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CASE REPORT
Electrophysiology

Autolytic attempt mimicking Brugada type 1 electrocardiogram pattern due to flecainide toxicity. A case report

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Background Brugada phenocopies are a group of heterogeneous disorders that mimic Brugada syndrome (BrS) electrocardiogram (ECG) changes elicited by reversible clinical conditions. We report a novel case on flecainide toxicity causing an ECG signature of Brugada type 1 pattern in the paediatric age.

Case summary A 13-year-old Caucasian boy with untreated attention-deficit/hyperactivity disorder referred to the Pediatric Emergency Department (PED) after unknown antiarrhythmic drug overdose. He deliberately ingested 10 tablets from a labelled white box of a 100-mg single dose. The ECG showed a coved-type ST-segment elevation in right precordial leads and prolongation of PR segment with a QTc limit interval. Values of troponins gradually increased and echocardiogram was normal. The altered ECG pattern was explained by the stabilizing membrane effect of flecainide involving the inhibition of rapid Na^+ channels. After offending drug removal, regression of ECG changes was observed and no cardiac events were documented during follow-up.

Discussion Flecainide-induced Brugada type 1 ECG pattern may occur in patients with no evidence of genetic susceptibility receiving a toxic dosage of this drug. With increasing dose, its action on conduction pathways manifests as prolongation of PR interval and QT and QRS complex duration and may cause BrS mimicry. A detailed clinical history considering symptoms and ECG findings may support early-raised suspicion for flecainide ingestion. The therapeutic approach implies primary detoxification, prevention of potential triggers, and management of eventual cardiotoxicity events. Finally, risk stratification for BrS should be always measured according to the clinical scenario and surveillance considered in a timely manner.

Keywords Flecainide intoxication • Brugada type 1 pattern • Brugada • Fast sodium inward current • Cardiac arrhythmias • Case report

ESC curriculum 5.8 Cardiac ion channel dysfunction • 5.2 Transient loss of consciousness

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Learning points

- Flecainide-induced Brugada pattern can be generally seen at standard therapeutic dose, and such patients may have a genetic cause (underlying sodium channel defect). However, it could also occur *de novo* even in patients with no genetic susceptibility receiving a toxic dosage of this drug.
- Flecainide produces a dose-dependent decrease in intracardiac conduction, manifested by prolongation of PR interval, the QRS complex duration, and some QT prolongation that may lead to ventricular arrhythmias.
- A detailed clinical history and high index of suspicion for flecainide are important, although we should always consider risk factors for Brugada syndrome and assure normalization of the electrocardiogram after withdrawal of the antiarrhythmic drug.
- Flecainide toxicity lacks standardized treatment protocol. Appropriate acute management includes primary detoxification, prevention of potential triggers, and management of eventual cardiotoxicity events.

Introduction

Brugada syndrome (BrS) is a genetic disorder described as an aberrant pattern of coved-type rectilinear-sloping ST-segment in right precordial leads (V1 and V2) with a high incidence of sudden cardiac death (SCD) in patients without structural heart disease.[1] Nevertheless, electrocardiographic abnormalities may not be always supported by a genetically cardiac inherited condition and it is mandatory to exclude other conditions that may explain the type 1 pattern, so-called phenocopies.[2] Flecainide is an oral class Ic antiarrhythmic drug that counteracts with fast-inward Na^+ channels generating a prolonged atrial effective refractory period and depressed cardiac action potential upstroke.[3] With increasing dose, flecainide's action on conduction pathways is manifested on electrocardiogram (ECG) as increased PR interval and QT and QRS complex duration. As far as toxicity threshold is concerned, it is suggested with a 50% increase in QRS duration or 30% prolongation in PR interval. Treatment of flecainide overdose includes consideration of activated charcoal in the early course of ingestion, sodium bicarbonate, inotropic agents if hypotension occurs, and transthoracic or transvenous pacing.[4]

This novel paediatric case report illustrates the importance of prompt symptoms recognition and early-raised suspicion of flecainide-induced mechanism on the grounds of a careful clinical history and distinctive Brugada type 1 ECG pattern.

