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Acute onset heart failure due to reverse type Takotsubo cardiomyopathy caused by a single dose of 4-Fluoroamphetamine in a healthy young individual

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ABSTRACT

Introduction: 4-fluoroamphetamine (4-FA) is a novel psychoactive stimulant with a global presence on the drug market. Despite the popularity of 4-FA, data on severe adverse effects are scarce. We present a case of laboratory confirmed 4-FA mono intoxication causing acute heart failure due to a reverse type Takotsubo cardiomyopathy.
Case: A 20-year-old male with no previous medical history and no reported previous drug use, presented to the emergency department (ED) with complaints of headache, nausea and vomiting, approximately 4.5 h after the ingestion of a single 4-FA pill. After 30 min his condition deteriorated with severe hypertension, tachycardia and respiratory failure. Echocardiography showed a reverse type Takotsubo cardiomyopathy. The patient was successfully treated with mechanical ventilation, a phosphodiesterase-3-inhibitor (PDE3-inhibitor) and diuretics. Three months after hospital admission, the patient was free of complaints and his left ventricular function fully recovered.
Conclusion: Recreational use of 4-FA may result in acute onset life-threatening cardiorespiratory toxicity, preceded by severe hypertension, even in drug-naïve patients without any medical history. Emergency physicians and cardiologists should be cautious not to underestimate life-threatening 4-FA complications.

1. Introduction

4-Fluoroamphetamine (4-FA) is a novel psychoactive stimulant (NPS). Data from drug testing facilities, forensic investigations, and case reports indicate a global presence of 4-FA on the drug market, which has been confirmed by various Early Warning System reports in European countries [1]. A survey conducted amongst young European adults (15–24 year old) reported a lifetime prevalence for NPS use of 8 % [2]. As a result, 9 % of all drug-related emergency department (ED) visits involved NPS use, with admission rates reported up to 70 % [3]. The Dutch use for 4-FA was 0.9 % in 2017 [4], although 4-FA is an illicit drugs since April 2017.

4-FA is an amphetamine type stimulant (ATS) similar to amphetamine and 3,4- methylenedioxymethamphetamine (MDMA). It inhibits and reverses monoamine reuptake transporters, thereby increasing extracellular levels of norepinephrine, dopamine, and serotonin in the brain [1]. However, pharmacokinetics and pharmacodynamics are altered, as chemical substitutions at the amphetamine core structure may significantly modify the absolute or relative potency of 4-FA at the level of the norepinephrine transporter and dopamine transporter relative to the serotonin transporter [5]. Therefore, 4-FA more effectively activates the serotonergic 5-HT_{2c} receptor compared to amphetamine [6]. Also, 4-FA has a higher toxicity (LD50) compared to amphetamine and MDMA in mice [7]. Data on the metabolism and excretion profile of 4-FA in humans are limited. Onset of effects are expected after 30−90 min, effects last for 4–8 hours [8], and peak concentrations are expected at 1.05 h (0.85–1.16 h) [9]. 4-FA is mostly excreted unchanged in the urine, although small amounts of amphetamine can be found in

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urine samples [10].

4-FA is usually ingested, with a median reported dose of 178 mg per tablet or capsule (range 100–210 mg; N = 14) and the median number of tablets or capsules ingested is 1.8 (IQR 1–2; N = 26). [1] Users of 4-FA are at a greater risk of taking an overdose compared to MDMA and amphetamine, due to users experiencing relative mild effects and late onset of effects [7].A 4-FA dose of 150 mg or more increases the risk for adverse events, like cardiotoxicity, especially when users simultaneously ingest alcohol and/or other recreational drugs, which is frequently reported [1]. Despite the popularity of 4-FA, data on severe adverse effects after 4-FA use are scarce, and mainly comprise case reports and small case series with multidrug intoxications. We present a case of laboratory confirmed 4-FA mono intoxication leading to acute heart failure as a result of a reverse type Takotsubo cardiomyopathy.

2. Case report

A 20-year-old male with no previous medical history and without previous drug use, presented to the ED by ambulance for complaints of headache, nausea and vomiting, approximately 4.5 h after ingestion of a single capsule alleged to contain 250 mg of 4-FA.

On initial assessment, his blood pressure (BP) was 200/125 mmHg, heartrate (HR) was 115 beats per minute (bpm), respiratory rate (RR) was 14/min, oxygen saturation (SpO_2) was 98 % on room air and his tympanic temperature was 34.8 °C. No further abnormalities were observed during initial assessment. Since drug-induced anxiety was suspected, he was given 20 mg of oxazepam orally and was observed, with cardiorespiratory monitoring, in the ED.

