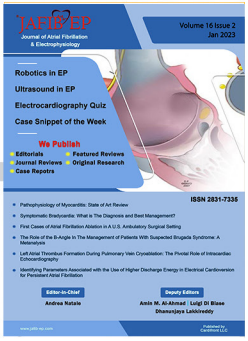
JAFIB EP

Case Report

Journal of Atrial Fibrillation & Electrophysiology



www.jafib-ep.com

Severe Flecainide Toxicity In An Elderly Patient: A Case Report

Carlos Rodríguez-López[1], Oscar González Lorenzo[1], Andrea Kallmeyer Mayor[1], Juan Martínez-Milla[1,2]

[1]Department of Cardiology. Hospital Universitario Fundación Jiménez Díaz. Madrid (Spain)
[2]Centro Nacional de Investigaciones Cardiovasculares (CNIC). Madrid. Spain

Abstract

An 80-year-old female with paroxysmal atrial fibrillation treated with flecainide 100 mg with a "pill-in-the-pocket" approach presented at the emergency department with cranioencephalic trauma and low level of consciousness followed by voluntary flecainide intoxication. The admission ECG revealed atrial fibrillation with ventricular rate of 86 bpm, wide QRS 170 ms complex with right bundle-branch block (RBBB) morphology and rSR' in precordial leads V1 and V2 resembling Brugada type I ECG pattern alternating with idioventricular rhythm with left bundle-branch block wide QRS complex and prolonged QTc interval. The patient developed hemodynamic deterioration and extreme bradycardia. Sodium bicarbonate and 20% lipid emulsion were administered to revert the flecainide effect. While supportive isoprenaline perfusion was started, urgent fluoroscopy-guided transfemoral temporary pacing was also initiated but unable to capture. Finally, the patient died despite advanced cardiopulmonary resuscitation.

Case Report

Introduction

Flecainide is a commonly used IC class antidysrhythmic with narrow therapeutic index which is indicated for rhythm control in patients with atrial fibrillation and other supraventricular or ventricular arrhythmias. It is a generally safe drug, however, the prescription must be especially careful in elderly patients or when potential drug interactions are expected. In cases of toxicity, patients may develop rhythm disturbances which might be potentially harmful and challenging to manage. Here we report a case of severe flecainide toxicity in an elderly patient and a review of the clinical presentation, electrocardiographic findings and possible therapeutic approaches.

Case presentation

We present the case of an 80-year-old female with paroxysmal atrial fibrillation treated with flecainide 100 mg with a "pill-in-the-pocket" approach and major depression disorder managed with sertraline 100 mg daily and trazodone 50 mg daily. She was found at her home lying on the floor with signs of cranioencephalic trauma. She was transferred to the emergency department with low level of consciousness and hypotension with blood pressure of 86/54 mmHg. The electrocardiogram (ECG) of admission showed atrial fibrillation with ventricular rate of 86 bpm, wide QRS 170 ms complex with right bundle-branch block (RBBB) morphology and rSR'in precordial leads V1 and V2 resembling Brugada type I ECG pattern (Figure 1B).

The patient was pale and presented profuse sweats, low level of consciousness and tachypnea despite a basal blood oxygen saturation of 94%. While blood samples extraction, a drastic change in the morphology and width of the QRS was observed on the monitor. This time, the ECG showed idioventricular rhythm with a heart rate of 72 bpm, a very wide QRS 206 ms with left bundle-branch block (LBBB) morphology and a corrected QT interval of 710 ms (Figure 1A). Any abnormalities were noticed in previous ECGs (Figure 1C). From that moment on, the patient presented constant changes in width and morphology of the QRS.

Chest X-ray did not show any relevant abnormalities and a cranial computerized tomography did not reveal signs of acute intracranial complication.

An echocardiogram was performed, but no structural or functional abnormalities were observed. Coronary anatomy was not assessed.

