18 Ajmaline, Flecainide and Propafenone Can Induce Ventricular Fibrillation in Patients with Brugada Syndrome

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18.1 Introduction

Brugada syndrome is an inherited arrhythmic disease characterized by a cove-shaped ST elevation pattern in leads V1, V2, and V3 with increased risk of sudden cardiac death, without any associated structural heart disease [1]. In patients with suspected Brugada syndrome, intravenous administration of Class IC antiarrhythmic drugs is a well-known method to unmask the syndrome in cases with non-diagnostic type ECG. The most effective among the three drugs is ajmaline, a potent sodium channel blocker having a short half-life [2].

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During injection of ajmaline, life-threatening arrhythmias can occur, like polymorphic ventricular tachycardia or ventricular fibrillation [3]. However, intravenous administration of antiarrhythmic drugs like ajmaline, flecainide, propafenone, procainamide, or disopyramide remains a critical stage in the diagnostic approach of concealed Brugada syndrome.

The presence of Brugada syndrome in pediatric population is low 0.009% compared with adult population 0.14–0.7% [4], but the experience of ventricular fibrillation in a child during drug challenge is always a dramatic event.

18.2 Spontaneous Ventricular Fibrillation After Ajmaline

Ajmaline injection in patients with Brugada syndrome can lead to ventricular tachycardia or ventricular fibrillation, sometimes with intractable episodes. Accordingly, the test should be performed in electrophysiological labs equipped with a defibrillator, a reanimation kit with intubation facilities, mechanical ventilator, and even the possibility to perform a veno-arterial extracorporeal membrane oxygenation placement for severe recurrent episodes of ventricular fibrillation.

In the study of McMillan et al., ajmaline was injected in 95 children with suspicion of Brugada syndrome (mean age = 12 years). In 20% of the patients, a type I ECG was unmasked. No sustained ventricular arrhythmia was observed during ajmaline injection. No patient presented at 3.6 years follow-up arrhythmic events or sudden cardiac death.

On the contrary, in the study of Conte et al., the incidence of ajmaline-induced ventricular arrhythmias was 4.4% in children less than 18 years old, positive for ajmaline challenge test. In total the authors injected ajmaline in 503 patients and 9 of them presented life-threatening ventricular arrhythmias, defined as refractory to the first external defibrillation. Six of the patients had ventricular fibrillation and three unstable polymorphic ventricular tachycardia. One of the patients had prolonged intractable VF with multiple unsuccessful defibrillations >10 and necessitated ECMO to restore sinus rhythm. She presented cerebral edema and neurologic sequelae and acute respiratory distress syndrome [5]. The mean dose injected in their study was 0.6 ± 0.2 mg/kg (total dose 34 ± 20 mg).

Brugada et al. report one case of ventricular fibrillation during injection for drug challenge in BS on 45 patients. Thirty-four had BS, and 11 were family members with positive SCN5A and received 1 mg/kg ajmaline (Fig. 18.1), 10 mg/kg procainamide, or 2 mg/kg flecainide. One of the patients that received ajmaline presented spontaneous ventricular fibrillation.

Rolf et al. also reported ventricular arrhythmias in 1.3% of 158 patients that received ajmaline. The explanation could be the continuation of infusion even after occurrence of clear signs of Brugada syndrome type 1 on the surface ECG. Therefore, termination criteria were implemented for the challenge test for all the three abovementioned medications (Table 18.2).

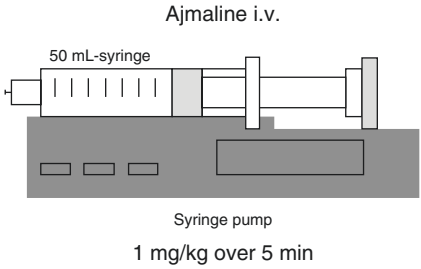

Fig. 18.1 Ajmaline dose during challenge test

Bermudez et al. reported the case of a 13-year-old patient with Brugada syndrome and sudden cardiac arrest by ventricular fibrillation. He presented severe postanoxic encephalopathy. Two weeks after the event an electrophysiological study was performed with administration of 1 mg/kg ajmaline. The patient developed runs of nonsustained VT with a pleomorphic morphology and sustained monomorphic ventricular tachycardia.