After 30 min his condition deteriorated very suddenly. He complained of dyspnoea, associated with a change in RR to 20/min and a drop in oxygen saturation to SpO_2 89 %. The electrocardiogram (ECG) showed a sinus tachycardia of 110 bpm, with premature ventricular complexes in bigeminy, a prolonged QT_c-interval of 487 ms and ST-depression in leads II, III, AVF and V3-V6 (Fig. 1). Runs of ventricular tachycardia were observed on the monitor. The patient subsequently developed respiratory failure due to acute heart failure and was

Table 1
Laboratory results of our patient during his time of admission.

Data	Reference value	Time of withdrawal		
		6 hours	28.5 hours	52.5 hours
Hemoglobin	8.5−11 mmol/L	12.2	10.1	
Leukocytes	4-10*10^9/L	22.8	12.6	
Thrombocytes	150-400*10^9/L	295	190	
Creatinin	59-104 micromole/L	64	77	81
eGFR (CKD-EPI formula)	60-kl/ 1.73m^2	>90	>90	120
Urea	2.1–7.1 mmol/L	3.6	4.6	6.5
LDH	−248 IU/L	203	363	
CK	−171 U/L	246	610	146
CK-MB mass	−7.6ug/L	5.7	38	
Ratio MB/CK	−0.015ug/IU	0.023	0.062	
Hs-Troponin	−0.014 ug/L	0.205	0.695	
BNP	< 7.6 ug/L	1196		1169
CRP	−10 mg/L	< 0.6	36	

Time of withdrawal is shown in number of hours post-ingestion. Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB mass = measurement of the MB iso-enzyme of creatine kinase; Hs-trop = high sensitive troponin; BNP = brain natriuretic peptide; CRP = C-reactive protein.