Summary figure

24 March 2022 (6 p.m.)	Our patient presented to PED with malaise and dizziness after ingestion of an unknown drug with cardiac tropism. Electrocardiogram showed coved-type ST-segment in V1–V2 leads in conjunction with a first-degree atrioventricular node block.
24 March 2022 (6:30 p.m.)	First approach included administration of activated charcoal. Electrolytes, cardiac enzymes, urine analysis, and chest X-ray were performed. Given the changes recorded in the ECG and clinical history that raised suspicion of flecainide ingestion, he underwent admission to Intensive Care Unit (ICU).
24 March 2022 (7:15 p.m.)	Center of Toxicology was contacted, reporting that flecainide reaches its plasma levels at 3–4 h of ingestion with a half-life of 20 h. A cardiological evaluation was completed with no relevant findings. Monitoring of renal function, hepatic enzymes and electrolytes was performed according to its pharmacokinetics.
24 March 2022 (11 p.m.)	Echocardiography showed functionally and structurally normal heart. Maximum peak of troponin I (hsTnI) was documented after 5 h of drug ingestion (23 ng/L) and no arrhythmic events were witnessed.
25 March 2022 (9 p.m.)	The ECG showed normalization of the repolarization pattern. Values of troponins stabilize after 18 h of ingestion (5 ng/L). Reassessment of blood tests did not show relevant changes.
25 March 2022 (12 p.m. onwards)	On admission to ward, he was haemodynamically monitored showing stable vital signs. Evaluation by the psychiatrist for the autolytic attempt was undertaken concluding his untreated attention-deficit/hyperactivity disorder (ADHD) to have precipitated this event and no evidence of suicidal ideation was found.
26 March 2022	The patient was finally discharged from the hospital after regression of ECG changes and measurement of risk stratification for BrS. He was not put under any psychiatric medication aside from his recommendation to adhere to methylphenidate.

Case summary

A 13-year-old Caucasian boy was referred to our PED after ingesting an unidentified antiarrhythmic drug. As per family reasoning, it was said that he deliberately ingested 10 tablets from a labelled white box of 100 mg single dose, which makes a total sum of 1 g of this compound. He was under follow-up because of ADHD with suboptimal adherence to methylphenidate. He had no previous cardiac condition and there was no evidence of family history regarding cardiac diseases.

After drug intake, he was found to be with paleness and dizziness. When arriving at the hospital, he was breathing on air (SatO2 100%) with normal blood pressure values (111/73 mmHg) and glucose levels showed 112 mg/dL (normal values 74–100 mg/dL). His body weight was 45 kg. Pulses were firm and rapid, and slight distal tremor was observed without any other remarkable findings. The first ECG (30 min after drug ingestion) performed showed a sinus rate of

75 beats/min with Brugada type 1 ECG pattern consisting of incomplete right bundle branch block and coved-type ST-segment elevation (>2 mm) in V1–V2 leads. A first-degree atrioventricular node block was also observed estimating a PR interval of 280 ms (*Figure 1A*). The QRS and QTc intervals were 120 and 450 ms, respectively.

While in the emergency monitoring room, a detailed clinical history taking into account drugs that may cause ST elevation supported by the colour and the labelling of the drug box the family patient referred, enabled us to figure out the ingestion of flecainide. Initially, activated charcoal was rapidly administered. There were no electrolyte disorders. No toxic substances were found in the urine analysis. Chest X-ray performed was normal. Liver enzymes showed serum alanine aminotransferase (ALT) 43 U/L (normal values 10–45 U/L). Troponin course was evaluated reaching its maximum peak after 6 h (23 ng/L, normal values 0–11.6 ng/L). An echocardiogram showed structurally and functionally normal heart.