18.2.1 Protocol of Administration

Arnalsteen-Dassonvalle et al. compared two protocols of ajmaline 1 mg/kg administration: a rapid protocol of infusion at 1 mg/s and a slow protocol over 10 min. They found no significant difference between the rapid and the slow protocols of infusion. No sustained ventricular arrhythmia was observed in the two groups. PVCs were observed in five of 32 patients from the slow challenge group and four of 32 patients from the rapid challenge group (Table 18.1).

We believe that the slow protocol is safer, because ajmaline might be interrupted if ventricular fibrillation occurs, and only a part of the total dose of 1 mg/kg would be injected.

Therasse et al. studied 672 patients, including 175 patients (26%) that received flecainide. Ventricular tachycardia and fibrillation occurred in 10 of the 497 patients that received ajmaline and none of the 175 patients that received flecainide [6].

Dobbels et al. analyzed all the studies published between January 2000 and August 2015 which reported ventricular arrhythmias after ajmaline. They found three predictors for malignant ventricular arrhythmia occurrence: younger age, conduction disturbance at the baseline ECG, and mutation in the SCN5A gene [7].

Gandjbakhch et al. reported the results of ajmaline challenge test in a large family with SCN5A mutation. A 34-year-old patient (Table 18.3) presented during ajmaline 1 mg/kg at 1 mg/s a polymorphic ventricular tachycardia associated with syncope. Two relatives of the patient received the same dose of ajmaline during the text and presented polymorphic ventricular tachycardia with syncope [8]. It is unlikely that this response be caused by the rapid infusion protocol, as a randomized study on 336 patients found that a rapid infusion protocol is not associated with a higher risk of ventricular arrhythmias [9].

Table 18.1 Ajmaline test for Brugada syndrome

1 mg/kg ajmaline	During 10 min
ECG	At 1 min
ECG	At 2 min
ECG	At 3 min
ECG	At 4 min
ECG	At 5 min
ECG	At 6 min
ECG	At 7 min
ECG	At 8 min
ECG	At 9 min
ECG	At 10 min
ECG	At 15 min
ECG	At 20 min
ECG	At 25 min
ECG	At 30 min

Table 18.2 Termination criteria for ajmaline test

1. A typical type-1 Brugada pattern (V1–V3)
2. Ventricular arrhythmias (VEs or VT]
3. QRS duration prolongs >30% from baseline
4. Type 2 or 3 AV block
5. Maximum dose given

18.2.2 Termination Criteria

See Table 18.2.

18.2.3 Reversal of Ajmaline with Isoprenaline

Isoproterenol stimulating β-receptors augments Ica and reduces ST segment elevation in leads V1–V3 in patients with BS. Isoproterenol was demonstrated to be effective in VF suppression in a 36-year-old male with Brugada syndrome and determined disappearance of the short-coupled PVCs, which can be triggers of ventricular fibrillation [10]. The effectiveness of isoproterenol was also confirmed by Watanabe et al. in a case series of patients with Brugada syndrome in which ventricular severe arrhythmias were successfully abolished with infusion of isoproterenol in six patients. In case of PVCs, ventricular tachycardia or ventricular fibrillation during the ajmaline test, isoprenaline should be administered. As an established protocol, when modifications of the ST segment occur, isoprenaline is injected at the end of the electrophysiological study to monitor modifications of the ST. The dose of isoprenaline is 2 μg/min over 10–30 min with continuous ECG monitoring.

In the study of Arnalsteen-Dassonvalle et al., patients received a higher dose of isoproterenol than usually described in electrical storms: 0.06 mg/min compared to 0.1–1 μg/min [11, 12].

18.2.4 Reversal of Ajmaline with Sodium Bicarbonate

Sodium bicarbonate is a good treatment for sodium channel blockers overdose and is indications for cardiac arrest, increased widening of QRS complex, and cardiogenic shock refractory to fluid therapy. After sodium bicarbonate the QRS duration decreases, and probably the QRS will normalize. The efficacy of the sodium bicarbonate is demonstrated by animal studies and human reports both in adult and in pediatric population. The effectiveness is likely mediated by the alkalemia induced by the bicarbonate and release of sodium ions to fast-acting sodium channels inside the affected myocardium.

Sodium bicarbonate is injected in doses of 150 mEq/L, 8.4% solution (Fig. 18.2).

