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LETTER TO EDITOR

Refractory cardiogenic shock caused by methadone poisoning and treated with hybrid extracorporeal membrane oxygenation☆

Keywords Methadone poisoning; Refractory cardiogenic shock; ECMO

Abbreviations

ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
CMV	cytomegalovirus
EBV	Epsein Barr virus
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HHV6	human herpes virus 6
HSV	herpes simplex virus 1
IBW	ideal body weight
ICU	intensive care unit
LV	left ventricle
LVEF	LV ejection fraction
PCR	polymerase chain reaction
PEEP	positive end-expiratory pressure
RIJ	right internal jugular
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TAPSE	tricuspid annular plane systolic excursion
VA	veino arterial
VTI	velocity time integral
VAA-ECMO	veno-arterial-venous extracorporeal membrane oxygenation

Methadone cardiotoxicity has been widely reported and includes principally QT interval prolongation leading potentially to torsade de pointes [1]. Hemodynamic instability, acute heart failure or more rarely cardiogenic shock have also been described following methadone overdose [2]. An excessive catecholamine release responsible for Takotsubo syndrome stress cardiomyopathy has been proposed to explain acute heart failure following methadone poisoning [2,3]. Here, we describe a patient with multiple organ dysfunction syndrome complicating refractory cardiogenic shock caused by massive methadone intoxication without typical electrocardiogram (ECG) changes and/or echocardiography abnormalities and in whom a veno-veno-arterial extracorporeal membrane oxygenation (VAV-ECMO) was required.

Case history

A 39-year-old man with a history of drug addiction, but free from drug use for 7 years, was found comatose by his family. Paramedics found him to be hypotensive, hypopnoeic, hypoglycaemic (0.56 $g.L^{-1}$), hypothermic and cyanotic. He had miosis and empty methadone blisters were found nearby him (total dose of 1820 mg). He received 0.4 mg of Naloxone and his Glasgow score increased from 3 to 11 with acute agitation. After tracheal intubation, norepinephrine and epinephrine were given intravenously. Upon arrival in hospital, the blood gas showed pH 7.13, $PaCO_2$ 61 mmHg, PaO_2 63 mmHg, SaO_2 96%, lactates 6.0 $mmol.L^{-1}$. Chest X-ray revealed bilateral acute pulmonary oedema (Fig. 1A). Transthoracic echocardiography showed biventricular failure dilated left ventricle (LV), LV ejection fraction (LVEF) 25-30%, LV outflow tract velocity time integral (VTI) 9 cm, absence of valvular disease, tricuspid annular plane systolic excursion (TAPSE) 6 cm. ECG revealed sinus tachycardia at 120 bpm with PR 160 ms, QRS 96 ms, QTc 369 ms, and upright and peaked P waves in leads II and III favouring a ''P-pulmonale'' wave. In the next few hours, the patient exhibited severe cardiogenic shock (refractory hypotension, hyperlactatemia 8.3 $mmol.L^{-1}$ and cardiac index under 2 $L.min^{-1}.m^2$) while the dose of epinephrine was increased to 2.1 $\mu g.kg^{-1}.min^{-1}$. After a skin disinfection, a 19 Fr cannula (Maquet Getinge, Gothenburg, Sweden) was introduced in the left common femoral artery, a 21 Fr venous canula in the left femoral vein and a distal reperfusion for his leg in the superficial femoral artery. Because the patient suffered from severe hypoxemia, a 15 Fr cannula was introduced in his right internal jugular (RIJ) vein to ensure a precardiac oxygenation and limit the Arlequin syndrome. The extracorporeal membrane oxygenation (ECMO) blood flow was started at 5 $L.min^{-1}$ while the RIJ line was partially clamped to limit its flow to 1 $L.min^{-1}$. His theoretical cardiac output had been set at 3 $L.min^{-1}.m^{-2}$ for a patient of 166 cm, 75 kg (corporeal area 1.83 m^2). The blood flow and FiO2 to the RIJ cannula were set for an inlet saturation above 70% before the pulmonary circulation and PaO2 in right arterial blood above 95%. The arterial blood-gas obtained from the right

☆ This case has been declared at the addictovigilance unit of Bordeaux on the 06 june 2020 under the number N° BX20200606.

