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COMMENTED CASE REPORT / *CAS CLINIQUE COMMENTÉ*

Three Cases of Cardiac Arrest with Massive Flecainide Intoxication Treated with Extracorporeal Assistance

Trois cas d'arrêt cardiaque sur intoxication sévère à la flécaïnide traités avec assistance circulatoire extracorporelle

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Abstract Flecainide acetate is a Vaughan Williams class 1C anti-arrhythmic agent. Overdose causes severe cardiac and neurologic disturbances and carries a risk of fatality. No antidote is currently available. We present three cases of massive flecainide intoxication in which the patients were kept alive by extracorporeal circulation. Extracorporeal support in cases of flecainide intoxication is the only approach that can alleviate acute cardiac dysfunction, preserve blood flow to vital organs, and maintain liver metabolism and renal excretion of the toxin, while waiting for the improvement of cardiac function. Furthermore, clinical practice highlights that age, duration of CPR, PH, and lactate levels should not be a hindrance to decision-making, and demonstrates the positive, long-term neurologic and cardiologic outcomes that can be achieved with the use of extracorporeal assistance in the setting of severe flecainide intoxication.

Keywords Flecainide · Venoarterial extracorporeal membrane oxygenation · VA-ECMO · Cardiac arrest

Résumé La flécaïnide est un antiarythmique de classe 1C selon la classification de Vaughan-Williams. Son surdosage entraîne de graves troubles cardiaques et neurologiques, avec un risque létal. À ce jour, aucun antidote n'est disponible. Nous vous présentons trois cas d'intoxication au flécaïnide maintenus en vie par circulation extracorporelle. Les trois cas ont présenté une durée de support différente. À l'heure actuelle, le support via circulation extracorporelle dans le cadre d'un arrêt cardiaque sur intoxication au flécaïnide est le seul qui permet de suppléer la dysfonction cardiaque aiguë, d'assurer un maintien de la perfusion des organes vitaux, de la métabolisation hépatique et l'excrétion rénale du toxique, en attendant la récupération de la fonction cardiaque. Cette pratique clinique met en évidence une série de facteurs (âge du patient, durée de réanimation, pH et lactatémie en ce compris durant la RCP) qui ne doivent pas être un frein à la prise de décision et souligne un excellent devenir neurologique et cardiaque à long terme.

Mots clés Flécaïnide · Assistance circulatoire extracorporelle · VA-ECMO · Arrêt cardiaque

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Abbreviations

AKI: Acute Kidney Injury
ABG: Arterial Blood Gas
CPR: Cardiopulmonary Resuscitation
CPC: Cerebral Performance Category score
ED: Emergency Department
IFE: Intra-lipid Fat Emulsion
LVEF: Left Ventricular Ejection Fraction
OHCA: Out of Hospital Cardiac Arrest
VTI: Velocity Time Integral
VA-ECMO: Venoarterial Extracorporeal Membrane Oxygenation

Case Report

We present three cases of massive flecainide intoxication in which the patient was kept alive by venoarterial extracorporeal circulation membrane oxygenation (VA-ECMO).

In the first case, a 71-year-old Caucasian woman arrived in the emergency department (ED) with gradual dyspnea (NYHA II) and palpitations for the past week. Her cardiological history included sick sinus syndrome treated by pacemaker implantation and atrial fibrillation. Her current medications included an anticoagulant (dabigatran, 150 mg), a