18.2.5 ECMO for Ventricular Fibrillation After Ajmaline

Poli et al. reported the case of a 32-year-old woman that presented polymorphic ventricular tachycardia and ventricular fibrillation without return to normal rhythm after 14 DC shocks. The patients was transferred to another hospital 50 km away and treated with extracorporeal membrane oxygenation. After 30 min of ECMO transvenous ventricular pacing was effective, and the patient further recovered normal sinus rhythm [13]. Survival of patients with cardiac arrest and prolonged time to return to spontaneous circulation shows to be rare. ECMO is an

Fig. 18.2 Sodium bicarbonate dose during ventricular arrhythmias induced by ajmaline testing (3 × 50 mg intravenously)

Table 18.3 How to prepare the ajmaline infusion for the challenge test

Understanding the numbers:

You are ordered to give 1 mg/kg of Ajmaline over 5 min to your 58-year-old, 70 kg patient with suspicion of Brugada Syndrome

1. The aminophylline vial has 50 mg/10 mL
2. You should take 2 vials of Ajamaline in the 50 mL syringe with 30 mL of serum (0.9% NaCl)
3. This gives a concentration of 100 mg/50 mL meaning 2 mg/mL
4. 1 mg x 70 kg=70 mg should be injected, equivalent of 35 mL
5. We will start the perfusion rate: 35x12= 420 mL/h

option in case of refractory cardiogenic shock or cardiac arrest in patients that have a reversible underlying pathology. Acute toxic exposure is an indication for ECMO because restoring circulation permits the intrinsic drug metabolism and elimination from the circulation. The problem with ECMO is the limited number of centers that can implant ECMO and manage patients having this support. ECMO can improve outcomes of survival and morbidity at 1 year follow-up associated with advanced life support, when the technique is indicated. Sodium channel blockers challenged should be performed in electrophysiological labs that are equipped with CPR facilities available and ECMO in the same hospital or nearby area. In the current medical literature, there are at least four case reports with ECMO following severe flecainide intoxication.

18.3 Spontaneous Ventricular Fibrillation After Flecainide

Flecainide test is widely used in patients with Brugada syndrome, especially in countries where ajmaline is not available. The ability to identify patients with concealed form of Brugada syndrome is clearly established [14].

Gasparini et al. injected flecainide in 22 patients with BS, eight of them with SCN5A. The dose infused was 2 mg/kg over 10 min. Three patients developed sustained ventricular tachycardia with duration of 7–10 min which ended spontaneously and recurrent ventricular fibrillation in three patients. The reproducibility of the test was 100%. Ventricular arrhythmias occurred especially in patients with SCN5A mutation 3/7 than without mutation 1/15.

Therasse et al. studied 672 patients, including 175 patients (26%) that received flecainide. Ventricular tachycardia and fibrillation occurred in 10 of the 497 patients that received ajmaline and none of the 175 patients that received flecainide.

In the study of Brugada et al., 2 mg/kg flecainide was infused over 5 min. Spontaneous ventricular fibrillation occurred in 1 of 53 patients and 5 patients presented frequent PVCs during infusion.

18.3.1 Challenge Test with Oral Flecainide

The challenge test can be also made with oral flecainide (Tables 18.4 and 18.5). The dose is 400 mg in single administration. Bioavailability in oral administration is around 70% (60–86%), and a higher bioavailability can be obtained with a higher dose.

In the study of Prasad et al. out of 29 patients 25 received oral flecainide 400 mg, the test was positive in 7 patients, and none presented spontaneous ventricular

Table 18.4 Flecainide test with tablets

Two tablets of 200 mg	400 mg
ECG	At 15 min
ECG	At 30 min
ECG	At 60 min
ECG	At 90 min
ECG	At 2 h
ECG	At 3 h
ECG	At 4 h
ECG	At 5 h
ECG	At 6 h

Table 18.5 How to prepare the flecainide infusion for a challenge test

Understanding the numbers:

You are ordered to give 2 mg/kg of Flecainide over 10 min to your 58-year-old, 70 kg patient with suspicion of Brugada Syndrome

1. The Flecainide vial has 15 mL and 10 mg/1 mL equivalent of 150 mg
2. You should take 1 vial of Flecainide in the 50 mL syringe with 35 mL of serum (0.9% NaCl)
3. This gives a concentration of 150 mg/50 mL meaning 3 mg/mL.
4. 2 mgx70 kg=140 mg should be injected, equivalent of 46.6 mL
5. We will start the perfusion rate: 46.6x6= 280 mL/h

arrhythmia. The authors observed a maximum time to positivity of 3 h and a maximum time to normalization of ECG of 6 h. Therefore, they recommend a maximum observation time of 6 h.