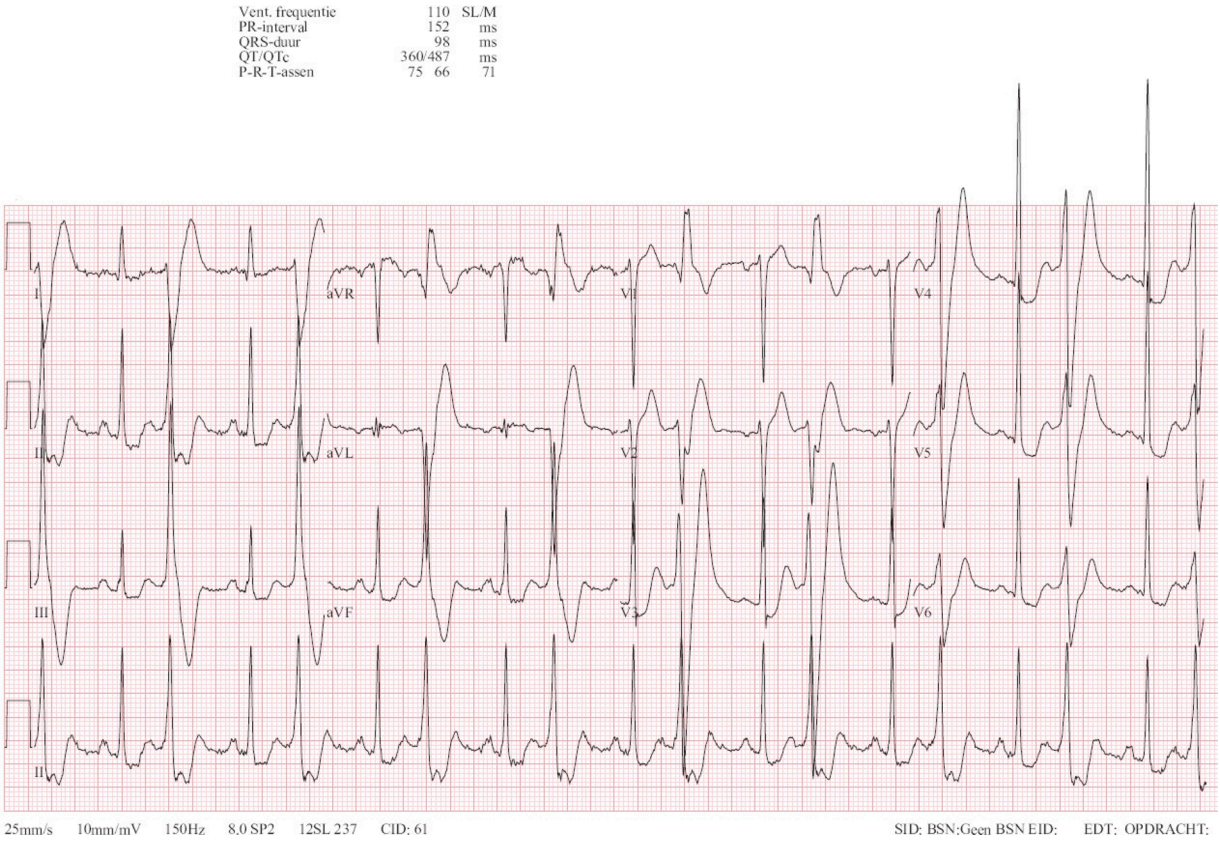

Fig. 1. Electrocardiogram.
ECG obtained approximately 6 h post-ingestion.
ECG description: Sinus tachycardia of 110 bpm, with premature ventricular complexes in bigeminy, a prolonged QT_c-interval of 487 ms and ST-depressions in II, III, AVF and V3-V6.

intubated and ventilated. Laboratory and arterial blood gas results are shown in Tables 1 and 2, respectively. A chest X-ray showed signs of peri-bronchial oedema. Subsequent echocardiography showed a moderately reduced left ventricular function with wall motion abnormalities matching a reverse type Takotsubo cardiomyopathy with dyskinesia of the basal parts and hyperkinesia of the apex of the heart (Fig. 2). Left ventricular ejection fraction was estimated to be 30 %, right ventricular function was normal and there were no signs of valvular disorders or left ventricular outflow tract obstruction (LVOTO).

During ICU admission, severe hypoxemia due to pulmonary oedema developed, which required respiratory support with positive end expiratory pressure (PEEP) up to 20 cm H_2O. Enoximone, a phosphodiesterase-3-inhibitor (PDE3-inhibitor), was started for treatment of the reverse type Takotsubo cardiomyopathy, after which hemodynamic improvement was observed and diuretics (Furosemide) could be started. Approximately 22 h post-ingestion, his condition improved and after several hours he was successfully extubated. No dysrhythmias were observed on continuous cardiac monitoring over the following 72 h. Prior to hospital discharge on day 4, repeat transthoracic echocardiography showed an improvement of LV function (LVEF 45 %) with hypokinesia of the basal segments. On outpatient follow-up 3 months later, all symptoms had resolved with full recovery of the left ventricular function.

Comprehensive toxicological screening of serum and urine samples was performed, following the previously described procedure [11]. Samples were collected 28.5 h after ingestion, and were analyzed with a urine toxicology point of care test and with the Toxtyper® (amaZon speed, Bruker, Billerica, United States of America). The Toxtyper® uses ultrahigh performance liquid chromatography coupled to an MS^N ion trap detector (LC-MS^N) and is equipped with a library of approximately 900 therapeutic drugs and drugs of abuse, including 4-FA. The LC-MS^N analysis confirmed the presence of 4-FA (parent compound) and also the following substances: midazolam, alpha-hydroxymidazolam (metabolite of midazolam), enoximone, lidocaine and rocuronium (all administered in ICU). Unfortunately, a qualitative analysis could not be performed, due to insufficient material. Analysis of additional drug capsules that were collected at admission, showed that each capsule contained approximately 216 mg of 4-FA.

3. Discussion

A case of acute onset cardiogenic shock and severe pulmonary oedema due to 4-FA induced reverse type Takotsubo cardiomyopathy is described. To our knowledge, this is the first case reporting severe cardiac toxicity after a laboratory confirmed, mono-intoxication with 4-FA in a previously healthy and drug-naïve patient.

Table 2
Arterial blood gas results of our patient during admission.

Data	Reference value	Time of withdrawal			
		6 hours	6.5 hours	9.5 hours	28 hours
pH	7.35-7.45	7.22	7.08	7.26	7.42
pCO_2	36-44 mmHg	47	75	49	38
pO_2	70-100 mmHg	48	114	100	78
Bicarbonate	22−29 mmol/L	18.7	21.2	21.6	24.6
Base excess	−3.0–3.0 mmol/L	−9.7	−12.0	−5.7	0.9
O_2-saturation	95-98 %	75.9	95.7	96.7	96.2
Glucose (ABG)	4-7.8 mmol/L	13.1	12.9		
Sodium (ABG)	135−147 mmol/L	137	137	134	136
Potassium (ABG)	3.5-5.0 mmol/L	4.0	3.0	6.3	3.9
Chloride (ABG)	96−109 mmol/L	106	108	111	106
Lactate (ABG	0.5-1.7 mmol/L	4.6	1.9	1.1	0.8

Time of withdrawal is shown in number of hours post-ingestion.

