Single Oral Flecainide Dose to Unmask Type 1 Brugada Syndrome Electrocardiographic Pattern

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Background: Brugada syndrome (BrS) includes a group of patients with a typical pattern of ST segment elevation in right precordial leads who are at risk for sudden cardiac death. The electrocardiogram pattern may be intermittent and unmasked by sodium channel blockers. The main objective of this study is to describe a serie of consecutive patients in whom oral administration of flecainide was used to unmask BrS type I electrocardiographic pattern.

Methods: We prospectively studied 14 symptomatic (palpitations/syncope) patients referred to our laboratory presenting a suggestive but not diagnostic Brugada ECG or family history of sudden death. Single oral dose of flecainide 400 mg was administered. Resting 12-lead ECG with upper and standard right precordial leads were performed after flecainide administration at 15, 30, 60 and 90 min and hourly until ECG became normal.

Results: Median age was 37.5 years (range = 22–50). None of them had structural heart disease. In 7 patients (50%) the typical coved-type ECG pattern of BrS was unmasked. PR interval, QRS duration and QTc median difference after-before test was 20 msec (min–max = –17–+57), 21 ms (min–max = 0 to +59) and 20 ms (min–max = –11–+77), respectively. There were no episodes of AV block, atrial or ventricular tachyarrhythmia.

Conclusions: In our experience we found that oral administration of flecainide in a single dose of 400 mg is useful to unmask type 1 Brugada electrocardiographic pattern.

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Brugada syndrome (BrS) is a heterogeneous genetic disease that predisposes to life-threatening ventricular tachyarrhythmia and sudden cardiac death (SCD). This condition is genetically transmitted as an autosomal dominant syndrome with incomplete penetrance and it is responsible for 20% of all sudden deaths in those without structural heart disease. A characteristic Brugada-type electrocardiogram (ECG) that consists of a coved type ST segment elevation in the precordial leads V_1 to V_3 usually identifies the syndrome. Unfortunately affected individuals may have a normal ECG or an abnormal ECG but not diagnostic, the so called type II and type III Brugada pattern. Those

dynamic ECG changes make more difficult the diagnosis. Class-I antiarrhythmic drug (AAD) test is used to unmask the diagnostic coved-type ECG pattern. Intravenous ajmaline, procainamide, flecainide and pilsicainide have been used diagnostically to induce the Brugada pattern in patients with known or suspected disease.^{1,2}

Our laboratory does not have intravenous flecainide, ajmaline or procainamide available to us, and for that reason, we started working with flecainide orally.

The aim of this study was to describe and analyze a serie of consecutive patients with suspected BrS, but not spontaneous coved-type ECG (type 1) in

whom a class-I AAD test (flecainide PO) was used to unmask the disease.³

Management of asymptomatic patients is controversial and risk stratification is required,⁴ for that reason an electrophysiological study (EPS) was performed to positive flecainide test, despite its controversial use. We also performed an EPS in most of the negative flecainide test patients as a part of the evaluation for syncope, familiar SCD, etc.

As far as we know, this is the first study that evaluates orally flecainide for this test in a suspected BrS population.

METHODS

Patients were included if they had a suspected BrS because of one or a combination of the following; arrhythmia related symptoms such as syncope or palpitations, a suggestive but not diagnostic Brugada ECG pattern and/or family history of SCD or BrS. A signed informed consent was obtained from each patient at the time of enrolment.

STUDY PROTOCOL

A systematic diagnostic strategy was designed consisted of an acute drug testing with oral flecainide. Single oral dose of flecainide 400 mg was administered in-hospital. Resting 12-lead ECG with upper and standard right precordial leads (V_1 and V_2 in 2nd and 3rd intercostal spaces) were performed after flecainide administration at 15, 30, 60, 90 min and hourly until ECG became normal. The test was closely monitored with a continuous ECG monitoring for a 24 hours period, and performed in a setting that was fully equipped for cardiopulmonary resuscitation.