rhythm medication (sotalol 160 mg three times per day), and long-acting flecainide (200 mg daily). At admission, her blood pressure was 87/49 mmHg and she had wide QRS complex tachycardia at 123 beats/min (Fig. 1). Arterial blood gas (ABG) testing revealed acidemia (pH 7.24) and hyperlactatemia (2.78 mmol/L). An initial cardioversion was a success. After that, the patient experienced three cardiac arrests with defibrillable rhythms and a return of spontaneous circulation with no neurological deficit, followed by a pulseless fourth cardiac arrest. During consultation with her husband, we learned that the patient had experienced tachycardia and had upgraded the dose of her cardiologic treatment. At this point, we developed the hypothesis that a flecainide overdose might be involved. CPR was started, and ABG analysis still showed acidemia (pH of 7.19) and hyperlactatemia (6.73 mmol/l). CPR was continued for 80 min, of which 66 min were conducted with an extra-thoracic compression device until VA-ECMO was initiated. Measured flecainide levels of 1648 ng/ml confirmed the overdose (therapeutic range 0.2–1 μg/ml) [2]. Coronary ischemia was excluded from a coronarographic exam. VA-ECMO was discontinued after 6 days when the patient recovered a rhythm, with an LVEF of 45% and a velocity time integral (VTI) under aorta of 15 cm. At discharge, the patient was able to have a normal life with minor neurologic deficits equivalent to cerebral performance category (CPC) score 1 as categorized by Ajam et al. [3].

The second case concerns a 46-year-old Caucasian male who arrived at the ED a few hours after voluntary ingestion of flecainide. He had a history of paroxystic atrial fibrillation. The exact treatment was unclear but he reported ingesting two tablets, about 40 pills of flecainide 150 mg. At admission, he presented with a blood pressure of 80/40 mmHg and a wide QRS complex tachycardia at 137 beats/min (Fig. 2). ABG revealed hyperlactatemia (4.31 mmol/l) without academia. Despite intensive medical support, the patient's state worsened until he experienced cardiac arrest with ventricular fibrillation. CPR was started and ABG testing during CPR showed a blood pH of 7.17 and a hyperlactatemia (6.29 mmol/l).

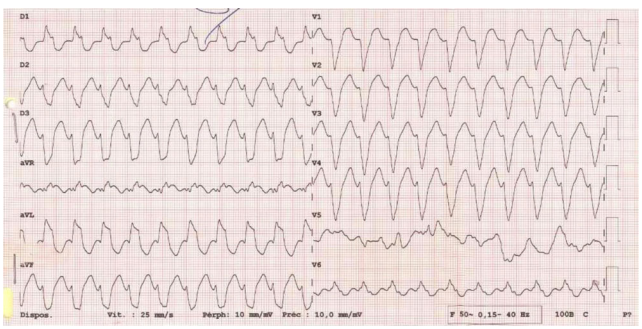

Fig. 1 Admission electrocardiogram — Case 1 shows a wide QRS complex tachycardia according to Brugada criteria [1]

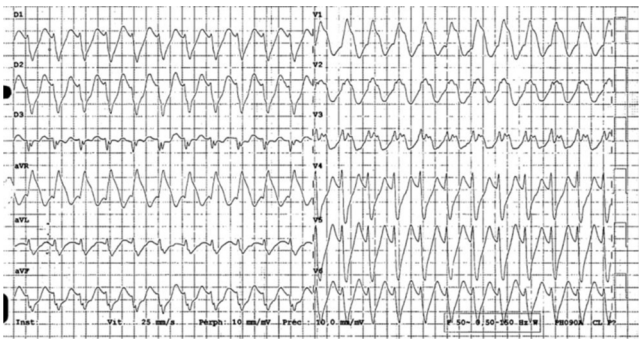

Fig. 2 Admission electrocardiogram — Case 2 shows a wide QRS complex tachycardia according to Brugada criteria [1]

Intra-lipid fat emulsion (IFE) was perfused, and CPR was continued for an additional 25 min, until VA-ECMO placement. VA-ECMO was discontinued after 4 days, when the patient recovered a rhythm, with an LVEF of 50%. At discharge, his CPC-score was 1 [3]. Five years later, the patient is still alive with good cardiac function.