18.4 Spontaneous Ventricular Fibrillation After Propafenone

Not only ajmaline, flecainide and procainamide can unmask Brugada syndrome but also propafenone which is also a class IC antiarrhythmic drug (Fig. 18.3, Table 18.6). It blocks the sodium channels and also it blocks the β-receptors. Both sodium-blocking agents and beta-blockers can unmask Brugada syndrome.

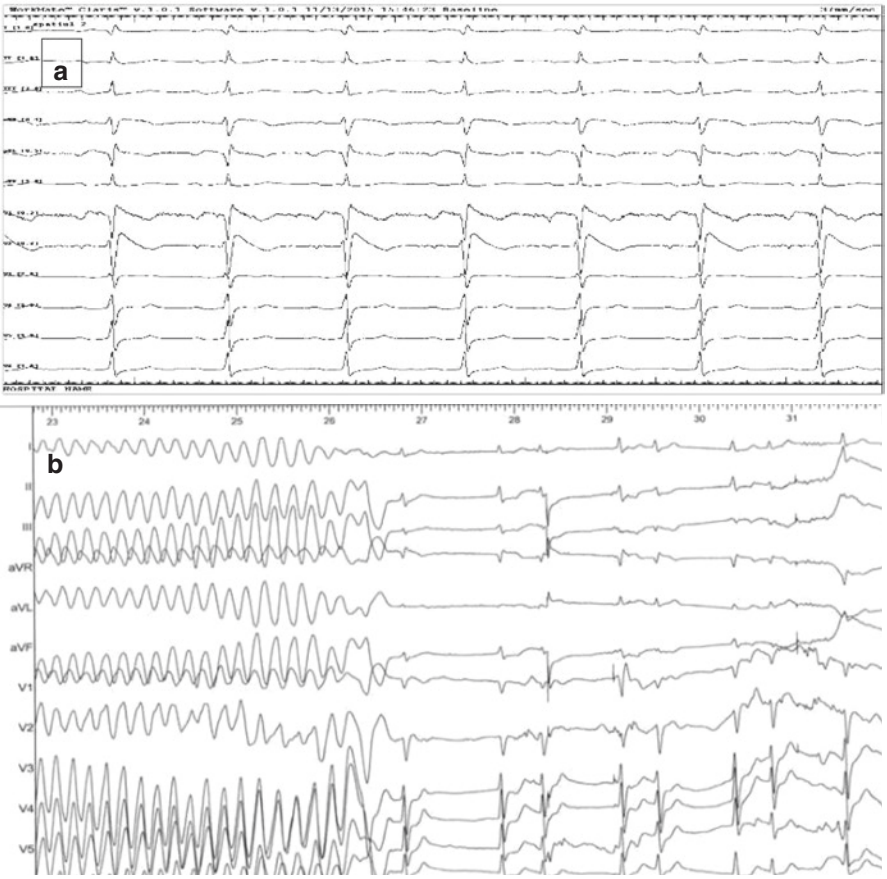

Fig. 18.3 Propafenone challenge test was performed with suspicion of Brugada syndrome. Four hundred milligrams was orally administered, and the patient developed Brugada pattern (**a**). One hour after propafenone the patient presented non-sustained ventricular fibrillation (**b**)

Table 18.6 How to prepare the propafenone infusion for a challenge test

Understanding the numbers:

You are ordered to give 2 mg/kg of Propafenone over 10 min to your 58-year-old, 70 kg patient with suspicion of Brugada Syndrome

1. The Propafenone vial has 70 mg and 20 mL
2. You should take 2 vials of Flecainide in the 50 mL syringe with 10 mL of serum (0.9% NaCl)
3. This gives a concentration of 140 mg/50 mL meaning 2,8 mg/mL.
4. 2 mgx70 kg=140 mg should be injected, equivalent of 50 mL
5. We will start the perfusion rate at 50 mL/h

Aksay et al. reported the case of a 43-year-old man who received 600 mg of propafenone for conversion of atrial fibrillation. ST segment elevation occurred in leads V1–V3, confirming the Brugada syndrome. Modifications disappeared from the ECG after 6 h.