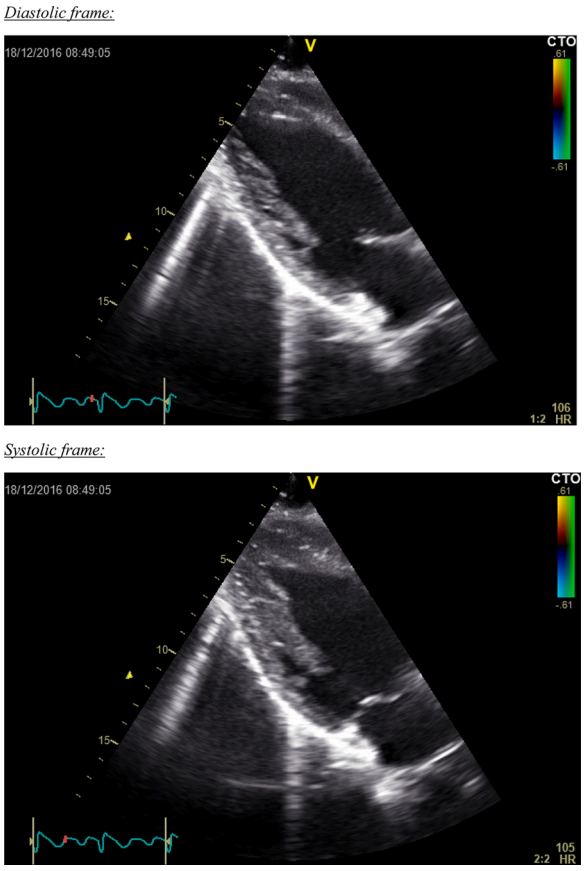

Fig. 2. Transthoracic cardiac ultrasound.
Transthoracic ultrasound obtained approximately 7 h post-ingestion. Transthoracic cardiac ultrasound description: 2-chamber view showing apical hyperkinesia and dyskinesia of the basal segments.

Recreational drug use is commonly associated with complications, including an increased risk of premature death. Sympathomimetic recreational drugs in particular, are associated with cardiovascular complications such as hypertension, hemorrhagic and ischemic stroke, ruptured aortic aneurysm, aortic dissection, tachy-arrhythmias, and acute coronary syndrome (ACS). ACS develops due to a combination of increased oxygen demand, decreased oxygen delivery due to coronary vasospasm and platelet and coagulation activation which can result in thrombus formation. Additionally, chronic Sympathomimetic drug use accelerates atherosclerosis [12,13]. Furthermore, cocaine [14–16], synthetic cannabinoids [17], and ATS [1,13,18–22] including 4-FA, have been associated with non-cardiogenic pulmonary oedema and (reverse type) Takotsubo cardiomyopathy.

Takotsubo cardiomyopathy occurs for more than 90 % of cases in middle-aged females as a response to stressful events and the typical variant with apical dysfunction is present in 75–80 % of patients. Typically, more than one coronary territory is effected in the absence of culprit coronary artery disease [23,24]. Female ATS users predominantly develop the reverse type variant [23] and 4-FA related Takotsubo cardiomyopathy has been associated with this atypical basal variant [20,25]. In younger patients, this may be explained by the relative abundance of adrenoceptors at the ventricular base compared to the apex [18]. It is thought that ATS cause oxidative stress through multiple pathways, such as metabolism to catecholamines, increased activity of xanthine oxidase, mitochondrial dysfunction, leucocyte activation and hyperthermia [18], leading to inhibition and reversal of monoamine reuptake transporters resulting in higher concentrations of monoamines,

including (nor)epinephrine [6]. In addition, this adrenergic storm may provoke severe vasoconstriction and microvascular dysfunction in the heart and brain [1]. Also, ATS metabolites promote oxidative stress in a time and concentration dependent manner [18].

