). This case series is the first to report a large number of fatalities (43) involving the quantitation of 5-Fluoro-ADB and its metabolite in postmortem blood, with particular emphasis on the autopsy findings and an investigation into PMR.

Methods

5-Fluoro-ADB fatalities from two medical examiner districts in the State of Florida, District 11 and District 14, from September 2016 to December 2018, are described. District 11 cases were submitted for routine testing by the Miami-Dade Medical Examiner Department (MDME) Toxicology Laboratory. Routine toxicology testing at the MDME Toxicology Laboratory includes a volatile analysis (ethanol, acetone, isopropanol, and methanol) using headspace gas chromatography coupled to a flame ionization detector (HS-GC/FID), as well as an enzyme multiplied immunoassay technique (EMIT) for amphetamines, benzodiazepines, benzoylecgonine, cannabinoids, opiates, and oxycodone. If urine is not

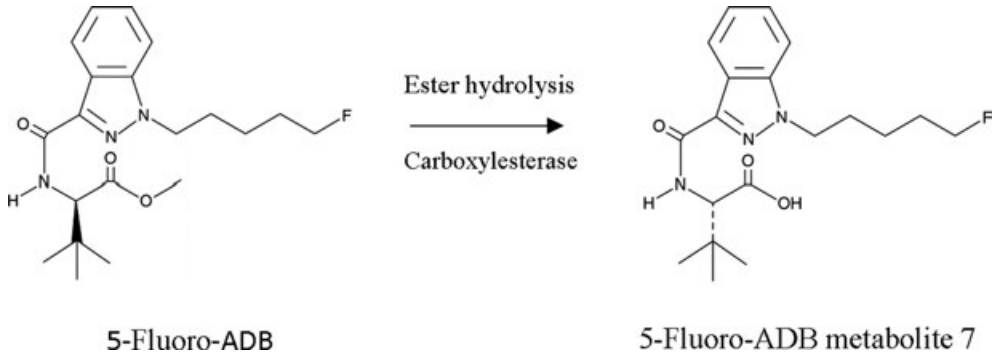

FIG. 2—*Proposed primary metabolic pathway of 5-Fluoro-ADB.*

available for testing, blood is submitted to enzyme-linked immunosorbent assay (ELISA) testing for benzodiazepines, benzoylecgonine, cannabinoids, opiates, and oxycodone. A comprehensive drug screen using solid-phase extraction followed by analysis using gas chromatography coupled to both a nitrogen phosphorous detector and mass spectrometer (GC-NPD/MS) is also performed for each case. Confirmatory testing is performed based on the results of the routine toxicology screen, and test requests specifically for synthetic cannabinoids are considered based on case history, evidence collected at the scene, and eye witness accounts of decedents smoking an unknown substance. District 14 medical examiner cases were all inmate fatalities with suspected synthetic cannabinoid use based on the medicolegal death investigation and were subsequently submitted to the MDME Toxicology Laboratory specifically for a synthetic cannabinoid screen. All cases where synthetic cannabinoid use was suspected received a targeted synthetic cannabinoid screen by HPLC-MS/MS at the MDME Toxicology Laboratory, with further confirmation and quantitation of 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7 performed by the University of Miami Toxicology Laboratory.

Seither et al. developed and validated an HPLC-MS/MS method for the quantitation of 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7 in postmortem blood (15). Briefly, Bond Elute Plexa PCX solid-phase extraction columns were used to isolate the target analytes from postmortem blood specimens. Extracts were submitted to an Agilent 1290 HPLC system coupled to an Agilent 6460 electrospray triple quadrupole mass spectrometer for analysis. Separation was achieved using an Agilent PFP Poroshell 120 (3 × 50 mm, 4 μm) analytical column with an aqueous mobile phase of 5 mM ammonium formate with 0.1% formic acid in LC/MS grade water, and an organic mobile phase of LC/MS grade acetonitrile with 0.1% formic acid. The linear range of the method is 0.01–10 ng/mL for 5-Fluoro-ADB and 2.0–500 ng/mL for 5-Fluoro-ADB metabolite 7, with a limit of detection of 0.01 ng/mL and 0.5 ng/mL, respectively. The method was validated based on the Scientific Working Group for Forensic Toxicology (SWGTOX) and United Nations Office on Drugs and Crime (UNODC) validation guidelines.