During stay at ICU, the patient was haemodynamically stable showing no arrhythmic events. Monitoring of renal and hepatic function did not show any progression. Prior to discharge, values of troponins stabilized and his ECG normalized (*Figure 1B*). Finally, he was evaluated by the psychiatrist for the autolytic attempt. There was no evidence of suicidal ideation and his untreated ADHD was responsible for having precipitated this impulsive behaviour. In this line, there was no need for psychotropic medication, although the patient was recommended to strictly adhere to his previous medication (methylphenidate).

Discussion

Brugada phenocopies (BrPs) include a variety of clinical conditions that can induce a Brugada type 1 ECG pattern indistinguishable from a true BrS but in the absence of a genetic condition. Some of the criteria used to define this condition include (i) presence of Brugada type 1 ECG changes, (ii) an underlying identifiable source and the disappearance of the aforesaid ECG pattern once the cause is corrected, and (iii) low probability of BrS because of no symptoms and negative clinical and family history.[5] Our case represents an induction of the Brugada type 1 ECG pattern due to flecainide toxicity with resolution after discontinuation of the drug in a patient with no apparent risk factors for BrS and no cardiac symptoms. To our knowledge, few case reports on this drug toxicity have been published especially occurring in paediatric patients.[6]

Flecainide, an orally administered class Ic antiarrhythmic drug, which acts as a potent sodium channel blocker, may alter the excitability and intracardiac conduction velocity and takes a patent action at the level of the His-Purkinke system.[3] Its overdose causes slow down conduction in all cardiac fibres including the atrium, the conduction pathway, and the ventricles prolonging PR, QRS, and QT intervals. Consequently, this may develop atrial nodal block and predisposition to suffer ventricular arrhythmias that could degenerate in ventricular fibrillation and SCD.[7,8] Intoxication by this drug is said to be rare but evident because of its narrow therapeutic window, with an estimated mortality rate of 22.5% due to cardiac arrhythmias.[6] Our patient's ECG meets the criteria to