The patient presented no abnormalities in the hemogram. She had a preserved renal function with creatinine of 0.7 mg/dl (0.51-0.95 mg/dl) and estimated glomerular filtration rate of 81 ml/min-1/1.73 m2. Potassium levels were 4.2 mmol/l (3.5-5.1 mmol/l) which discarded hyperpotassemia as the etiology of the case. The venous gasometry revealed metabolic acidosis with pH 7.29 (7.35-7.45), pCO2 42 mmHg (35-45 mmHg), bicarbonate 20.2 mmol/L (22-28 mmol/L) and high levels of lactate 3.20 mmol/L (0.5-2.2 mmol/L). Troponin I was 0.02 ng/dl (<0.08 ng/dl), negative as the rest of myocardial damage markers.

Key Words

Electrocardiogram, Atrial Fibrillation, Lipid Emulsion, Toxicity, Flecainide

Corresponding Author
Carlos Rodríguez-López, M.D.
Hospital Universitario Fundación Jiménez Díaz.
Av. de los Reyes Católicos, 2, 28040 Madrid, Spain

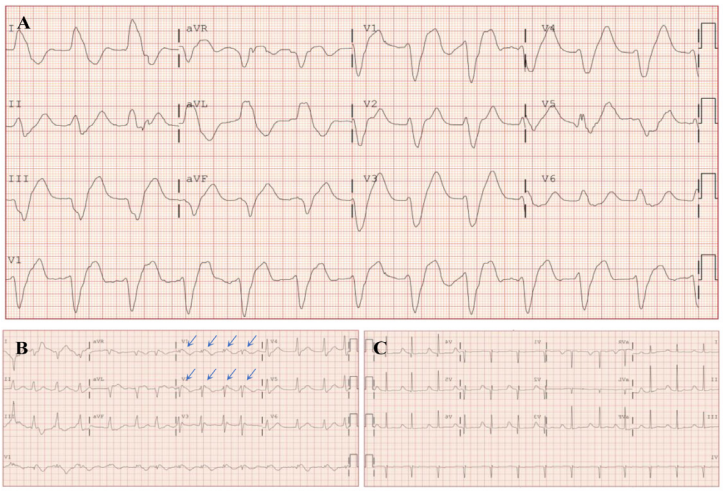


Figure 1: **(A) ECG at admission showing idioventricular rhythm with heart rate of 72 beats per minute (bpm) with wide QRS 206 ms and left bundle-branch-block (LBBB) morphology and QTc 710 ms. (B) ECG at admission, showing atrial fibrillation with ventricular rate of bpm, wide QRS 170 ms with RBBB and rSR' morphology in V1 and V2 resembling type I Brugada syndrome ECG pattern (blue arrows). (C) Previous ECG, sinus rhythm and narrow QRS.**

Urine test for toxics resulted negative and ethanol levels were slightly elevated 12 mg/dl (<10 mg/dl).

Consequently, fluid therapy was initiated to maintain blood pressure. After that, the patient confirmed that she had ingested more than ten pills of flecainide (which means more than 1000 mg of flecainide) and several tablets of trazodone. Therefore, we suspected flecainide toxicity in the context of a probable intended suicidal overdose as primary etiology of the case, despite determination of flecainide blood levels was not available.

Then, she was admitted to the acute cardiovascular care unit presenting hemodynamic instability requiring vasoactive drug support with norepinephrine. Administration of oral activated carbon was considered, but the ingestion took place more than 6 hours ago, so this strategy was considered futile.

Soon after, the patient developed progressive refractory hemodynamic deterioration. Administration of 250 ml of intravenous (IV) sodium bicarbonate 1/6 M perfusion and IV 20% lipid emulsion with initial bolus of 1.5 m l/kg followed by 15 ml/kg/h perfusion for 20 minutes, which have been pointed as potentially beneficial strategies, was initiated [1,2]. An urgent fluoroscopy-guided transfemoral transient pacemaker was placed due to 35 bpm bradycardia but it was unable to capture regardless maximum output settings, well positioning and correction of metabolic acidosis (Figure 2), a phenomenon that has only been previously reported a few times in the literature [3,4]. Meanwhile, supportive isoprenaline perfusion was initiated. In the following hours, she required orotracheal intubation. Extracorporeal membrane oxygenation (ECMO) was considered [2,5] but finally discarded due to frailty of the patient. After 6 hours of hospitalization, the patient suffered cardiac arrest and after 25 minutes of advanced cardiopulmonary resuscitation, she died.