Results

Toxicology Results

Table 1 summarizes the details for each case, organized by date of death, including a description of the terminal event, autopsy findings, cause of death, the qualitative identification of 5-Fluoro-ADB, and/or 5-Fluoro-ADB metabolite 7 in urine, and the quantitative values obtained in the blood specimens. Urine was obtained at autopsy and submitted for testing from 28 cases; all 28 urine specimens were positive for 5-Fluoro-ADB metabolite 7, with 7 of those cases also testing positive for 5-Fluoro-ADB. One case (case 16) identified the presence of 5-Fluoro-ADB metabolite 7 in the urine specimen only, with no identification of 5-Fluoro-ADB or 5-Fluoro-ADB metabolite 7 in the corresponding blood specimens. Another case (case 1) also identified 5-Fluoro-ADB metabolite 7 in the urine specimen only, however, confirmation was not achieved on the blood specimens due to the unsuitability of the sample submitted.

When possible, 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7 were quantified in both central and peripheral blood. Central blood concentrations ranged from 0.01 to 2.2 ng/mL, with a mean of 0.34 ng/mL (n = 30) for 5-Fluoro-ADB and 2.0 to 166 ng/mL, with a mean of 41 ng/mL (n = 37) for 5-Fluoro-ADB metabolite 7. Peripheral blood concentrations ranged from 0.01 to 0.77 ng/mL, with a mean of 0.15 ng/mL (n = 21) and 2.0 to 110 ng/mL, with a mean of 21 ng/mL (n = 27) for 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7, respectively. See Table 2 for summary.

Postmortem Findings

Several observations were recorded at autopsy and are summarized in Table 1. Nonspecific findings, including pulmonary congestion and edema and aspirated gastric contents, were noted, as well as more specific findings such as lung weights, cardiac weights, and volume of gastric contents. The cardiac weights measured for the decedents were between 280 and 710 g, with average heart weights contingent on the height and weight of the person ((16)). Right and left lung weights varied between 270 and 1,460 g, with adult men right lungs averaging 180 to 250 g (normal right lung weights are typically larger than normal left lung weights). The volume of gastric contents collected at autopsy was notably large, with 78% of the cases exceeding 100 mL.

Discussion

Previous literature cited has limitations in the ability to identify 5-Fluoro-ADB in blood, which includes higher detection limits than required, the use of nondeuterated internal standards, the use of noncertified reference materials, and/or the lack of metabolite identification and quantification.

TABLE 1—*Summary of terminal event, autopsy findings, cause of death, and toxicological data for 43 medical examiner cases*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
1	51-year-old homeless black male; witnessed to drink beer and smoke "tobacco" which was synthetic marijuana; decedent began pacing the roadway and collapsed; death grip paraphernalia was found at the scene	5'5", 103 lbs Heart 280 g Lungs R-550 g L-450 g Stomach 250 mL Findings: pulmonary bullae, pulmonary edema, mild atherosclerosis of left anterior descending coronary artery, nephrosclerosis	Not Detected	Detected	Specimen not suitable		Specimen not suitable		Acute Combined Drug Toxicity (5-Fluoro-ADB, AM-2201, and Ethanol)
2	46-year-old white male; homeless; found unresponsive in alley behind a business	5′9″, 169 lbs Heart 380 g Lungs R-850 g L-880 g Stomach 400 mL Findings: pulmonary edema, cardiomegaly, mild coronary atherosclerosis, cerebral edema, nephrosclerosis	Not Detected	Detected	Not detected	43	0.01	11	Acute 5-Fluoro-ADB Toxicity
3	59-year-old black male inmate serving a 30 year sentence for 2nd degree murder found unresponsive in open bay dormitory	6′2″, 168 lbs Heart 380 g Lungs R-590 g L-470 g Stomach 50 mL Findings: atherosclerotic coronary artery disease, pulmonary congestion	Not Detected	Detected	< LOQ	33	Not detected	19	Acute 5-Fluoro-ADB and N-ethylpentylone Toxicity
4	44-year-old black male inmate found unresponsive on cell floor by prison staff; handrolled cigarette paraphernalia found at the scene	5′7″, 178 lbs Heart 390 g Lungs R-610 g L-720 g Stomach 100 mL Findings: pulmonary congestion, left ventricular hypertrophy	Not Detected	Detected	Not detected	16	Not detected	11	Acute Combined Drug Toxicity (N-ethylpentylone and 5-Fluoro-ADB)
5	29-year-old white male; found slumped over in bed by members of a group home where he was living	5′2″, 156 lbs Heart 280 g Lungs R-570 g L-650 g Stomach 150 mL Findings: pulmonary congestion	Detected	Detected	None available	None available	Not Detected	110	Probable Acute 5-Fluoro-ADB Toxicity
6	39-year-old black male; found unresponsive in park, slumped over a picnic table bench; witness indicates that decedent was with other persons using illicit substances	5′11″, 349 lbs *Heart 710 g* Lungs R-820 g L-770 g Stomach 120 mL Findings: cardiomegaly, pulmonary edema, hepatosteatosis, morbid obesity, status post colectomy (remote)	Detected	Detected	0.37	2.5	0.37	2.4	Multiple Drug Toxicity (Ethanol, Cocaine, and 5-Fluoro-ADB)
7	46-year-old white male; found lying on the ground in the alleyway behind a repair shop	5′7″, 213 lbs *Heart 530 g* Lungs R-500 g L-440 g Stomach 1,000 mL Findings: cardiomegaly, coronary artery atherosclerosis, calcified bicuspid aortic valve	Not detected	Detected	0.17	37	Not detected	26	Acute 5-Fluoro-ADB Toxicity