Heart failure is the most common complication in the acute phase of Takotsubo cardiomyopathy, occurring in 12–45 % of patients, with an in-hospital mortality of 2–5 %. [23,24] The RR is an important prognostic factor in patients with acute decompensated heart failure (ADHF) [26]. A raise of this patients RR by 42 % at time of deterioration, does not only exceed the percentage indicative for ICU admission and mechanical ventilation (18 % and 33 % respectively), it nearly reaches the rise in RR associated with mortality (44 %) [26]. Regardless of the etiology of ADHF in the ED, the aim of treatment is to ensure adequate oxygenation and ventilation via supplemental oxygen, non-invasive ventilation or mechanical ventilation, if required [27]. Additionally, loop diuretics such as furosemide, can be considered to improve pulmonary vascular congestion [27]. Subsequently, hypertensive patients require vasodilators, usually nitroglycerin, for afterload reduction [27]. For refractory ADHF patients, with severe compromised organ perfusion, inotropic (dobutamine), inodilator (milrinone) or vasopressive (noradrenaline) support can be used [27]. The treatment for heart failure due to reverse type Takotsubo cardiomyopathy is mostly supportive and similar to ADHF treatment [28]. In addition, the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers, to reduce cardiac workload and to control hypertension, is advised [28,29]. Also, aldosterone antagonists may be cardioprotective, because aldosterone potentiates the effects of catecholamines on the cardiovascular system by further raising systemic BP [24]. Furthermore, for Takotsubo cardiomyopathy induced cardiogenic shock without a left ventricular outflow tract obstruction (LVOTO), PDE3-inhibitors and dopamine may be effective [24]. PDE3-inhibitors, like milrinone and enoximone, prevent degradation of cyclic adenosine monophosphate, leading to increased intracellular calcium concentration and thereby improve myocardial contractility independently of ß-receptor stimulation [30]. Compared to dobutamine, milrinone is more effective and better tolerated with less tachycardia and myocardial oxygen consumption [30], despite the fact that milrinone decreases systemic vascular resistance and potentially leads to arterial hypotension [30]. Therefore, PDE3-inhibitors have been recommended for cardiogenic shock in Takotsubo cardiomyopathy [30]. In refractory shock, left ventricular assist devices may be indicated, and extracorporeal membrane oxygenation may be considered in case of severe LVOTO [28].

This patient presented with severe hypertension after 4-FA use and was initially treated with benzodiazepines, in accordance with the American Heart Association advise for cocaine or methamphetamine-induced hypertensive emergencies. [31] In retrospect, more strict anti-hypertensive treatment might have decreased the risk of developing complications [29]. Since 4-FA induced hypertension has also been related to intracranial bleeding [1,32], we suggest a strict blood pressure treatment with high dose benzodiazepine and nitroglycerine intravenously. Previously, four other 4-FA cases complicated by cardiogenic shock due to Takotsubo cardiomyopathy have been described [1,19,20] and for two of these patients the provided management is available [19,20]. One hypotensive patient, with laboratory confirmed 4-FA, naproxen, naltrexone, fluoxetine, trazodone, nicotine and cotinine use, was treated with a combination of dopamine, epinephrine and an intra-aortic balloon pump, followed by dopamine, dobutamine and milrinone [19]. The other patient, a frequent 4-FA user, with a toxicologically confirmed 4-FA mono-intoxication, presented without hypotension, but with acute pulmonary oedema and biventricular dysfunction. He was treated with a combination of furosemide, beta-blockers and ACE-inhibitors and his myocardial function improved on day 4 [20]. In contrast we have treated our hypertensive patient initially with benzodiazepines, followed by enoximone and diuretics thereafter. Due to the absence of cardiovascular risk factors and the patients young age, the possibility of coronary artery disease was deemed very low. Also, there was a very plausible alternative explanation for his complaints, a sympathomimetic toxidrome. On ultrasound, the treating cardiologist noted regional wall motion abnormalities not matching the typical distribution pattern of coronary artery disease. Therefore, the risk of a bleeding complication performing a coronary angiogram, was considered not to outweigh the benefits. However, a CT-coronary angiogram, to rule out coronary pathology, can be considered for drug-induced Takotsubo cardiomyopathy patients.

The overall prognosis for non-drug-induced Takotsubo cardiomyopathy is good, 95 % of patients recover completely within several weeks and recurrence rates are low (5 %) [24]. In a small study on ATS Associated Cardiomyopathy (n = 20), all 6 patients with Takotsubo cardiomyopathy recovered within six weeks [22]. It is expected that discontinuation of ATS use will improve prognosis and decrease the risk of recurrence [28].

4. Conclusion

Recreational use of 4-FA may cause acute onset and life-threatening cardiorespiratory toxicity, preceded by severe hypertension, even in drug-naïve patients without any medical history. Emergency physicians and cardiologists should not underestimate life-threatening 4-FA complications.

Conflict of interest

The authors declare no conflict of interest.

Informed consent

Written consent was given by the patient.

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