Matana et al. presented the first case of concealed Brugada syndrome that was unmasked by propafenone [15].

In 1997, there were described the first cases of Brugada syndrome with ventricular fibrillation spontaneous induction after propafenone administration [16]. Kose et al. reported the case of a patient that presented ventricular fibrillation during propafenone challenge test. A 46-year-old patient had repeated episodes of syncope (3 episodes). He had no familial history of syncope or sudden cardiac death. During provocation propafenone test, 2 mg/kg were injected intravenously during 10 min. The type 2 pattern present in the beginning of the test transformed in type 1 at 7 min interval after infusion, and after 2 more min, the patient developed ventricular fibrillation. The patient returned to sinus rhythm after an electrical shock of 200 J. The patient was implanted with an internal defibrillator [17].

Rodriguez-Manero et al. from the Brugada group reported 611 patients with Brugada syndrome of whom 35 presented atrial fibrillation as the first clinical manifestation of the syndrome. Eleven patients developed ECG pattern after class IC antiarrhythmic drug for atrial fibrillation, one patient presented sudden cardiac death after propafenone administration, and one presented ventricular fibrillation after flecainide [18].

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20:1391–6.
2. Antzelevitch C, Brugada P, Borggrefe M, Brugada P, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference. Circulation. 2005;111:659–70.
3. Wellens HJ, Bar FW, Vanagt EJ. Death after ajmaline administration. Am J Cardiol. 1980;45:905.

4. Wolpert C, Echternach C, Veltmann C, Antzelevitch C, Thomas GP, Spehl S, et al. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm. 2005;2:254–60.
5. Conte G, Sieira J, Sarkozy A, et al. Life-threatening ventricular arrhythmias during ajmaline challenge in patients with Brugada syndrome: incidence, clinical features, and prognosis. Heart Rhythm. 2013;10:1869–74.
6. Therasse D, Sacher F, Petit B. Sodium-channel blocker challenge in the familial screening of Brugada syndrome: safety and predictors of positivity. Heart Rhythm. 2017;14:1442–8.
7. Dobbels B, De Cleen D, Ector J. Ventricular arrhythmia during ajmaline challenge for the Brugada syndrome. Europace. 2016;18:1501–6.
8. Gandjbakhch E, Fressart V, Duthoit G. Malignant response to ajmaline challenge in SCN5A mutation carriers: experience from a large familial study. Int J Cardiol. 2014;172:256–8.
9. Arnalsteen-Dassonvalle E, Hermida JS, Kubala M, Six I, Quenum S, Leborgne L, et al. Ajmaline challenge for the diagnosis of Brugada syndrome: which protocol? Arch Cardiovasc Dis. 2010;103:570–8.
10. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation. 1999;100:1660–6.
11. Jongman JK, Jepkes-Bruin N, Ramdat Misier AR, Beukema WP, Delnoy PP, Oude Lutttikhuis H, et al. Electrical storms in Brugada syndrome successfully treated with isoproterenol infusion and quinidine orally. Neth Heart J. 2007;15:151–5.
12. Maury P, Couderc P, Delay M, Boveda S, Brugada J. Electrical storm in Brugada syndrome successfully treated using isoprenaline. Europace. 2004;6:130–3.
13. Poli S, Toniolo M, Maiani M, Zanuttini D, Rebellato L, Vendramin I, et al. Management of untreatable ventricular arrhythmias during pharmacologic challenges with sodium channel blockers for suspected Brugada syndrome. Europace. 2018;20:234–42.
14. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. 2013;15:1389–406.
15. Matana A, Goldner V, Stanic K. Unmasking effect of propafenone on the concealed form of the Brugada phenomenon. Pacing Clin Electrophysiol. 2000;23:416–8.
16. Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation. 1997;95:2277–85.
17. Kose N, Akın F. Ventricular fibrillation developing during the provocation test with propafenone in a patient with Brugada syndrome. Int J Cardiol. 2013;163:S81–S211.
18. Rodríguez-Mañero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, de Asmundis C, Chierchia GB, Wauters K, Rao JY, Bayrak F, Van Malderen S. Brugada prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. Am J Cardiol. 2013;111:362–7.