Discussion

We report a severe case of flecainide toxicity, which is an uncommon situation but with highly relevant complications, especially in elderly patients. With this case, we aim to emphasize early recognition of flecainide toxicity electrocardiographic signs of flecainide toxicity and to review potentially beneficial therapeutic strategies, as well as the need of caution when prescribing flecainide in elderly patients, particularly if they present comorbidities or possible pharmacological interactions.

Flecainide is a class IC lipophilic antidysrhythmic with narrow therapeutic index (200-800 µg/L) and 12-30 hours half-life, which mainly blocks sodium channels affecting the phase 0 of the action potential, prolonging the PR, QRS, and QTc interval. This drug has also negative inotropic effect due to antagonism on calcium channels [1]. It is mainly used in patients without structural heart disease for rhythm control strategy in atrial fibrillation and to treat other supraventricular and ventricular arrythmias[6]. Whereas there are no stablished contraindications, it must be used with caution in elderly patients, reserving it for specific situations such as intolerance or failure of other antidysrhythmic drugs or very symptomatic paroxysmal episodes of atrial fibrillation, as this patient had. Flecainide is mainly metabolized in the liver by cytochrome P450 2D6 isoenzyme and mostly eliminated by renal excretion. Consequently, the concomitant use of drugs which share the same metabolic pathway (such as selective serotonin reuptake inhibitors like sertraline or benzodiazepines like trazodone) as well as conditions that impair renal clearance might lead to an increase of flecainide systemic effect [7].

In cases of overdose, patients may present bradycardia, wide QRS complex tachycardia and ventricular fibrillation [1]. It has also been described Brugada type I ECG pattern in patients without channelopathy with flecainide supratherapeutic blood levels [8]. This ECG pattern might be explained by the blockade of sodium channels produced by flecainide, which are also the ones that are congenitally affected in the Brugada syndrome. Moreover, flecainide toxicity might set as supraventricular tachycardia with very wide QRS with LBBB or RBBB morphology. According to a systematic review, if QRS is less than 200 ms it is more likely to manifest as RBBB and shorter QTc interval (Figure 1B) while if it is over 200 ms, QRS usually has a LBBB morphology, loss of P waves and longer QTc interval, which perfectly fits our patient electrocardiograms. Additionally, longer QRS complexes have been related with requirement of mechanical circulatory support and mortality [9]

There is no specific treatment or antidote for flecainide toxicity, but several strategies have been proposed as potentially beneficial, added to mechanical hemodynamic and ventilatory support, as well as correcting electrolyte imbalance [5]. However, the evidence to support these therapies remain to be scarce and is based on animal models and case reports. Firstly, sodium bicarbonate leads to a serum alkalinization and elevation of sodium concentration which might interfere the sodium channel blockade effect of flecainide. According to this, a pH target of 7.5 has been proposed [3].On the other hand, the use of intravenous lipid emulsion perfusion is based on the "lipid-sink theory" favouring the redistribution of the lipophilic drug into the intravascular lipid phase. It is believed that a 20% lipid emulsion infusion might also participate as a metabolic stimulator of the myocyte,