Positive flecainide test patients were evaluated with an EPS to determine ventricular vulnerability. A protocol involving up to 3 extra stimuli was applied to the right ventricular apex at cycle lengths ≥ 200 msec. If not inducible sustained ventricular arrhythmia (ventricular fibrillation/ventricular tachycardia; VF/VT) from the right ventricular apex, then stimulation was applied to the right ventricular outflow tract (RVOT). Almost all patients with negative flecainide test were evaluated with an EPS as part of their evaluation for syncope, familiar SCD, etc.

DIAGNOSTIC CRITERIA

According with the Report of the Second Consensus Conference of BrS¹ a positive acute drug testing was diagnosed in the presence of a type 1 ECG Brugada pattern characterized by a coved ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave in > 1 right precordial lead (V_1 to V_3). Vulnerability was considered positive in presence of sustained ventricular arrhythmia (VF/VT) during ventricular extra-stimuli test.

STATISTICAL ANALYSIS

Categorical Data are Presented as Number and Percentage.

Continuous data are presented as median, minimum, maximum and interquartile range [25–75 percentiles]. Wilcoxon test was used to compare ECG measures before and after flecainide test. A value of $P < 0.05$ was considered significant.

OBJECTIVES

The main objective was to describe a series of consecutive patients in whom oral flecainide (400 mg) was administered to unmask BrS type I electrocardiographic pattern.

RESULTS

Fourteen patients were included between June 2009 and July 2011, 11 men (78.5%) and median age was 35.2 years (min-max = 21–50). None of them had structural heart disease by Doppler echocardiogram.

Patients were referred to our laboratory for having one or a combination of the following; arrhythmia related symptoms such as syncope ($n = 5$) or palpitations ($n = 3$), a suggestive but not diagnostic Brugada ECG pattern ($n = 12$) and/or family history of SCD or BrS ($n = 6$) (see Table 1).

ACUTE DRUG TESTING

Oral flecainide test with 400 mg was performed to all the patients included in the study ($n = 14$). In 7 patients (50%) the typical coved-type ECG pattern of BrS was unmasked (Fig. 1). In all the cases the diagnostic pattern appeared close to the maximum flecainide effect (2–4 hours).^{5,6}

Table 1. Patients Clinical Characteristics

Case	Age (years)	Symptoms	Family history	Basal ECG	Flecainide test	VF/VT inducibility
1	22	No	No	Type II	Negative	Negative
2	43	Syncope	No	Type II	Positive	Negative
3	31	No	Yes (father with BrS)	Type II (Type I with fever)	Positive	Negative
4	45	No	Yes (brother SCD)	Type II	Positive	Positive
5	37	No	Yes (brother SCD)	Normal	Negative	Negative
6	26	No	No	Type II	Negative	Negative
7	50	Palpitations	No	Type II	Positive	Negative
8	40	No	Yes (2 sisters-SCD)	Type II	Positive	Negative
9	29	Syncope	No	Type II	Negative	Positive
10	38	Syncope	Yes (cousin-SCD)	Normal	Negative	Negative
11	44	Syncope	No	Type II	Positive	Positive
12	28	Palpitations	No	Type II	Negative	Negative
13	39	Syncope	Yes (brother with BrS)	Type II and short QT	Negative	Negative
14	21	Palpitations	No	Type II	Negative	Not done

SCD = sudden cardiac death; BrS = Brugada syndrome; VF/PVT = ventricular fibrillation/polymorphic ventricular tachycardia.

Figure 1. Patient number 2 before (A) and after (B) flecainide administration.

Median PR interval was 160 msec (min-max = 120-200, IQR = 142-185) before and 193 msec (min-max = 153-207, IQR = 160-200) after flecainide administration ($P = 0.01$). Median QRS duration increased from 90.5 ms (min-max = 60-110, IQR 80-100) to 110 (min-max 95-159, IQR 108.7-121.2) ($P = 0.003$). The median QTc interval, determined using the Bazett method, changed from 408 ms before (min-max 360-437, IQR 390-432) to 422 ms after (min-max 380-485, IQR 417-452) ($P = 0.03$). PR interval, QRS duration and QTc median difference after-before test was 20 msec (min-max = -17-+57), 21 ms (min-max = 0 to +59) and 20 ms (min-max = -11-+77), respectively.