TABLE 1—*Continued.*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
8	62-year-old black male inmate became unresponsive after smoking "k2" (witnessed)	5′4″, 172 lbs Heart 380 g Lungs R-850 g L-660 g Stomach 100 mL Findings: pulmonary congestion	Not detected	Detected	Not detected	2.0	0.02	2.0	Acute 5-Fluoro-ADB Toxicity
9	50-year-old white male; habitual user of synthetic marijuana; found unresponsive by son who was smoking with him earlier	5′10″, 175 lbs Heart 410 g Lungs R-810 g L-720 g Stomach 550 mL Findings: severe atherosclerosis left anterior descending coronary artery, mild atherosclerosis left main and left circumflex coronary arteries and thoracoabdominal aorta cardiomegaly, nephrosclerosis	Detected	Detected	0.31	81	0.05	4.6	Acute 5-Fluoro-ADB Toxicity
10	37-year-old white male inmate found unresponsive in his cell during a routine check; 2 wicks and cups with brown substance found at the scene	5′5″, 170 lbs Heart 400 g Lungs R-850 g L-810 g Stomach 350 mL Findings: pulmonary congestion and edema	Not detected	Detected	0.01	64	0.03	34	Acute 5-Fluoro-ADB Toxicity
11	28-year-old black male inmate found unresponsive in cell; history of asthma; 2 wicks found at the scene	5′9″, 159 lbs Heart 300 g Lungs R-710 g L-600 g Stomach 150 mL Findings: globoid heart, mild cerebral edema	Not detected	Detected	Not detected	29	0.02	23	Acute 5-Fluoro-ADB Toxicity
12	48-year-old white male inmate found unresponsive by guard; history of seizures	5′9″, 212 lbs *Heart 480 g* Lungs R-1,000 g L-750 g Stomach 400 mL Findings: cardiomegaly, pulmonary congestion, cerebral edema	Detected	Detected	0.04	18	0.02	11	Acute 5-Fluoro-ADB Toxicity
13	56-year-old white male; last seen by a witness splashing in the water of a canal; appeared to be drowning; may have used synthetic cannabinoids	5′7″, 146 lbs Heart 400 g Lungs R-970 g L-730 g Stomach 250 mL Findings: heavy lungs, cardiomegaly, nephrosclerosis	Not detected	Detected	2.2	166	< LOQ	41	Acute 5-Fluoro-ADB Toxicity
14	62-year-old black male inmate decided to remain in cell during recreational time; found unresponsive; suffered from anxiety and depression; known to smoke tobacco and drink socially; not known to use illicit drugs	5′10′', 160 lbs Heart 330 g Lungs R-870 g L-380 g Stomach 20 mL Findings: pulmonary edema	Not detected	Detected	0.11	41	0.27	21	Acute 5-Fluoro-ADB Toxicity