The third case was a 21-year-old North-African woman who arrived in the ED after voluntary ingestion of flecainide. She had no relevant medical history and was not taking any chronic cardiovascular medications. She reported having ingested 20 pills of flecainide (100 mg) with unknown doses of betahistine and amoxicillin. At admission, she presented with a systolic blood pressure of 60 mmHg and a wide QRS complex bradycardia at 60 beats/min (Fig. 3). ABG upon admission revealed acidemia (pH 7.28). Despite intensive medical support and endocavitary cardiac pacing, the patient's state worsened until she experienced cardiac arrest with ventricular fibrillation at 3 h after admission (Fig. 4). CPR was started and continued for 30 min. Flecainide levels of 2,620 ng/ml confirm the overdose (therapeutic range 0.2–1 μg/ml) [2]. A cardiac ultrasound showed that

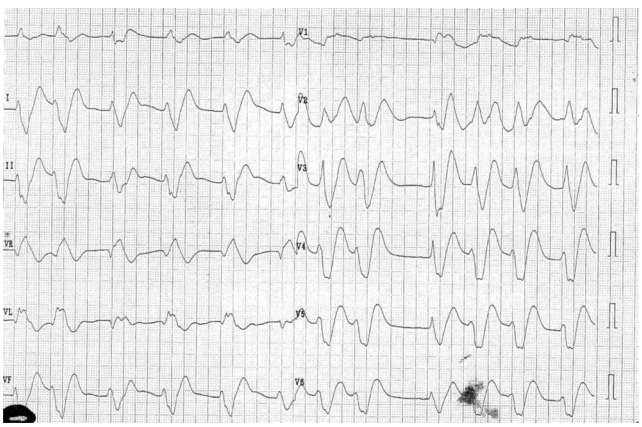

Fig. 3 Admission electrocardiogram — Case 3 shows a ventricular rhythm

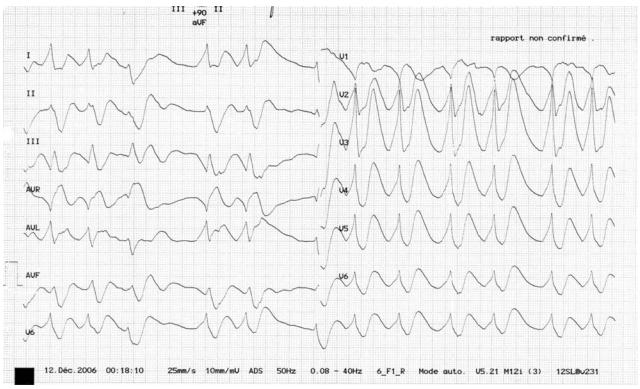

Fig. 4 Cardiac arrest electrocardiogram — Case 3 shows ventricular fibrillation

her LVEF was 15%. Two hours after admission, VA-ECMO was working. VA-ECMO was discontinued after 18 h, when she recovered a rhythm and a normal LVEF. At discharge, her CPC-score was 1 [3]. Thirteen years later, the patient is still alive with good cardiac function.

Discussion

Flecainide acetate is a Vaughan Williams class 1C antiarrhythmic agent. It acts by blocking fast inward sodium channels and is used to prevent tachyarrhythmias. Its plasma half-life is about 20 h and its therapeutic range in plasma is between 0.2 and 1 µg/ml. Flecainide excretion is mainly renal [2]. The major toxicities associated with flecainide are cardiovascular (auriculoventricular block, brady-arrhythmia, ventricular dysrhythmia, and reduced blood pressure), neurological (paresthesia, ataxia, sedation, epilepsy, coma, and respiratory depression), and respiratory (ARDS, intra-alveolar hemorrhage) [4]. Due to its fast inward sodium channels' blocking action, flecainide's "membrane stabilizing action" effect can result in a transient hypokalemia and lactic acidosis that should not be corrected [5]. Patients who are not normally treated with flecainide who have ingested 5.5 mg/kg or more flecainide should be referred for medical assessment [6]. No antidote is available, and there is no known way to accelerate elimination of flecainide from the body [2].