ELECTROPHYSIOLOGICAL STUDY

EPS was performed in 13 patients (92.8%). Median HV interval was 48 ms (min-max = 39 ms-59 msec, IQR 42 ms-48 msec). In two patients sustained VF/ Polymorphic VT was induced and ended with external biphasic defibrillation. Both have had a positive flecainide test and implantable cardioverter defibrillator (ICD) was implanted.

ADVERSE EVENTS

There were adverse events neither during the acute drug testing nor during the Eps.

EVENTS DURING FOLLOW-UP

Median follow-up of positive flecainide test patients was 19 months (min-max 5-26 months). The 2 patients with ICD did not have documented arrhythmia (follow up 5 and 14 months). One non-inducible patient suffered a syncope episode after 9 months of follow-up and an ICD was implanted, no more arrhythmic events happened after the implantation (16 months). The other non-inducible patients ($n = 4$) did not have arrhythmic events during the follow up. Median follow-up of negative flecainide test patients was 9 months (min-max 2.26 months) and no one had arrhythmic events.

GENETIC TESTS

There are no genetic tests available in our country for inherited cardiac disorders and only four patients were able to send their blood samples

to perform the test abroad. Two brothers with familiar history of SCD (case number 4 and 5) were positive for SCN5A mutation. Case number 4 was unmask with oral flecainide and sustained ventricular arrhythmia was induced during EPS and case number 5 was negative in both studies (see table 1). Another patient (case number 8), whose two older sisters had died suddenly at the age of 26 and 38, had a negative EPS after a positive flecainide test. The genetic test was negative for BrS but positive for KCNE2 gene (Heterozygous LQTS 6). The last one (case number 13) was a patient with history of syncope and a brother with BrS. Flecainide test and inducibility were negative and genetic test confirmed a short QT syndrome and an ICD was implanted.

DISCUSSION

The BrS is characterized by ST-segment elevation in the right precordial ECG leads (V_1 to V_3) and a high incidence of sudden death in patients with structurally normal hearts.

Primarily sodium channel blockers (class 1A and 1C AADs) can unmask the ECG manifestations of the BrS, when concealed. Drug challenge generally is not performed in patients displaying the type 1 ECG under baseline conditions because the additional diagnostic value is considered to be limited, the added prognostic value is not clear, and the test is not without risk for provoking arrhythmic events.⁷⁻¹⁰

The syndrome may also be unmasked or precipitated by a febrile state, vagotonic agents, alpha-adrenergic agonists, beta-adrenergic blockers, tricyclic or tetracyclic antidepressants, anesthetic drugs, a combination of glucose and insulin and hypokalemia, as well as by alcohol and cocaine toxicity.¹¹⁻¹³ One of our patients was unmask by a febrile state and then reproduced by oral flecainide.

Several AADs have been used for the diagnostic in the BrS, especially ajmaline. Flecainide, pilsicainide and procainamide were also used, although it has been reported by Wolpert et al.¹⁰ that intravenous flecainide has a 32% lower sensitivity to uncover a type-1 Brugada ECG than ajmaline and Wilde et al.¹⁴ reported in the first consensus that the sensitivity of procainamide was considered relative low.

Roos et al.⁹ evaluated the importance of Class I AAD test to unmask BrS in the evaluation of

patients with syncope. They founded that one of three patients with BrS presents first with syncope, one-third of the Brugada patients have a normal ECG at investigation for syncope, and the correct diagnosis would have been missed without a class-I AAD test. Those findings support the importance of this type of tests for the appropriate evaluation of patients with suspicious BrS and syncope of unknown etiology.

Our laboratory does not have intravenous AADs like flecainide, ajmaline, pilsicainide or procainamide available to us, and for that reason we started working with flecainide orally. This approach is currently recommended but there is no evidence to support it.¹

In this article we described and analyzed a serie of consecutive patients with suspected BrS, but not spontaneous coved-type ECG under basal conditions in whom oral flecainide was used to unmask the disease.