TABLE 1—*Continued.*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
15	37-year-old white male found unresponsive in vehicle; several bags of white powder found at scene; suffered from depression	6′0″, 205 lbs *Heart 490 g* Lungs R-850 g L-790 g Stomach 10 mL Findings: cardiomegaly, pulmonary congestion, edema, and anthracosis	None available		0.15	73	0.08	15	Acute Poly-Drug Toxicity (Cocaine, Heroin, 5-Fluoro-ADB)
16	28-year-old white male discovered unresponsive on his knees by mother; known social cigarette smoker and heroin, cocaine, and benzodiazepine user; attended alcoholics anonymous meetings	5′10″, 220 lbs *Heart 530 g* Lungs R-1,190 g L-950 g Stomach – empty Findings: cardiomegaly, mild coronary atherosclerosis, focal myocardial pallor, pulmonary congestion and edema, hepatomegaly	Not detected	Detected	Not detected	Not detected	Not detected	Not detected	Poly-Drug Toxicity (Cocaine, Fentanyl, Cyclopropyl Fentanyl)
17	34-year-old white male inmate found unresponsive by prison guards; reportedly using narcotics; known to smoke cigarettes heavily and drink alcohol socially; also known to abuse benzodiazepines	5′8″, 197 lbs Heart 390 g Lungs R-680 g L-600 g Stomach 500 mL Findings: pulmonary congestion, cerebral edema	Not detected	Detected	0.11	31	0.19	41	Acute 5-Fluoro-ADB Toxicity
18	44-year-old black male inmate discovered unresponsive in his cell by prison guards; cellmates reported that he had been smoking “k2” prior to his death	5′11″, 194 lbs *Heart 480 g* Lungs R-530 g L-480 g Stomach 500 mL Findings: cardiomegaly, left ventricular hypertrophy, aspiration of stomach contents, Greenfield filter in-situ inferior vena cava	Not detected	Detected	0.01	21	0.12	14	Aspiration Associated with 5-Fluoro-ADB Toxicity, Part II: Cardiomegaly, hypertensive-type
19	49-year-old black male inmate found unresponsive in a bathroom stall regurgitation from the mouth; known to smoke cigarettes, drink alcohol, and use illegal drugs	5′10″, 216 lbs Heart 440 g Lungs R-780 g L-670 g Stomach 100 mL Findings: cardiomegaly, severe atherosclerosis of first diagonal branch left descending coronary artery, moderate aortic athersclerosis, mild nephrosclerosis	Not detected	Detected	0.66	10	0.56	10	Acute Combined Drug Toxicity (5-Fluoro-ADB, MMB-2201, and N-ethylpentylone)
20	50-year-old white male inmate found lying supine on the floor unresponsive; reported to have ingested unknown substance; was a known substance abuser	5′3′, 132 lbs Heart 350 g Lungs R-750 g L-570 g Stomach 250 mL Findings: cardiomegaly, cardiac dilatation mild to moderate coronary atherosclerosis, pulmonary congestion and edema, nephrosclerosis	Not detected	Detected	0.76	6.8	0.77	12	5-Fluoro-ADB Toxicity

TABLE 1—*Continued.*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
21	52-year-old male inmate found in prone position on his bunk; reported to have been smoking "k2" prior to death	5′9″, 159 lbs Heart 410 g Lungs R-810 g L-690 g Stomach 600 mL Findings: focal moderate right coronary atherosclerosis, right atrial dilation, pulmonary emphysema, status post appendectomy (remote)	None available		< LOQ	120	None available		5-Fluoro-ADB Toxicity
22	28-year-old male inmate found on the ground unresponsive with another person who was flailing around and speaking incoherently; transported to ER and pronounced; reportedly smoking "k2"	5′10″, 201 lbs Heart 440 g Lungs R-960 g L-810 g Stomach 450 mL Findings: mild cardiomegaly, bilateral pleural effusions, pulmonary edema and congestion, hepatic and renal congestion	None available		0.21	34	None available		5-Fluoro-ADB Toxicity
23	40-year-old male inmate went unresponsive at the prison; transported to ER and pronounced. Reported to have been smoking "k2" earlier.	6′3″, 256 lbs *Heart 520 g* Lungs R-880 g L-900 g Stomach 800 mL Findings: cardiomegaly, mild coronary atherosclerosis, pulmonary congestion and edema, hepatic and renal congestion, erythematous gastric mucosa	None available		0.05	38	None available		Synthetic Cannabinoid Toxicity (5-Fluoro-ADB and AB-CHMINACA)
24	56-year-old male inmate had been smoking "k2" 30 min prior with friends; friends walked outside and upon returning found decedent unresponsive on the bed	5′8″, 156 lbs Heart 330 g Lungs R-270 g L-280 g Stomach 90 mL Findings: mild atherosclerosis left anterior descending artery	None available		0.64	2.4	0.15	4.9	Acute 5-Fluoro-ADB Toxicity
25	48-year-old male inmate found unresponsive with leafy substances; transported to hospital and diagnosed with subarachnoid hemorrhage with some herniation; brain dead and coded multiple times before being pronounced	6′1″, 201 lbs *Heart 530 g* Lungs R-1,460 g L-1,520 g Stomach 350 mL Findings: cerebral edema, apical pulmonary emphysema, pulmonary edema and congestion, hepatic congestion	Detected	Detected	None available	None available	AM BLOOD: 0.12	AM BLOOD: 27	5-Fluoro-ADB Toxicity
26	68-year-old male inmate along with a group of prisoners smoking "k2" all passed out; noted to be shaking and then went unresponsive	6′0″, 162 lbs Heart 380 g Lungs R-1,280 L-860 g Stomach 100 mL Findings: moderate coronary and aortic atherosclerosis, apical pulmonary emphysema, pulmonary edema and congestion, hepatic and renal congestion	Not Detected	Detected	< LOQ	28	None available		5-Fluoro-ADB Toxicity

