The Role of Flecainide in the Management of Catecholaminergic Polymorphic Ventricular Tachycardia

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Abstract

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but severe genetic cardiac arrhythmia disorder, with symptoms including syncope and sudden cardiac death due to polymorphic VT or ventricular fibrillation typically triggered by exercise or emotions in the absence of structural heart disease. The cornerstone of medical therapy for CPVT is β -blockers. However, recently flecainide has been added to the therapeutic arsenal for CPVT. In this review we summarise current data on the efficacy and role of flecainide in the treatment of CPVT.

Keywords

Antiarrhythmic therapy, catecholaminergic ventricular tachycardia, flecainide, genetic, inherited channelopathies, sudden death

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but severe genetic cardiac arrhythmia disorder. Clinically, CPVT most often presents in childhood with symptoms such as syncope or sudden cardiac death due to polymorphic ventricular tachycardia (VT) or ventricular fibrillation typically triggered by exercise or emotions in the absence of structural heart disease.¹

Mutations in the *RYR2* gene, which encodes the cardiac ryanodine receptor calcium release channel (RyR2), can be identified in the vast majority of the CPVT cases and follow an autosomal dominant inheritance pattern,² whereas a small percentage of cases are due to homozygous or compound heterozygous mutations in the gene encoding cardiac calsequestrin (*CASQ2*).³ Both RyR2 and CASQ2 are involved in intracellular calcium homeostasis in the cardiomyocyte. Mutations in these genes mainly cause diastolic calcium leakage from the sarcoplasmic reticulum through the RyR2 receptor, eventually resulting in delayed afterdepolarisations and triggered activity, which is most pronounced during states of sympathetic activation.⁴ Other genes that have been discovered and only represent a small percentage of CPVT cases are *TRDN* (encoding triadin) and *CALM1* (encoding calmodulin).^{5,6} Mutations in the *CALM2* gene have been associated with overlapping features of the congenital long-QT syndrome and CPVT.⁷ A yet-to-be-identified gene on chromosome 7p14–p22 has been linked to a highly malignant autosomal recessive form of CPVT. This phenotype is characterised by exercise-induced ventricular arrhythmia, and patients have a minor QT prolongation.⁸ Approximately 40 % of the CPVT cases remain mutation negative.^{9,10}

Untreated, CPVT has a high mortality rate of up to 30 % among individuals with the classic phenotype who are aged <40 years.^{9,11} Since CPVT was first described,¹² β -blockers have been acknowledged for their efficacy in its treatment, and they have remained the cornerstone of therapy to date.¹³ However, a significant percentage of CPVT cases remain symptomatic despite receiving adequate β -blocker therapy or suffer from severe side-effects such as fatigue due to β -blocker therapy.^{2,9,14} Up until a few years ago, patients who remained symptomatic despite receiving β -blocker therapy could only be additionally protected by an implantable cardioverter defibrillator (ICD).

In 2009, flecainide was shown to reduce the rate of ventricular arrhythmias among patients with CPVT.¹⁵ This has been considered an important discovery and current guidelines now recommend flecainide in patients with recurrent syncope or PVT while on β -blockers.¹³ Here, we review the efficacy of flecainide therapy and its role in the treatment of patients with CPVT.

Flecainide

Flecainide, a class 1c antiarrhythmic drug, was synthesised in 1972 and approved by the US Food and Drug Administration in 1984 for the suppression of VT. Orally administered flecainide is rapidly absorbed and has a 90 % bioavailability after ingestion. Flecainide is metabolised by cytochrome P450 (CYP)2D6 and CYP1A2 before it is renally excreted. In healthy subjects, peak plasma levels are reached after 2–3 hours and steady-state levels are achieved within 3–5 days. The elimination half-life of flecainide is 12–27 hours.^{16,17}

Table 1: Clinical Studies of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia Treated With Flecainide