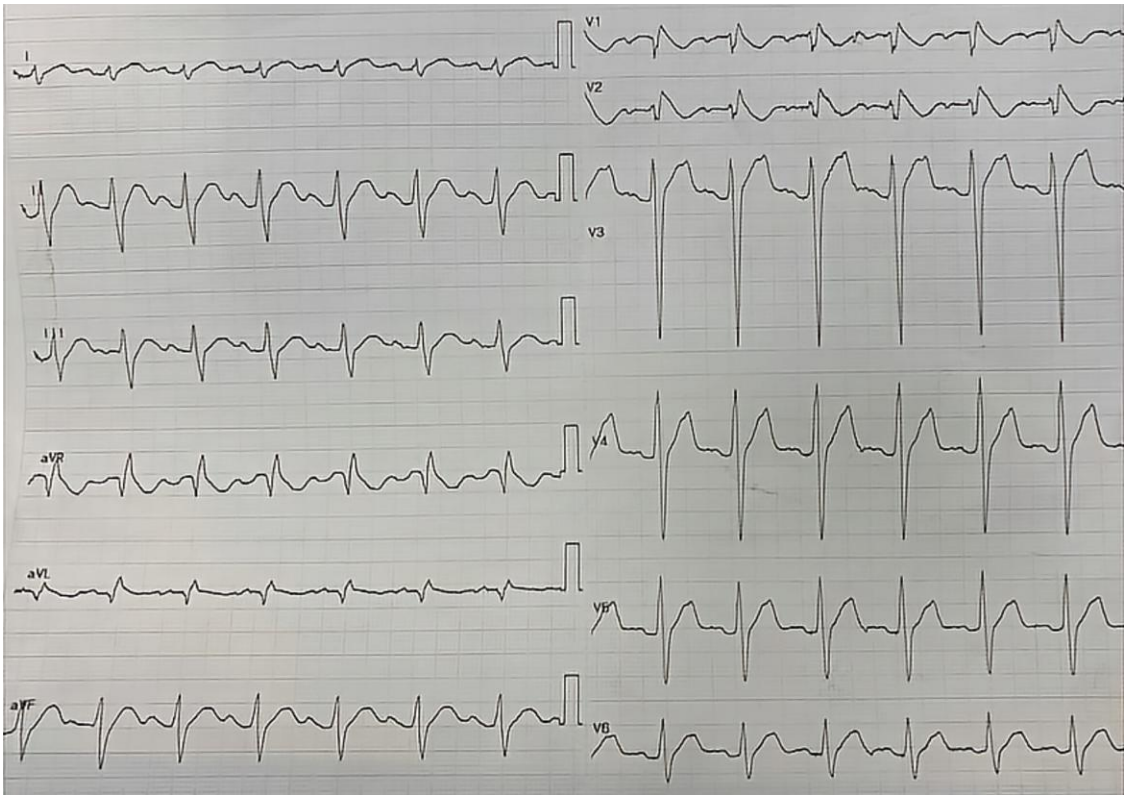


Figure 1 (*A*) Electrocardiogram on initial admission demonstrating an apparent first atrioventricular (AV) nodal block [PR interval (280 ms)] and a right bundle branch block (RBBB) morphology, coved-type ST-segment elevation with T-wave inversion in leads V1 and V2 (Brugada type 1 pattern). Beta angle for the patient at admission electrocardiogram (ECG) showed an estimated 60° measurement. AV, atrioventricular; RBBB, right bundle branch block; ECG, electrocardiogram. (*B*) ECG prior to hospital discharge showing resolution of Brugada pattern with incomplete right bundle branch block (RBBB) persistence. Beta angle showing an estimated 25° measurement. RBBB, right bundle branch block.

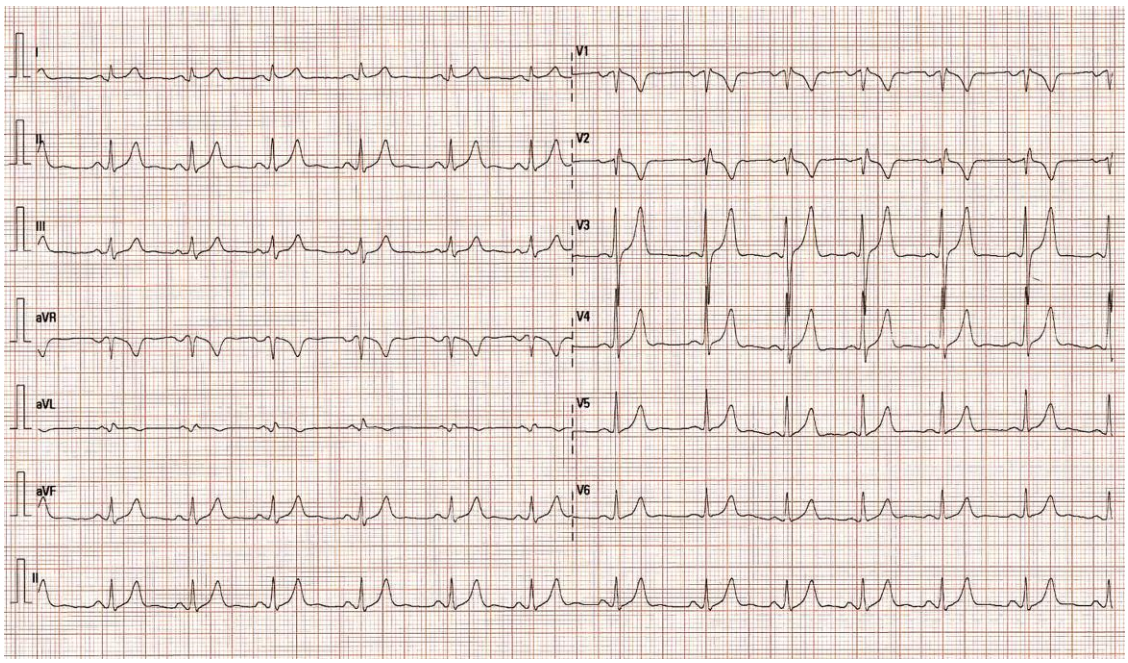


Figure 1 Continued

catalogue a flecainide intoxication (30% prolongation in PR interval with an estimating PR interval of 280 ms[4] showing a 'coved-type' ST-segment elevation in right precordial leads). Prior to discharge, we observed regression of ECG changes and no cardiac events were registered either at ICU or at the paediatric ward.