TABLE 1—*Continued.*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
27	20-year-old male inmate found on bed with vomit; expected synthetic cannabinoids; observed on video shaking; witnesses stated he smoked "k2"	5′5″, 153 lbs Heart 330 g Lungs R-690 g L-590 g Stomach 200 mL Findings: pulmonary edema and congestion	Detected	Detected	1.9	39	0.09	14	5-Fluoro-ADB Toxicity
28	24-year-old male inmate found unresponsive; reported to have smoked synthetic cannabinoids	5′11″, 180 lbs Heart 400 g Lungs R-780 L-700 g Stomach 1,500 mL Findings: mild nephrosclerosis, pulmonary edema and congestion, aspirated gastric contents	Not detected	Detected	< LOQ	24	None available		5-Fluoro-ADB Toxicity
29	27-year-old male inmate traveling on bus, went unresponsive; transported to hospital and was pronounced	5′5″, 158 lbs Heart 350 g Lungs R-560 g L-650 g Stomach 110 mL Findings: pulmonary, hepatic, and renal congestion, aspirated gastric contents, cholelithiasis hepatic fibrosis	None available		0.08	37	None available		Synthetic Cannabinoid Toxicity (5-Fluoro-ADB)
30	53-year-old male inmate on camera going unresponsive others admitted to smoking "k2" with the decedent; history of tuberculosis and hypertension	5′6″, 214 lbs *Heart 580 g* Lungs R-900 L-830 Stomach 1,600 mL Findings: hypertensive cardiomegaly, mild to moderate coronary atherosclerosis, aspirated gastric contents, nephrosclerosis, cortical renal scars, pulmonary and hepatic congestion	None available		0.50	46	None available		Synthetic Cannabinoid Toxicity (5-Fluoro-ADB)
31	34-year-old male inmate seen 5 min prior up walking around, found unresponsive in bed with vomitus	5′9″, 166 lbs Heart 360 g Lungs R-790 L-710 g Stomach 400 mL Findings: mild coronary atherosclerosis, aspirated gastric contents, pulmonary edema and congestion, hepatic and renal congestion, mild cerebral edema	None available		0.20	78	None available		5-Fluoro-ADB Toxicity
32	54-year-old male inmate found unresponsive in bed; witnessed to be smoking substance earlier	5′6″, 181 lbs *Heart 330 g* Lungs R-650 g L-600 g Stomach 200 mL Findings: moderate to severe coronary atherosclerosis, apical pulmonary emphysema, pulmonary edema and congestion with anthracosis, hepatosteatosis, renal congestion	None available		0.18	128	None available		5-Fluoro-ADB Toxicity

TABLE 1—*Continued.*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
33	46-year-old male inmate found unresponsive; transported to the hospital; witnessed to be smoking "a substance"	5′8″, 179 lbs Heart 420 g Lungs R-1,090 g L-1,120 g Stomach 500 mL Findings: pulmonary edema and congestion, aspirated gastric contents, cholelithiasis	None available		0.07	41	None available		5-Fluoro-ADB Toxicity
34	54-year-old male inmate found unresponsive with vomit; smoked "k2" an hour earlier; transported to hospital and pronounced	5′8″, 222 lbs *Heart 990 g* Lungs R-1,230 g L-770 g Stomach 500 mL Findings: left basal ganglia left hemorrhagic stroke, remote right frontal infarct, severe cerebrovascular atherosclerosis, moderate coronary atherosclerosis, cardiomegaly, pulmonary edema and congestion, nephrolithiasis, prostolithiasis	None available		0.01	< LOQ	None available		5-Fluoro-ADB Toxicity
35	52-year-old male inmate on video smoking synthetic marijuana; goes unresponsive	5′8″, 184 lbs *Heart 470 g* Lungs R-880 g L-840 g Stomach 300 mL Findings: apical pulmonary emphysema, pulmonary, hepatic and renal congestion, mild nephroslcerosis, coronary, aortic and cerebral atherosclerosis, mild hypertensive cardiomegaly	None available		0.03	12	None available		ADB-FUBINACA and 5-Fluoro-ADB Toxicity; Contributing: Hypertensive and Atherosclerotic Heart Disease
36	38-year-old male inmate suspected of "k2" use	6′1″, 186 lbs Heart 380 g Lungs R-1,350 g L-1,240 g Stomach 125 mL Findings: pulmonary edema, pulmonary, hepatic and renal congestion	None available		0.02	7	None available		5-Fluoro-ADB Toxicity
37	54-year-old male inmate witnessed to roll something up and smoke it, starting having altered mental status; became violent, physically restrained, pepper sprayed, taken to shower to wash off, went unresponsive in chair	5′6″, 174 lbs *Heart 510 g* Lungs R-490 L-430 g Stomach 10 mL Findings: bullous emphysema and pulmonary congestion, cardiomegaly, renal congestion, thickening of mitral valve, liver congested and mottled parenchyma	None available		0.07	8	None available		Hemorrhagic Stroke Due To Hypertensive Cardiomegaly (990 g) Contributing: ADB-FUBINACA and 5-Fluoro-ADB Toxicity