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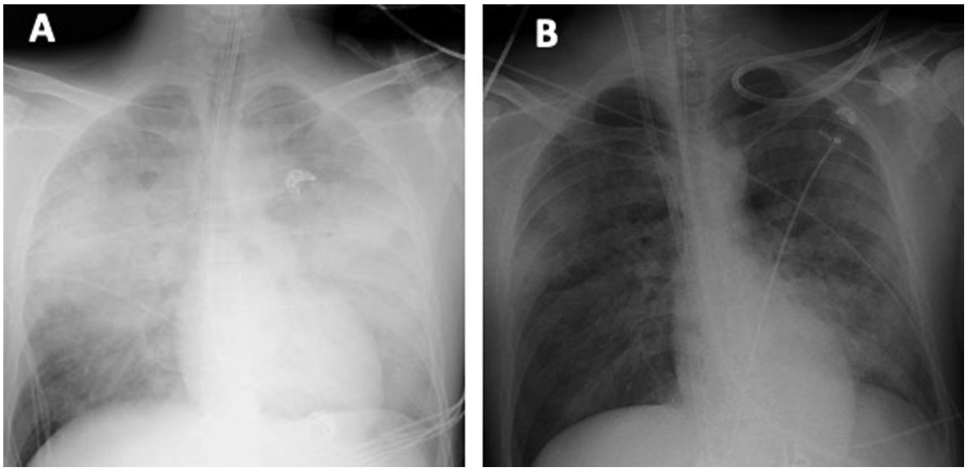

Figure 1. Posterior-anterior chest X-ray at the intensive care unit admission showing severe alveolar oedema (A) and under extracorporeal life support one day after the addition of intra-aortic balloon pump (B).

radial artery under VAV-ECMO showed pH 7.26, PaCO2 31.5 mmHg, PaO2 338 mmHg, lactates 12.8 mmol.L^{-1} (maximal lactates). Mechanical ventilation was set at 6 ml.kg^{-1} of IBW x 10 c/min, positive end-expiratory pressure (PEEP) 8-10 cmH_2O, sweep gas on ECMO controlled for normal PaCO2. On ECMO day 1, epinephrine and norepinephrine infusions were reduced and an intravenous infusion of dobutamine was initiated at 5 μg.kg^{-1}.min^{-1}. The LVEF was 15%, VTI 1 cm with intraventricular sludge and an antero-lateral thrombus 1 × 1 cm. An intra-aortic balloon pump was introduced for LV unloading. A resolution of pulmonary oedema could be rapidly observed (Fig. 1B). During the first days, the patient exhibited some organ failures including acute kidney injury (KDIGO 2) and hepatic failure (aspartate aminotransferase [ASAT] 4306 UI.L^{-1}, alanine aminotransferase [ALAT] 1162 UI.L^{-1}, PT failed at 45% with 22% factor V, all were normalised on day 4). Troponin-I (normal <30 ng.L^{-1}) was measured on the 1st day at 80 ng.L^{-1} and the peak was obtained at 5746 ng.L^{-1} on day 2. The serum creatinine peak was reached on the 1st day (192 μmol.L^{-1}) and was normal after the 3rd day without extrarenal epuration. Lactates were normalised on day 2. The jugular cannula (converting as a veino arterial [VA] ECMO) and the intra-aortic balloon pump were removed on the 3rd day. The VA-ECMO was removed on the 5th day without reintroduction of inotrope or pressor amines. He was extubated on day 6. He did not exhibit any neurological injury. Finally, the patient was discharged from the intensive care unit on the 10th day, his ECG was normal with the disappearance of his ''p-wave pulmonary''. Echocardiography gradually improved, with normalisation on day 10 (LV VTI 16 cm, LVEF 55%, normal LV size, TAPSE 14 cm). There were no signs of either regional wall motion anomalies or genetic hypertrophic or obstructive cardiomyopathy.