The first-line therapeutic approach is activated charcoal, hemodynamic support with intravenous perfusion, vasopressors, sodium bicarbonate, and cardiac pacing. There is a benefit associated with administration of activated charcoal to decrease the ingested dose, even after an interval of 90 min [7]. In cases involving extended release pills, the charcoal must be repeated. The choice of vasopressor to use depends on the type of shock. Adrenaline and dobutamine are used for cardiogenic shock, while noradrenaline should be used

Table 1 Summary table of pre-existing studies

	Year	Gender	Age	Intoxication kinetics		Co-intoxication	Therapeutics						
							Antidotes			Hemodynamics			
				Taken	Doses		Bicar	IFE	Others	Pacing	Dobu	Noradre	Adre	Others
Yasui et al. [17]	1997	F	20	1X	Blood dose 5.45 µg/ml at 2 h ingestion	Alcohol	NO	NO		YES	NO	NO	NO	
Corkeron et al. [18]	1999	F	20	1X	DSI 3–4 g	Alcohol Paracetamol	YES	NO		YES	NO	NO	YES	
Auzinger and Scheinkestel [19]	2001	M		1X	DSI 6 g–20.520 µg/ml at admission	/	YES	NO		YES	NO	NO	YES	Atropine
Vivien et al. [20]	2010	F		1X	DSI 12 g	Betaxolol	YES	NO		0	YES	NO	YES	Glucagon
Sivalingam et al. [14]	2013	F		1X	Blood dose 4.13 µg/ml	/	YES	YES	Charcoal	NO	NO	NO	NO	
Reynolds et al. [4]	2015	F		1X	11.085 µg/ml at 4 h ingestion	/	YES	NO		YES	NO	NO	YES	$CaCl_2$
Brumfield et al. [13]	2015	F		1X	/	/	YES	YES		NO	NO	NO	NO	

Table 2 Summary table of pre-existing studies

	ECMO				Outcome		Others
	Pre-ECMO resuscitation time	**Support time**	**Decision to stop**	**Complication**	**Living**	**Time of death/ neurologic outcome**	
Yasui et al. [17]	2 h	4 h	Complications	Hemorrhage AKI	NO	87 h post-ingestion	
Corkeron et al. [18]	5 h	30 h	Increase cardiac output ECG normalized	Coagulation disorder AKI Venous Thrombosis Femoral nerve palsy	YES	Good neurologic outcome at 48 h post ECMO	
Auzinger et Scheinkestel [19]	3 h	26 h	Normalization of consciousness Decrease ECMO condition	Coagulation disorder Hemorrhage	YES	Good neurologic outcome	
Vivien et al. [20]	90 min with 20 min of CPR	48 h	Normalised cardiac output ECG normalized	Hemorrhage	NO	3d post-admission brain death	Organ donor
Sivalingam et al. [14]	Unknown, but 10 min of CPR	24 h	/	/	YES	Good neurologic outcome	
Reynolds et al. [4]	50 min of CPR	5d	LVEF	Lodge syndrome	YES	Good neurologic outcome	
Brumfield et al. [13]	10 min of CPR	/	/	/	YES	Good neurologic outcome	

DSI: dose supposed ingested; Bicar: bicarbonate; IFE: Intralipid Fat Emulsion; Dobu: Dobutamine; Noradre: Noradrenaline; Adre: Adrenaline; ECMO: Extra-corporeal Membrane Oxygenation; CPR: cardio-pulmonary ressucitation, AKI: Acute Kidney Injury. Therapeutic range: 0.2–1 µg/ml

for vasoplegic shock [5]. The indication for sodium bicarbonate 8.4% therapy (250 ml + 2 g KCl) has been reviewed by Kit et al. and include cardiac arrest, arrhythmia (excluding torsade de pointe), significant widening of QRS interval, and hypotension refractory to intravenous fluid therapy. The approach when significant widening of QRS duration is over 100 or 160 ms is still debated [8]. Cardiac pacing is helpful with brady-arrhythmia without severe contractility disorder [5].