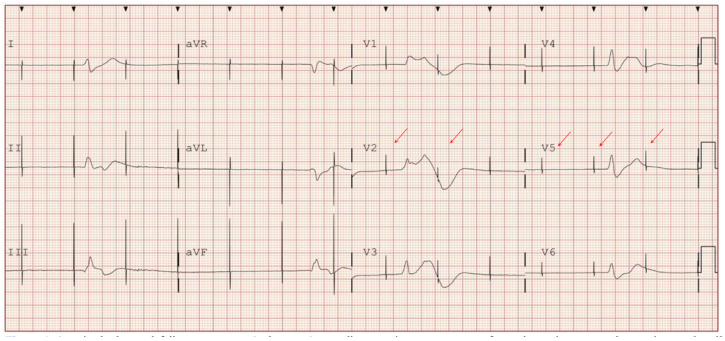


Figure 2: **Agonic rhythm and failure to capture (red arrows) regardless maximum output of fluoroscopy-guided transfemoral temporary pacemaker settings and well positioning.**

opening the calcium channels increasing cardiomyocyte contractility and reducing the sodium channel blockade [3,10]. More research is needed to support the efficacy of these strategies as inconclusive results have been observed in animal models [10], but case reports provide several successful experiences with them [11,12].

In conclusion, flecainide is a frequently used drug for atrial fibrillation rhythm control but in case of toxicity it can lead to severe complication with scarce evidence to guide its management. Therefore, flecainide must be cautiously used in patients with comorbidities or with possible pharmacological interactions.

Acknowledgements

This work would not have been developed without the invaluable work of our beloved Juan Martínez Milla M.D PhD, who passed away unexpectedly at the age of 33 years old. His memory as a brilliant cardiologist and a formidable person will endure in the hearts and souls of his relatives, friends, and colleagues. Rest in peace.

Funding

This work received no specific funding from any entity.

Disclosures

All authors have no relationships with industry and other entities relevant to the content of this article to disclose.

References

1. Goldfrank LR, Hoffman RS. Goldfrank's manual of toxicologic emergencies. 11th ed. New York: McGraw-Hill Medical; 2007. 1126 p..
2. Ghataoura R, Patil S. Flecainide toxicity: a presentation to the emergency department with literature review. BMJ Case Rep 2020;13(2):e232691..
3. Heldens M, van der Nat G a. M, Melman PG. Renal failure, shock, and loss of pacemaker capture: A case of flecainide intoxication. Neth J Med 2019;77(5):189-92.
4. Rivner H, Lambrakos LK. Flecainide Toxicity Leading to Loss of Pacemaker Capture and Cardiac Arrest. JACC Case Rep 2021;3(4):586-90.
5. Sivalingam SK, Gadiraju VT, Hariharan MV, Atreya AR, Flack JE, Aziz H. Flecainide toxicity—treatment with intravenous fat emulsion and extra corporeal life support. Acute Cardiac Care 2013;15(4):91-2.
6. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). European Heart Journal. 2020;41(5):655-720.
7. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2021;42(5):373-498.
8. Reiffel JA. Does a Brugada Pattern ECG Precipitated by Excessive-Dose Flecainide Provide a Diagnosis of a Brugada Syndrome Patient and/or Contraindicate Its Use?: A Case Study. Circ: Arrhythmia and Electrophysiology 2011;4(4).
9. Valentino MA, Panakos A, Ragupathi L, Williams J, Pavri BB. Flecainide Toxicity: A Case Report and Systematic Review of its Electrocardiographic Patterns and Management. Cardiovasc Toxicol 2017;17(3):260-6.
10. Cave G, Harvey M, Quinn P, Heys D. Hypertonic sodium bicarbonate versus intravenous lipid emulsion in a rabbit model of intravenous flecainide toxicity: no difference, no sink. Clinical Toxicology 2013;51(5):394-7.
11. Ellsworth H, Stellpflug SJ, Cole JB, Dolan JA, Harris CR. A life-threatening flecainide overdose treated with intravenous fat emulsion. Pacing Clin Electrophysiol. 2013;36(3):e87-89.
12. Mullins ME, Miller SN, Nall CE, Meggs WJ. Intravenous lipid emulsion therapy for flecainide toxicity. Toxicology Communications 2017;1(1):34-6.