Concerning the differential diagnosis, all our investigations were negative. Coronary angiography, full body CT-scan were normal. We also looked for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza virus, Brucella, Chlamydia, Coxiella, Rickettsia, Syphilis, Zika, toxoplasma, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human herpesvirus 6 (HHV6), Epsein Barr virus (EBV), adenovirus, cytomegalovirus (CMV), B19, Chikungunya, herpes simplex virus 1 (HSV) 1 and 2 by polymerase chain reaction (PCR) [by bronchoalveolar lavage or blood sample] or serology. Dengue serology was compatible with a recent infection in the past 3 months (trip to Thailand 4 months previously). Auto-immune myocarditis test results were negative. Blood samples were subjected to toxicological screening using ultraperformance liquid chromatography—high-resolution time-of-flight mass spectroscopy. The analytical system consisted of an Acquity I class system (Waters, Milford, MA, USA) coupled to a Xevo XS G2 QTOF analyser (Waters). Data were analysed with an exact mass database from Waters for >1500 toxicologically relevant drugs and metabolites. The following drugs were identified acetaminophen, methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), etomidate and laudanosine. Quantifications were performed for acetaminophen, methadone, and EDDP. The respective plasma concentrations of methadone and EDDP upon arrival in the ICU (intensive care unit) were 1723 ng.mL^{-1} and 167 ng.mL^{-1}. These high levels decreased progressively over the following 10 days. One month later, a segmental toxicological hair analysis was performed (liquid chromatography—tandem mass spectrometry). Hair analysis was negative in all segments for illicit drugs and substitution therapy, corresponding to an absence of drug consumption before admission (0 to 6 cm of hair).

Discussion

Previous case reports described cardiogenic shock following methadone overdose, which was treated with inotropic drugs [2]. The use of VA-ECMO has been previously reported to treat opioid-induced pulmonary oedema [4]. The present case is the first to report multiple organ failure syndrome complicating refractory cardiogenic shock treated by VAV-ECMO. The severity of cardiogenic shock of our patient can be explained by the high plasma level of methadone (i.e. 1723 ng.mL^{-1} on intensive care unit [ICU] admission) which has been described as lethal [1]. Although the underlying mechanism of methadone cardiotoxicity remains unclear, QT prolongation and torsade de pointes have been described but did not apply in this case [1,5]. As previously

reported, cardiac function was fully restored after 10 days [2]. The presumed cause of rapidly reversible cardiogenic shock was Takotsubo adrenergic cardiomyopathy which was previously described in patients with methadone poisoning [2]. It should be pointed out that our patient did not exhibit the typical echocardiographic pattern or ECG changes. Despite the absence of cardiac magnetic resonance imaging findings, the recent consensus regarding Takotsubo cardiomyopathy suggests that our patient exhibited adrenergic cardiomyopathy. The main supporting evidence is the ad-integrum reversibility after a few days of treatment [6]. An increase in circulating catecholamine levels has been observed after methadone injection in some species [7]. Excessive circulating catecholamines have been involved in the pathophysiology of this cardiomyopathy. Only a few case reports have described refractory cardiogenic shock after massive methadone poisoning and this concerned children [4]. Methadone has very good bio-availability (80%) with a long half-life (7-65 hours) and is mostly metabolised with cytochrome P450 3A4 and CYP2D6 [8]. Adrenergic cardiomyopathy has been described due to methadone withdrawal but he had not taken methadone in the months before intoxication, according to the hair analysis [3]. He had not taken any medication which could interact with CYP450. The elimination of methadone is, for the most part, assured by the kidney (15-40% during the first 24 hours) and he presented severe acute kidney injury. This could increase the toxicity of the drug [5]. Our patient had a methadone plasma level of 1723 $ng.mL^{-1}$ which is described as a lethal dose [9,10]. Concerning the final diagnosis, he did not have the typical pattern of Takotsubo cardiomyopathy but recent international expert consensus on Takotsubo syndrome proposed a new algorithm for the diagnosis [6]. This case demonstrates that we should be very aggressive during the treatment of refractory cardiogenic shock caused by poisoning, a fortiori, with a young healthy patient. Methadone or opioid poisoning can present many serious clinical symptoms. The patient is currently in good health and in the care of a cardiologist and an addictologist.

Conclusion

This case report describes multiple organ dysfunction syndrome complicating refractory cardiogenic shock following massive methadone intoxication. Neither ECG changes nor echocardiography abnormalities suggesting the diagnosis of Takotsubo syndrome could be observed on admission. It emphasises that such a diagnosis should be routinely suspected in patients with a history of drug abuse and access to methadone, even in the absence of typical ECG and/or echocardiography changes, and should be aggressively treated as it may be completely reversible. Also, direct methadone toxicity cannot be excluded. Toxicological analyses combining blood and hair testing should be performed to determine the cause of overdose and to exclude the use of other toxic substances.

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None.

Disclosure of interest

The authors declare that they have no competing interest.

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