Second-line therapy includes IFE therapy 20% (1.5 ml/kg bolus followed by 0.2–0.5 ml/kg/h) [9] and VA-ECMO to supplement cardiac function. The exact action of IFE is unclear, but the lipophilic properties of IFE seem to neutralize the flecainide's toxicity [10]. Some cases have been described with different approaches resulting in good outcomes, but these need more investigation to validate their efficacy in this setting [11–15]. In addition, due to its micellar action, blood dose tracking is distorted and the American College of Medical Toxicology recommends IFE when there is hemodynamic instability, but not in cardiac arrest patients [16].

VA-ECMO must be considered in every cardiotropic-intoxicated patient cardiac arrest with minimal no-flow time, and also in patients with refractory shock despite first-line therapy. There is no consensus, but Megarbane et al. proposed a definition in 2009 that includes systolic arterial pressure lower than 90 mmHg despite adequate filling (at minus 1,000 ml), infusion of sodium bicarbonate

molars (at least 375 ml), continuous adrenaline infusion (at least 3 mg/h), and presence of a renal defect defined by oliguria or an elevation of creatinine (greater than 120 mmol/l for males, greater than 90 mmol/l for females) and / or respiratory failure defined by a reported PaO_2/FiO_2 < 150 mmHg [5]. In the current literature, the use of VA-ECMO has been described in seven reports (Tables 1, 2). In the first from Yasui et al. in 1997, VA-ECMO was placed 2 h after reanimation of a refractory cardiogenic choc, and the support was stopped after 10 h because of a hemorrhage. At 72 h, very poor neurologic outcome compelled the discontinuation of therapy [17]. The second case was described by Corkeron et al. 2 years later. VA-ECMO was placed 5 h after reanimation of a refractory cardiogenic choc, and the support was stopped after 30 h with a normal neurological outcome except for a femoral palsy [18]. In the early 2,000 s, Auzinger et al. placed VA-ECMO 3 h after OHCA and VA-ECMO were stopped 26 h after admission with a normal neurological outcome [19]. In 2009, Vivien et al. started VA-ECMO after three cardiac arrests and the support was stopped after 48 h, with good restoration of cardiac function but the patient was in cerebral death [20]. In 2013, Sivalingam et al. described VA-ECMO placement in refractory cardiac shock after an OHCA preceded by CPR for 10 min. VA-ECMO was stopped after 24 h with a CPC score of 1 [14]. Finally, in 2015, Reynolds et al. described the placement of VA-ECMO after 50 min of CPR. VA-ECMO was stopped after 5 days with a good neurologic outcome [4]. Also in 2015, in a case described by Brumfield et al., VA-ECMO was started after three rounds of advanced life support (ALS) and was stopped with a good neurologic outcome [13].

Our first case shows, despite the age of our 71-year-old patient and prolonged CPR, VA-ECMO proved beneficial, with a favorable cardiologic outcome and a preserved neurologic state. This is similar to the case described by Reynolds et al. in which they performed CPR for 50 min. In this case, concurrent medication with a class III anti-arrhythmic (sotalol) and an acute kidney injury (AKI) increased the risk of ventricular rhythm disorder. This serves as a reminder of the importance of asking about other cardiotropic agents that may be treated with specific antidotes (e.g., calcium channel inhibitor, beta-blockers) [5]. Furthermore, although flecainide has a 20-hour half-life in plasma, with chronic intake, some of the flecainide is bound to plasma proteins (blood testing only measures the unbound flecainide), leading to delayed release that extends the duration of supply. We also hypothesize that the prolonged duration of VA-ECMO needed was due to the heart being exhausted by 80 min of CPR.