According to the second consensus on BrS, we registered the right precordial leads in the regular and in a superior position (up to the second intercostal space above normal) to increase the sensitivity of the ECG for detecting the Brugada phenotype during the drug challenge.

Reiffel described how a "supratherapeutic" dose of flecainide (600 mg) used as a pill-in-the-pocket treatment of a lone paroxysmal atrial fibrillation (AF) crisis precipitated an ECG strongly suggestive of Brugada type 1 pattern. Since there is lack of evidence regarding oral flecainide use at a 600 mg dose for both patients who are tested for BrS and normal subjects, the findings of this clinical case are difficult to evaluate.^{15,16} Shahrzad et al.¹⁷ observed some clinical and electrocardiographic predictors of positive response to the intravenous sodium channel blockers in patients suspected of the BrS. During test, a transient episode of a second-degree atrioventricular block and isolated ventricular ectopies, a QRS prolongation $\geq 30\%$, baseline QRS duration in $V_1 \geq 110\text{ms}$ and a ST-segment elevation $\geq 0.17\text{ mV}$ in V_2 had a good sensitivity and specificity for a positive response. We founded in our study a significative prolongation of the QRS and PR interval after drug administration. However, there were neither 2nd nor 3rd degree AV block in our patients and despite the fact that PR interval increased, its value was close to the normal limits and without clinical significance.

Risk stratification aimed at the identification of patients at risk for sudden death is an important goal of research teams worldwide. The inducibility of VT/VF during EPS may forecast risk, although some studies failed to find an association between inducibility and recurrence of VT/VF among both asymptomatic and symptomatic patients with BrS.^{18–22} The role of EPS is still a controversial topic in patients with BrS; Priori et al. published the most recent evidence regarding this topic the Risk Stratification in BrS. Results of the PRogrammed ELEctrical stimUlation preDICTive valUE (PRELUDE) Registry which showed the EPS unable to identify high-risk patients.²²

On the other hand, Makimoto et al.²³ evaluated the clinical impact of the number of extrastimuli in programmed electrical stimulation in patients with Brugada type 1 electrocardiogram. They concluded that the number of extrastimuli that induced ventricular arrhythmia served as a prognostic indicator of patients with Brugada type 1 electrocardiogram. Double extrastimuli were adequate for risk stratification of patients with BrS although the Second Consensus suggest three of them.

Recently, an article by Junttila et al.²⁴ described the poor prognosis associated with the acute induction of the Brugada type 1 ECG pattern. In particular, 11 of 26 patients with drug-induced changes suffered sudden and/or resuscitated cardiac death with the majority of these life-threatening cases being related to propofol infusion, whereas the rest were secondary to use of sodium channel blockers (antiarrhythmic and local anesthetics). However, this series of patients probably represents a selected group and may not indicate the true spectrum and prognosis of the drug-induced Brugada ECG pattern.

Long-term follow-up of patients diagnosed with BrS from the FINGER registry²⁵ have shown that event rates in asymptomatic patients is low (0.5% per year) and bigger in patients with aborted SCD (7.7% per year) or syncope (1.9% per year). Probably the absence of cardiac events in our study was due to the small sample size, short follow-up and lack of high risk patients (no one had aborted SCD).

LIMITATIONS

The small number of patients in a single center study, with no control group is a strong limitation.

For that reason, we cannot draw any conclusion about the sensitivity, specificity or safety of this diagnostic approach. However, since there are no other study with flecainide orally in a larger group (in fact, in the bibliography there are only few case reports) and the lack of intravenous sodium channel blockers in several EP laboratories, this series seems to have some relevance.

Due to the impossibility to dispose of intravenous ajmaline and flecainide, we could not compare the results with other drug or administration via.

The discussion about the role of EPS in the setting of BrS is far to be resolved, but the aim of our study was to describe a series of patients in whom oral flecainide test was made.

CONCLUSIONS

In our experience, we found that oral administration of flecainide in a single dose of 400 mg is a useful method to unmask type 1 Brugada electrocardiographic pattern. Larger and comparative studies with validated drugs are needed to assess the diagnostic yield of this approach.

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