TABLE 1—*Continued.*

Case	Terminal Event Case Information	Autopsy Findings	Urine		Central Blood (ng/mL)		Peripheral Blood (ng/mL)		Cause of Death
			5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	5-Fluoro-ADB	5-Fluoro-ADB Metab 7	
38	29-year-old male inmate found unresponsive; suspected to have been smoking "k2"; scene investigation revealed a small piece of paper with burns; witnesses deny knowledge.	5′7″, 184 lbs *Heart 530 g* Lungs R-600 g L-580 g Stomach 500 mL Findings: cardiomegaly, pulmonary, hepatic and renal congestion, minimal aspirated gastric contents	Not detected	Detected	0.10	9.8	0.07	15	5-Fluoro-ADB Toxicity
39	54-year-old male inmate found unresponsive; never regained consciousness, family refused organ donation, weaned from vent and pronounced; hand rolled cigarette found at the scene	5′5″, 175 lbs Heart 370 g Lungs R-740 g L-580 g Stomach 250 mL Findings: cerebral edema, adult respiratory distress syndrome, hepatic and renal congestion, pulmonary edema and congestion	None available		None available		AM SER: 0.12	AM SER: 42	5-Fluoro-ADB Toxicity
40	62-year-old male inmate found unresponsive; roommate appeared intoxicated, believed to be synthetic marijuana	5′2″, 149 lbs Heart 350 g Lungs R-550 g L-430 g Stomach 600 mL Findings: moderate to severe coronary atherosclerosis, mild pulmonary emphysema, aspirated gastric contents, nephrosclerosis and cortical renal cyst	Detected	Detected	0.08	80	< LOQ	15	5-Fluoro-ADB Toxicity
41	56-year-old male inmate went unresponsive after smoking a "k2" with cellmate; copious vomitus in mouth and on clothes; leafy substance found in socks; received prior discipline for drugs	5′6″, 162 lbs Heart 350 g Lungs R-590 g L-510 g Stomach 600 mL Findings: aspirated gastric contents, pulmonary and hepatic congestion, minimal coronary atherosclerosis	Not Detected	Detected	0.23	23	0.03	12	5-Fluoro-ADB Toxicity
42	32-year-old male inmate found unresponsive in his cell with vomitus around mouth and on clothes; cellmate reported that he had been using "k2" earlier; plastic cup tested positive for 5-Fluoro-ADB	5′6″, 147 lbs Heart 340 g Lungs R-720 g L-650 g Stomach 400 mL Findings: moderate to severe coronary atherosclerosis - myocardial scars left ventricle, mild aortic atherosclerosis, pulmonary and hepatic congestion, aspirated gastric contents	Not Detected	Detected	0.70	63	0.01	15	5-Fluoro-ADB Toxicity
43	50-year-old male inmate found unresponsive in cell with vomit on his clothes; fellow inmates stated he had been smoking "k2" earlier	5′7″, 255 lbs *Heart 520 g* Lungs R-670 g L-660 g Stomach 200 mL Findings: dilated cardiomegaly, aspirated gastric contents, pulmonary, hepatic and renal congestion	Not Detected	Detected	0.28	35	0.05	14	5-Fluoro-ADB Toxicity

TABLE 2—*Summary of quantitative data—central and peripheral blood concentrations for 5-fluoro-ADB and 5-fluoro-ADB metabolite 7*

Analyte		Central Blood (ng/mL)		Peripheral Blood (ng/mL)
5-Fluoro-ADB	Range	0.01–2.2	Range	0.01–0.77
	Mean	0.34	Mean	0.15
	Median	0.15	Median	0.07
5-Fluoro-ADB Metabolite	Range	2.0–166	Range	2.0–110
	Mean	41	Mean	21
	Median	34	Median	15