The second case demonstrates classical intoxication (one drug, one time) with a short duration of CPR, but a prolonged duration of VA-ECMO because of his complications

Table 3 Summary table of three cases

	Gender	Age	Intoxication kinetics		Co-intoxication	ABG admission		ABG CA		Therapeutics			Hemodynamic			Worst ABG during first 24 h	
			Taken	Dose		pH	Lactate (mmol/l)	pH	Lactate (mmol/l)	Bicar	IFE	Antidote	Pacing	Dobu	Nor-adre	Adre	Milri none	pH	Lactate (mmol/l)
Case 1 (2018)	F	71	Chronic with accumulation	Blood dose 1.648 µg/ml at 2 h post-admission	Sotalol	7.24	2.78	6.73	7.19	NO	NO	NO	NO	NO	YES	YES	NO	7.17	8.09
Case 2 (2013)	M	46	1X	DSI 6 g	/	7.42	4.31	6.29	7.17	YES	YES	NO	YES	YES	YES	YES	NO	7.17	6.29
Case 3 (2005)	F	21	1X	DSI 2 g, blood dose 2.620 µg/ml	Betahistine Amoxicillin	7.28	/	/	/	YES	NO	YES	YES	YES	YES	YES	YES	7.06	12.23

Table 4 Summary table of three cases

	ECMO					Duration of stay			Outcome	
	Pre-ECMO resuscitation	**Initial type of ARCA**	**Support time**	**Withdrawal criteria**	**Complication**	**ICU**	**Hospital**	**Living**	**CPC score**	**LVEF**
Case 1 (2018)	80 min CPR	Schockable	6 d	LVEF 45% VTI under aorta of 15 cm	Hemorrage Pneumonia AKI	20	26	YES	1	> 60% at the end of hospitalisation
Case 2 (2013)	5 h with 25 min of CPR	Schockable	4 d	Improvement cardiac index Decrease ECMO condition	Hemorrage AF AKI Pneumonia Thrombosis	60	89	YES	1	55% five years later
Case 3 (2005)	3 h with 30 min of CPR	Schockable	18 h	Improvement cardiac index Decrease ECMO condition	AKI	8	12	YES	1	Normal at the end of hospitalisation

DSI: Dose supposed ingested; CA: Cardiac Arrest; Bicar: Sodium bicarbonate; IFE: Intralipid Fat Emulsion; Dobu: dobutamine; Noradre: noradrenaline; Adre: Adrenaline; ECMO: Extra-corporeal Membrane Oxygenation; CPR: Cardio-pulmonary resucitation; LVEF: Left Ventricular Ejection Fraction; VTI: Velocity Time integral; AKI: Acute Kidney Injury; AF: Atrial Fibrillation; ABG: arterial blood gas. Therapeutic range: 0.2–1 µg/ml

(septicemia, thrombosis, AKI). In contrast, our third case, a young woman with similar intoxication kinetics but without complications, benefitted from a short administration of VA-ECMO with a quick positive outcome.

At this time, extracorporeal support in cases of flecainide intoxication is the only treatment that can relieve acute cardiac dysfunction, preserve blood flow to vital organs, and maintain liver metabolism and renal excretion of the toxin, while waiting for the improvement of cardiac function. Furthermore, even in cases of poor neurological outcome, patients who have been supported by VA-ECMO can be considered for organ transplantation [20].

Our three cases reveal that conventional therapies used to treat flecainide intoxication may fail rapidly. Clinical practice highlights the fact that age, duration of CPR, pH, or lactate levels should not be a hindrance to decision-making with regard to starting VA-ECMO which has been associated with good long-term neurologic and cardiologic outcomes (Table 3, 4). Therefore, we believe that ECMO should be considered early in cardiac arrest, refractory tachy–brady-arrhythmia, insufficient cardiac output (uncontrolled lactic acidosis and low SvO_2), refractory low blood pressure despite maximum inotropic agent therapy, or LVEF < 20% or Aortic VTI < 8 cm/s [21].

Conflicts of interests: the authors have no conflicts of interest to declare.