Study	Design	Number of patients	Female	RYR2 mutation/ CASQ2 mutation/ no mutation identified/ genetic testing not performed	Age at start of flecainide (years)*	Combined with β -blocker	Daily flecainide dosage	Follow-up*	Cardiac events	Compliant	Side-effects
Watanabe et al. 2009 ¹⁵	Case report	2	1 (50 %)	1/1/0/0	36 and 12	1 (50 %)	3 mg/kg, NR	12 weeks	0	–	No
Biernacka et al. 2010 ³³	Case report	1	1 (100 %)	NR	32	1 (100 %)	100 mg	3 months	0	–	–
Van der Werf et al. 2011 ²³	Retrospective cohort study	33	24 (73 %)	32/1/0/0	25 (7–68)	31 (94 %)	150 mg (100–300; 1.5–4.5 mg/kg)	20 months (12–40)	1/33 (3 %); appropriate ICD shock	No	6 (18 %)
Pott et al. 2011 ³⁴	Case report	1	0 (0 %)	1/0/0/0	11	1 (100 %)	90 mg/day (0.20 mg/L)	17 months	0	–	No
Sy et al. 2011 ³⁵	Retrospective cohort study	5/27 (19 %)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hong et al. 2012 ³⁶	Case report	1	0 (0 %)	0/1/0/0	14	1 (100 %)	100 mg	12 months	1: appropriate ICD shock	NR	–
Jacquemart et al. 2012 ³⁷	Case report	1	0 (0 %)	1/0/0/0	11	1 (100 %)	4 mg/kg	2 years	0	–	No
Watanabe et al. 2013 ²⁵	Retrospective cohort study	12	6 (50 %)	0/0/12/0	22 $\pm$ 11	12 (100 %)	165 $\pm$ 46 mg (2.9 $\pm$ 1.3 mg/kg)	48 $\pm$ 94 months	2/11 (18 %); 1 SCD, 1 ACA	No	0 (0 %)
Khouri et al. 2013 ²⁴	Retrospective cohort study	10	4 (40 %)	0/10/0/0	17 $\pm$ 2.5	10 (100 %)	200 mg (150–300 mg)	15.5 $\pm$ 10.4 months	2/10 (20%); appropriate ICD shocks (both preceded by supraventricular tachycardia)	Yes	0 (0 %)
Mantzziari et al. 2013 ³⁸	Case report	1	1 (100 %)	1/0/0/0	14	1 (100 %)	100 mg	12 months	0	–	No
Wanguemert et al. 2014 ³⁹	Case report	1	0 (0 %)	1/0/0/0	NR	1 (100 %)	NR	NR	0	–	No
Miyake et al. 2013 ⁴⁰	Retrospective cohort study	3/24 (13 %)	8 (33 %)	1/0/1/1	NR	3 (100 %)	NR	29 (7–82) months	0	–	No
Roses-Noguer 2014 ⁴¹	Retrospective cohort study	7/13 (53 %)	4 (57 %)	3/2/2/0	NR	7 (100 %)	2.3 $\pm$ 1 mg/kg	4.0 years (1.7–19.9)	2/7 (29 %); appropriate ICD shock	NR	No
Roston et al. 2015 ¹⁴	Retrospective cohort study	51/211(24 %)	NR	NR	NR	43 (96 %)	NR	1.3 years (0.9–2.7)	8 (16 %; 7 suboptimal dose)	No (6/8)	5 (10 %)
Padfield et al. 2015 ²⁶	Retrospective cohort study	8	NR	8/0/0/0	NR	0 (0 %)	150 mg (100–200 mg)	37.1 months (1.4–75.5)	0	–	1 (12.5 %)
De Ferrari et al. 2015 ²⁷ †	Retrospective cohort study	15/63 (24 %)	NR	NR	NR	13 (87 %)	3.5–4.0 kg/kg	NR	13/14 (93 %) [†]	NR	NR

ACA = aborted cardiac arrest; ICD = implantable cardioverter defibrillator; NR = not reported; SCD = sudden cardiac death. *Mean $\pm$ standard deviation or median (range) † In this study a total of 22 patients received flecainide. However, outcomes are only reported in the subgroup of 14 patients who experienced cardiac events before and/or after left cardiac sympathetic denervation. In 13 of 14 patients (93%) ventricular arrhythmias were not suppressed. However, it is unknown if this is synonymous with experiencing cardiac events.