Diagnosis of Brugada ECG type 1 pattern due to flecainide intoxication should be based on a careful clinical history that identifies the causal drug and may be supported by non-specific symptoms (malaise, nausea, and vomiting) that manifest after ingestion and could play a role in the early self-detoxification phase.[7] Thereby, in our patient, ingestion of flecainide was explained on the grounds of antiarrhythmic drug exposure causing ST elevation and supported by the colour and the labelling of the drug box the family referred. Clinical history did not find any previous unexplained cardiac arrest, syncope, previous ventricular ectopic heart beats, or any episode of arrhythmias. As far as family history is concerned, there was neither any first or second degree relative with definite or suspected BrS nor any related genetic abnormalities. No episodes of SCD were encountered within the family tree whatsoever.

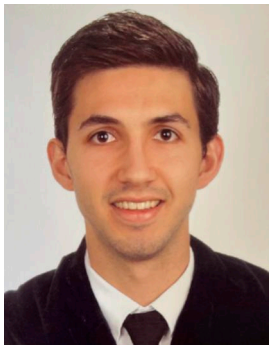
Since a definite treatment is not available for intoxications with antiarrhythmic drugs of class Ic, the therapeutic attitude implies early diagnosis, primary detoxification, prevention of potential triggers that could induce elevation of the ST-segment, and management of cardiotoxicity events. In this patient, isolated administration of activated charcoal was given because of short time interval after ingestion and related symptoms compatible to ingestion of flecainide. Nonetheless, treatment with hypertonic sodium bicarbonate has been partially used in isolated cases of flecainide intoxication, being effective in reducing the duration of the QRS interval and transient improvement of blood preassure.[9] The mainstay of this medical therapy has been the use of high-dose sodium bicarbonate based on the increase in extracellular sodium concentration to offset the cardiotoxic effects. Given the clinical response of the patient in the absence of arrhythmias, as well as its scarce evidence in the paediatric population, we did not consider this approach.

Class Ic antiarrhythmic drugs such as flecainide may be responsible for mimicking BrS, and therefore, risk stratification for BrS should be always considered.[10] Taking into consideration a negative family history (no definite or suspected BrS up to second degree relatives) and no cardiac events or genetic predisposition documented, we could possibly address low probability for BrS. In this sense, surveillance should be recommended and evaluation of complementary tests should be considered in a timely manner according to the clinical scenario.

Conclusion

The BrPs are a group of heterogeneous disorders that simulate BrS syndrome ECG changes. Class Ic antiarrhythmic drugs such as flecainide may be responsible for mimicking BrS in patients with no genetic susceptibility receiving a toxic dose of this drug. The main approach should always include measuring risk factors for BrS and assure normalization of the ECG after withdrawal of the antiarrhythmic drug.

Lead author biography



As a potential paediatric cardiologist, my main area of research has been enthusiastically focused on the field of prevention of cardiovascular disorders, including the study, diagnosis and treatment of major inherited cardiovascular diseases in paediatrics. This background has been fully complemented by a deep interest in clinics hoping to integrate clinical experience with knowledge to focus on risk stratification and sudden cardiac death in childhood.

Consent: The authors declare that written consent was acquired from the patient for the submission and publishing of this case report,

including images and textual content; in accordance with COPE guidelines.

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Data availability

The data used to support the findings of this case report are included within this manuscript.

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