References

1. Brugada P, Brugada J, Mont L, Smeets J, Andries EW, (1991) A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. Circulation 83: 1649–1659
2. Centre belge d'information pharmacothérapeutique, (2018) Flecainide CBIP. Available at: http://www.cbip.be/fr/keywords/Flecainide?type=trade_family. Accessed July 26, 2018

3. Ajam K, Gold LS, Beck SS, Damon S, Phelps R, Rea TD, (2011) Reliability of the cerebral performance category to classify neurological status among survivors of ventricular fibrillation arrest: a cohort study. Scand J Trauma Resusc Emerg Med 19: 38
4. Reynolds JC, Judge BS, (2015) Successful treatment of flecainide-induced cardiac arrest with extracorporeal membrane oxygenation in the ED. Am J Emerg Med 33: 1542.e1–1542.e2
5. Megarbane B, Deye N, Baud FJ, (2009) Assistance circulatoire périphérique au cours des intoxications aiguës pas cardiotropes. Réanimation 18: 428–438
6. DATATOX – Tox base. Available at: http///www.toxbase.org. Accessed 21 Jan 2019 at 11.13 am (UK time)
7. Nitsch J, Köhler U, Neyses L, Lüderitz B, (1987) Inhibition of flecainide absorption by activated charcoal. Am J Cardiol 60: 753
8. Kit YC, Yin LH, Leung MK, Gay KP, Tak WY, (2009) CASH as a mnemonic for indications of sodium bicarbonate for sodium channel blocker intoxication. Am J Emerg Med 27: 1013–1015
9. Centre antipoison belge, (2018) Centre antipoison — Émulsions lipidiques par voie intraveineuse (ELI) (Intralipid 20%). Available at: https://www.centreantipoisons.be/professionnels-de-la-sant/mulsions-lipidiques-par-voie-intraveineuse-eli-intralipid-20. Accessed July 26, 2018
10. Rothschild L, Bern S, Oswald S, Weinberg G, (2010) Intravenous lipid emulsion in clinical toxicology. Scand J Trauma Resusc Emerg Med 18: 51
11. Mukhtar O, Archer JR, Dargan PI, Wood DM, (2015) Lesson of the month 1: acute flecainide overdose and the potential utility of lipid emulsion therapy. Clin Med (Lond) 15: 301–303
12. Ellsworth H, Stellpflug SJ, Cole JB, Dolan JA, Harris CR, (2013) A life-threatening flecainide overdose treated with intravenous fat emulsion. Pacing Clin Electrophysiol 36: e87–e89
13. Brumfield E, Bernard KRL, Kabrhel C, (2015) Life-threatening flecainide overdose treated with intralipid and extracorporeal membrane oxygenation. Am J Emerg Med 33: 1840.e3–1840.e5
14. Sivalingam SK, Gadiraju VT, Hariharan MV, Atreya AR, Flack JE, Aziz H, (2013) Flecainide toxicity—treatment with intravenous fat emulsion and extra corporeal life support. Acute Card Care 15: 90–92
15. Moussot PE, Marhar F, Minville V, Vallé B, Dehours E, Bounes V, Ducassé JL, (2011) Use of intravenous lipid 20% emulsion for the treatment of a voluntary intoxication of flecainide with refractory shock. Clin Toxicol (Phila) 49: 514
16. American College of Medical Toxicology, (2011) ACMT position statement: interim guidance for the use of lipid resuscitation therapy. J Med Toxicol 7: 81–82
17. Yasui RK, Culclasure TF, Kaufman D, Freed CR, (1997) Flecainide overdose: is cardiopulmonary support the treatment? Ann Emerg Med 29: 680–682
18. Corkeron MA, van Heerden PV, Newman SM, Dusci L, (1999) Extracorporeal circulatory support in near-fatal flecainide overdose. Anaesth Intensive Care 27: 405–408
19. Auzinger GM, Scheinkestel CD, (2001) Successful extracorporeal life support in a case of severe flecainide intoxication. Crit Care Med 29: 887–890
20. Vivien B, Deye N, Mégarbane B, Marx JS, Leprince P, Bonnet N, Roussin F, Jacob L, Pavie A, Baud FJ, Carli P, (2010) Extracorporeal life support in a case of fatal flecainide and betaxolol poisoning allowing successful cardiac allograft. Ann Emerg Med 56: 409–412
21. Combes A, (2019) Critical Care Canada website. Available at: https://criticalcarecanada.com/presentations/2012/an_ecmo_primer.pdf. Accessed January 28, 2019