The method applied by Seither et al., validated with the appropriate certified reference materials and with an acceptable limit of quantitation for both 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7, was successfully applied to 43 medical examiner cases. Overall, the blood concentrations observed for 5-Fluoro-ADB were typically <1.0 ng/mL, which is consistent with previously reported values (10,13,17). Potential factors that contribute to low blood concentrations include nonenzymatic degradation during the pyrolysis process when smoking, rapid metabolism of 5-Fluoro-ADB by carboxylesterases found in the liver, lung, and intestinal wall, and the accumulation of 5-Fluoro-ADB in adipose tissue (5,13,18,19). Low blood concentrations may also be the result of postmortem changes including time interval between death and autopsy, storage condition (temperature) of the body, and position of the body (20). Due to the lipophilicity of 5-Fluoro-ADB, PMR may also occur which can significantly affect the drug concentration after death (5). PMR involves the redistribution of drugs into the blood from surrounding organs such as the liver, lungs, and myocardium as well as diffusion from the stomach to nearby organs such as the heart and liver (20,21). As a result, some drugs may exhibit blood concentrations that are greater in central blood sources when compared to peripheral blood sources. Although the majority of specimens were obtained after death and, as a result, could be subject to postmortem changes and redistribution, two antemortem samples (antemortem blood from case 25 and antemortem serum from case 39) were tested. Similar to the postmortem specimens, 5-Fluoro-ADB concentrations in the antemortem samples were less than 1.0 ng/mL, supporting rapid drug metabolism after use or the possibility of 5-Fluoro-ADB undergoing nonenzymatic degradation during the smoking process.

The data obtained from 24 cases in which central and peripheral blood pairs were submitted for testing were evaluated to investigate PMR (summarized in Table 3). For 5-Fluoro-ADB, the central to peripheral blood concentration ratio (C/P) averaged 7.8, with a median C/P of 1.7 and a range of 0.1 to 70. Fourteen cases (58%) resulted in 5-Fluoro-ADB C/P >1, while two cases resulted in C/P equal to 1 and four cases exhibited a peripheral blood concentration higher than the central blood concentration (C/P <1). For 5-Fluoro-ADB metabolite 7, C/P averaged 2.7, with a median of 1.7 and a range of 0.5–17.6. Seventeen cases (71%) resulted in 5-Fluoro-ADB metabolite 7 C/P >1, while three cases resulted in C/P equal to 1 and 4 cases exhibited a peripheral blood concentration higher than the central blood concentration (C/P <1). The C/P range obtained for both 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7 is quite large, and the median C/P for 5-Fluoro-ADB (1.7) and metabolite (1.7) may be more representative of the extent of postmortem redistribution. It is well-understood that as the postmortem interval increases, the decomposition progresses and additional drug is released from central cavity organs resulting in the C/P ratio increasing (11,12). In general, reported blood concentrations from central blood sources were typically higher than the peripheral blood source concentrations for both 5-Fluoro-ADB and 5-Fluoro-ADB metabolite 7 which suggests that they both undergo postmortem redistribution to some extent.

TABLE 3—*Summary of Central to Peripheral Blood Concentration Ratios for 5-Fluoro-ADB and 5-Fluoro-ADB Metabolite 7*

Ratio	5-Fluoro-ADB	5-Fluoro-ADB Metabolite 7
Mean	7.8	2.7
Median	1.7	1.7
Range	0.1–70	0.5–17.6

Demographically, all 43 decedents were men between the ages of 20 and 68 years, with a median age of 48 years and a mean age of 45 years. The majority were found unresponsive either slumped over in bed, on a park bench, or in a motor vehicle, and many were known to abuse illicit substances per family and friends. Of particular importance is that a large majority of the decedents, 79% (34 out of the 43), were incarcerated at the time of the terminal event, with half of them witnessed or observed on video to be smoking "a substance" or "k2" within minutes prior to death. Although the presence of 5-Fluoro-ADB among the prison population may be surprising, the prevalence of synthetic cannabinoids, in general, is quite common in correctional institutions, particularly in Europe and Canada (22).

In terms of pathological findings, several observations were noted and summarized in Table 1. A common, nonspecific finding among the majority of cases was pulmonary congestion and edema and the presence of aspirated gastric contents, both potentially due to a drug overdose, natural disease, drowning, or resuscitation efforts. Of particular interest, however, are the cardiac weights measured at autopsy. In the majority of the cases, the cardiac weights were greater than the predicted cardiac weight for body height (58% of the cases) and weight (74% of the cases) (16). A smaller number of cases had cardiac weights (italicized in Table 1) that were greater than the upper 95% confidence limit for height (35% of cases) and weight (19% of cases) (16). The relative cardiomegaly alone may be a sign of subclinical cardiac disease if a cardiac condition had not already been diagnosed. Adverse effects of 5-Fluoro-ADB include symptoms similar to serotonin syndrome (psychomotor agitation, anxiety, seizures, muscle rigidity, increased body temperature, and tachycardia), and therefore 5-Fluoro-ADB may affect the heart by increasing both heart rate and blood pressure.

