Ivabradine- Flecainide as Breaktrough Drug Combination for Congenital Junctional Ectopic Tachycardia: A Case Report and Literature Review

Abstract

Congenital Junctional Ectopic Tachycardia (CJET) is a rare tachyarrhythmia that remains difficult to manage with suboptimal control in most cases. Here, we report literature research on the use of Ivabradine in the treatment of pediatric Junctional Ectopic Tachycardia (JET), both congenital and postoperative, and describe the successful use of Ivabradine in combination with Flecainide for CJET therapy resistant to multiple antiarrhythmic agents. This new drug combination was effective in completely suppressing JET.Ivabradine in combination with Flecainide may be considered a new therapeutic strategy of CJET with satisfactory efficacy/tolerability ratio in patients resistant to conventional drug combinations.

Introduction

Junctional ectopic tachycardia (JET) is a tachyarrhythmia originating in the atrioventricular (AV) node and AV junction also involving the bundle of His complex (BH) [1]. Basing on the etiology, it is possible to classify JET in congenital and postoperative.

Congenital Junctional Ectopic Tachycardia (CJET) is a rare arrhythmia that can occurs in infants with a structurally normal heart and without previous cardiac surgery. This is often refractory to conventional medical therapy. Persistent JET in children can result in ventricular dysfunction, heart failure and high morbidity and mortality [1-2].

Ivabradine is a novel heart rate controlling drug that acts inhibiting the funny current responsible for spontaneous depolarization of cardiac pacemaker cells.

In this paper we conducted a literature review about the use of Ivabradine in children with JET, both congenital and postoperative.

In addition to this, we described the therapeutic management of CJET using the new - and never described before- association of Ivabradine with Flecainide.

Case presentation

We report the case of a one-year-old female patient. On day two of life, CJET was diagnosed (Figure 1) in absence of structural cardiopathies or previous surgery. Amiodarone (300 mg/m^2/day) was started as first-line therapy with a satisfactory result in terms of heart-rate control. Later onset of severe hypothyroidism induced withdrawal of Amiodarone and introduction of Flecainide (5 mg/kg/day) and Propranolol (4 mg/kg/day). This second-line therapy did not show acceptable arrhythmia control.

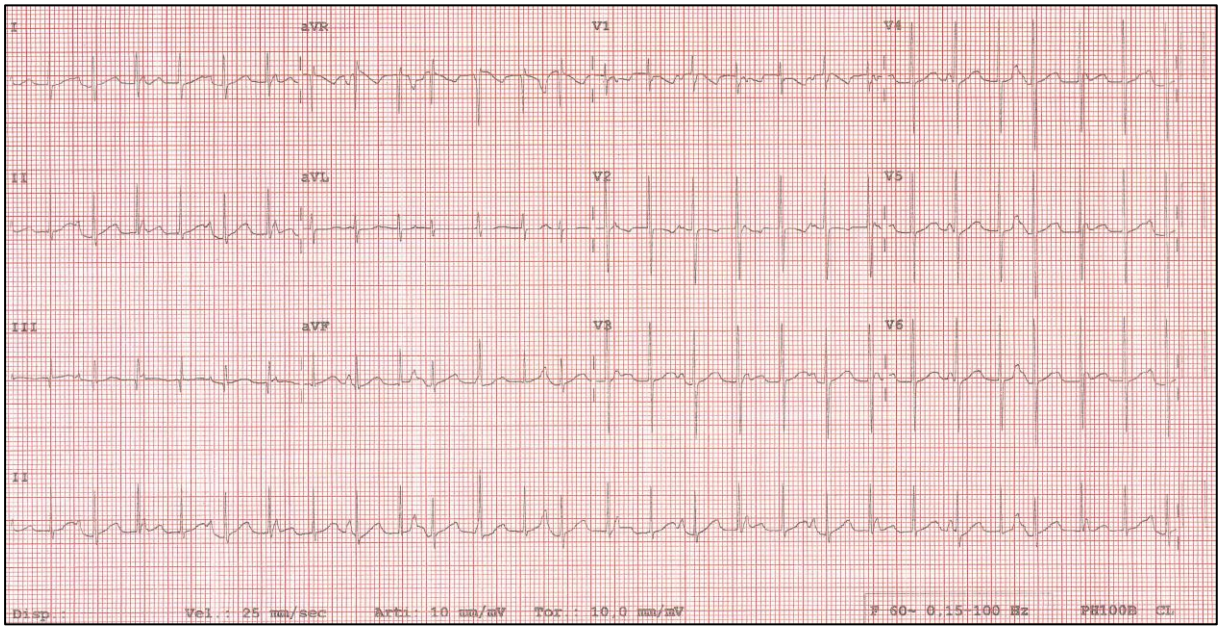

Figure 1- Junctional Ectopic Tachycardia (JET) at diagnosis.