Experimental Studies

In 2009, the first study on the efficacy of flecainide in patients with CPVT showed that flecainide dramatically reduced rates of calcium sparks *in vitro* and ventricular arrhythmias *in vivo* in a *CASQ2*-knockout mouse model.¹⁵ In *in vitro* studies in isolated cardiomyocytes flecainide reduced the duration of RyR2 channel opening. This effect was most pronounced in the setting of RyR2 activation by high luminal calcium with flecainide. This situation mimics spontaneous calcium release through the sarcoplasmic reticulum, which triggers ventricular arrhythmias in patients with CPVT. Flecainide reduced spontaneous calcium spark frequency in isolated cardiomyocytes. *In vivo* flecainide completely suppressed VT in all mice. This discovery led to the successful treatment of two severely affected patients.¹⁵ The proposed mechanism of action is that, apart from the known sodium channel-blocking effect, flecainide has an additional direct-blocking effect on the RyR2 channel, through which it inhibits triggered activity.¹⁵ However, two other groups have independently opposed this mechanism and proposed an alternative mechanism by an effect that could solely be attributed to the sodium channel-blocking properties of the drug.^{18–20} It has also been suggested that a potential action of flecainide is by an indirect effect on RyR2 through binding to calmodulin or other modulators of RyR2.²¹

Propafenone

Apart from flecainide, the only other class 1c antiarrhythmic drug available in the US that has been shown to block RyR2 channels is propafenone.²² Propafenone was effective in suppressing calcium waves *in vitro* and reduced the rate of ventricular arrhythmias in *CASQ2*-knockout mice.²² Propafenone was also tested in a 22-year-old patient with CPVT carrying the p.L4105F *RYR2* mutation who suffered from frequent appropriate ICD discharges and who was refractory to conventional therapy (excluding flecainide). Propafenone was prescribed because flecainide is not available in Turkey. The use of propafenone led to a significant decrease in the frequency of ICD discharges and complete ventricular arrhythmia suppression on exercise testing at 12 months of follow-up.²²

Clinical Studies

Since 2009, there have been 15 published clinical studies on flecainide treatment in patients with CPVT (see Table 1). The first relatively large cohort included 33 genotype-positive patients (1 *CASQ2* and 32 *RYR2* mutation carriers) and evaluated the efficacy of flecainide in difficult-to-treat patients who were either symptomatic on maximally tolerated therapy or had persistent severe ventricular arrhythmias despite maximally tolerated therapy.²³ The vast majority of these patients used flecainide in combination with a β -blocker (94 %), whereas two patients used flecainide as monotherapy due to significant side effects of β -blockers. Partial or complete suppression of the ventricular arrhythmias was achieved in 76 % of patients. During a mean follow-up of 20 months, one patient suffered from an episode of several appropriate ICD shocks due to confirmed non-compliance.²³ Subsequently, the efficacy of flecainide was confirmed in a relatively large cohort of homozygous *CASQ2* D307H mutation carriers.²⁴ In this study, all patients used flecainide in combination with β -blockers. After the initiation of flecainide, the ventricular arrhythmia burden decreased in all patients and during a mean follow-up of 15.5 ± 10.4 months, and two patients suffered from appropriate ICD shocks, which in both cases were preceded by supraventricular tachyarrhythmias.

Flecainide also suppressed ventricular arrhythmias in patients without a proven pathogenic mutation in the *RYR2*, *CASQ2* or *KCNJ2* genes.²⁵

Figure 1: ECGs at Maximum Heart Rate During Exercise Testing Before and After Drug Treatments in a Female Patient with Catecholaminergic Polymorphic Ventricular Tachycardia

A: At baseline before medication; polymorphic NSVT and VES were observed. B: After bisoprolol (5 mg/day); VES, bigeminy and a couplet. C: With metoprolol 50 mg/day and flecainide 150 mg/day ventricular arrhythmias were completely suppressed. CPVT = catecholaminergic polymorphic ventricular tachycardia; NSVT = non-sustained ventricular tachycardia; VES = ventricular extrasystoles.

This study consisted of 12 patients, all of whom showed ventricular arrhythmias despite maximal tolerated therapy. During a mean follow-up of 48 months, two patients experienced a cardiac event due to non-compliance. To the best of our knowledge, only sporadic cases have been treated with flecainide monotherapy, most often due to the significant side-effects of β -blockers. In a small retrospective cohort consisting of nine patients carrying *RYR2* mutations, all intolerant to β -blockers, no patient suffered from treatment failure during a median follow-up of 37.1 months.²⁶ Therefore, flecainide monotherapy may potentially be considered an option for patients that are intolerant to β -blockers.