Another interesting finding is the volume of gastric contents collected during the autopsy. In general, the volume of gastric contents collected was more substantial than the volumes noted in average routine medical examiner cases (empirical observation over decades). For the majority of cases (78%), greater than 100 mL of gastric contents were collected, with 30% having between 101 and 300 mL, 28% having between 301 and 500 mL and 19% having greater than 500 mL. Note that the volume of gastric contents collected at autopsy is an approximation based on collection in a 2,000 mL Guardian™ Suction Container. In terms of digestion, the splanchnic circulation (blood flow to the digestive or gastrointestinal tract) receives approximately one-quarter of the cardiac output, and increases after a meal. As a consequence, the act of eating food places stress on the heart in order to accommodate the gastrointestinal tract's requirement for increased blood flow. The superimposition of 5-Fluoro-ADB with its stimulant properties to induce anxiety,

agitation, and tachycardia, may precipitate a cardiac event (dysrhythmia) and sudden death in the early postprandial period when the heart is working harder to increase cardiac output. The sizable quantity of gastric contents in many of the cases suggests that the consumption of 5-Fluoro-ADB occurred during a meal or in the early postprandial period. In the incarcerated population, it is speculative that drugs may be distributed or shared during meal times when there is increased opportunity for interaction between inmates, and between inmates and institutional staff. It is therefore hypothesized, but reasonable, that individuals with cardiomegaly, or other cardiac disease, may have an increased susceptibility to the adverse effects of 5-Fluoro-ADB with its ability to increase heart rate and blood pressure. With the addition of the physiological demand placed on cardiac output in the postprandial period, it is possible and rational that the combination of these factors can precipitate a dysrhythmia and sudden death.

Upon reviewing the medical examiner case in its entirety, the manner of death for each was determined to be an accident, with all but one case listing 5-Fluoro-ADB in the cause of death. Out of the 43 cases, 79% attribute the sole cause of death to 5-Fluoro-ADB. A small percentage of cases (7%) listing 5-Fluoro-ADB in the cause of death also contribute cardiac abnormalities, hypertensive cardiomegaly (case 18 and 37) and hypertensive and atherosclerotic heart disease (case 35). The remaining cases involved the presence of other illicit substances, including ethanol (case 1 and 6), cocaine (case 6, 15, and 16), heroin (case 15), fentanyl (case 16), n-ethylpentylone (case 3, 4, and 19), and/or other synthetic cannabinoids (AM-2201, MMB-2201, AB-CHMINACA, and ADB-FUBINACA) (case 1, 19, 23, 35, and 37). Worth noting is that case 1 and 4 include 5-Fluoro-ADB in the cause of death even though only the metabolite was identified in the specimens (identification in the urine in case 1 and identification in both the blood and urine in case 4). Reports suggest that synthetic cannabinoids similar to 5-Fluoro-ADB also undergo ester hydrolysis, therefore 5-Fluoro-ADB metabolite 7, when detected alone, does not prove exposure to 5-Fluoro-ADB (1). However, in case 1 and 4 with only the metabolite identified, exposure was confirmed by the positive identification of 5-Fluoro-ADB in the paraphernalia collected at the scene.

Conclusion

This series of cases highlights the prevalence of 5-Fluoro-ADB in medical examiner casework between September 2016 to December 2018, particularly among the prison population in Florida Medical Examiner District 11 and 14. The high number of cases (42 out of the 43 reported cases) that include 5-Fluoro-ADB in the cause of death illustrates the importance of the toxicology laboratory's ability to identify these substances when processing casework. The observation that the calculated concentrations were low confirmed the necessity for sensitive analytical techniques to be able to identify 5-Fluoro-ADB in postmortem blood specimens. Based on the data obtained, 5-Fluoro-ADB metabolite 7 is present in much greater concentrations in blood than 5-Fluoro-ADB, suggesting that the metabolite may be useful as a marker for synthetic cannabinoid abuse. Furthermore, the utility of screening central blood is evident based on its increased concentration, possibly due to postmortem redistribution, when compared to peripheral blood concentrations. The toxicological and pathological findings suggest that individuals with cardiomegaly and other cardiac conditions may be more susceptible to the adverse effects of 5-Fluoro-ADB. Superimposing cardiac abnormalities and the physical demand on cardiac output in the postprandial period, it is concluded that 5-Fluoro-ADB may precipitate a dysrhythmia and sudden death.

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