A placebo-controlled, randomised crossover trial of flecainide in patients with CPVT assessing the efficacy of flecainide in reducing cardiac events in CPVT is ongoing (ClinicalTrials.gov ID NCT0117454). One study that focused on left cardiac sympathetic denervation (LCSD) reported a high number of patients without ventricular arrhythmia suppression despite treatment with flecainide and β -blockers and/or LCSD.²⁷ However, it is

unknown whether these patients also experienced cardiac events. In addition, this is a highly symptomatic cohort of whom 19 % experienced cardiac events within 2 years after LCSD. Overall, the studies published so far have reported treatment failure to be most frequently associated with non-compliance or suboptimal flecainide dosing (see Table 1).

Role of Flecainide in Treatment of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

At present, exercise restriction and β -blocker treatment are the cornerstone of therapies in patients with CPVT.¹³ The current consensus is to treat each patient with a clinical or genetic diagnosis of CPVT with the highest tolerable dose of β -blockers. A robust comparison between different types of β -blockers has not been performed, but there is growing evidence that nadolol, a long-acting drug, is the most effective β -blocker in terms of ventricular arrhythmia suppression and cardiac event rates.^{9,28} Other nonselective β -blockers such as propranolol might be an alternative in those countries where nadolol is not available.¹³

Flecainide is the first addition to β -blockers when ventricular arrhythmia suppression seems incomplete. Current expert consensus guidelines have given a class IIa recommendation for the use of flecainide in patients with CPVT.^{13,29} In addition, flecainide is considered an 'emerging recommendation' according to the 2015 European Society of Cardiology VT guideline.²⁹ Figure 1 shows the effect of β -blocker therapy and flecainide added to β -blockers in a CPVT patient. Flecainide should be considered in patients who continue to have ventricular arrhythmias and/or symptoms despite maximum tolerated β -blocker dose in patients with or without an ICD.¹³ A dose-response effect has been observed in previous studies on flecainide and optimal dosing for ventricular arrhythmia suppression in adults is approximately 150–300 mg/day, while dosages below 100 mg/day have been associated with a lack of therapeutic response.²³ In most cases, treatment failure has so far been associated with low flecainide dosing and/or non-compliance. At present, the only measure of efficacy of flecainide is the ventricular arrhythmic burden on the exercise test. It is, however, important to realise that cases in which the ventricular arrhythmia burden on the exercise test was not a reliable predictor of cardiac events (i.e.

who experienced a cardiac event while a previous exercise test did not show significant ventricular arrhythmias) have been described.³⁰ Therefore, optimal therapeutic range can be evaluated by comparing the ventricular arrhythmia burden on the exercise test before and after the initiation of flecainide. It is unknown whether the once- or twice-daily administration is beneficial, but a slow-release drug is preferred to avoid non-compliance. Overall, the reported side-effects of flecainide are mild and have led to discontinuation in only a small proportion of patients (see Table 1).

LCSD and/or ICD implantation may be considered in patients who remain symptomatic or continue to have persistent arrhythmias despite treatment with β -blockers and flecainide. Although the beneficial effects of flecainide in patients with CPVT patients seem overt, one must exercise caution with regard to the pro-arrhythmic effects of flecainide. The Cardiac Arrhythmia Suppression Trial (CAST) has shown that class I antiarrhythmic drugs are associated with an increased rate of sudden cardiac death in post-infarct patients when compared with placebo.³¹ Therefore, a contraindication has been issued for patients with a structural heart disease and a history or suspicion of coronary artery disease. It is thought that flecainide can become pro-arrhythmic due to myocardial conduction velocity slowing, which may consequently trigger re-entry and may be particular relevant in the setting of myocardial ischaemia. It is recommended that heart rate-related QRS prolongation is closely monitored on the exercise test; if the QRS interval is prolonged by >25 %, flecainide dosing should be decreased or discontinued. It is, however, reassuring that in the published reports a proarrhythmic effect of flecainide has not been observed in patients with CPVT. Furthermore, data accumulated over the past 27 years indicate that flecainide is safe to use in carefully selected patients without structural heart disease.³² Additionally, long-term (27–29 years) follow-up data have been reported for two patients with CPVT patients on flecainide.^{23,25}

Conclusion

Preliminary results with flecainide in patients with CPVT are encouraging. However, a larger study with long-term follow-up is needed to fully elucidate the efficacy of flecainide, in particular its ability to prevent cardiac events in the long term. ■

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