For this reason, a third-line therapy was started with Propranolol (4 mg/kg/day) -Ivabradine (0,25 mg/kg/day) in combination. This association was able to ensure satisfactory heart-rate control, however without restoring sinus rhythm. Despite this, the patient was discharged with this therapeutic regimen and underwent follow-up.

After four months, the recurrent elevated heart rate associated with echocardiographic evidence of biatrial and left ventricle dilation led the patient to re-hospitalization. In agreement with fellow endocrinologists, it was decided to reintroduce Amiodarone as the best therapeutic option although the risk of hypothyroidism. High doses of Amiodarone (350 mg/m^2/day) alone were not able to prevent high heart rate phases. Therefore, Ivabradine (0.25 mg/kg/day) was added with a better heart rate control but not as expected. Consequently, it was decided to try a new therapeutic strategy, never tried before in the management of JET. It was introduced Ivabradine (0.3 mg/kg/day) – Flecainide (5 mg/kg/day) association with complete conversion to normal sinus rhythm within few hours (Figure 2).

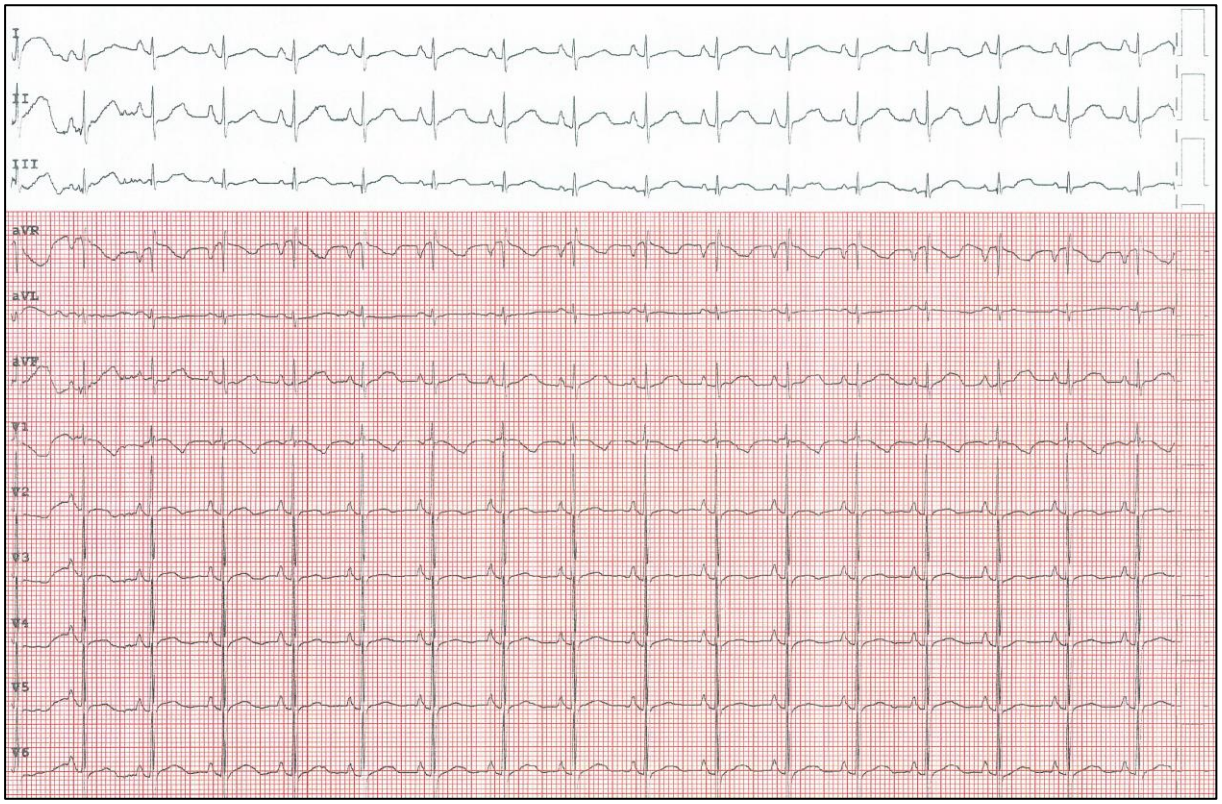

Figure 2- Restoration of sinus rhythm in patient with JET treated by Ivabradine in combination with Flecainide.

During sleep, the patient showed too low heart rate. For this reason, the doses of both drugs were reduced as following: Ivabradine (0.25 mg/kg/day) and Flecainide (4 mg/kg/day). This therapeutic choice led to satisfactory results: excellent heart rate values, most of the time in sinus rhythm with only few hours/day in Junctional rhythm at heart rate values not so higher than those in sinus rhythm. At discharge echocardiography showed normal sized cardiac chambers and normal biventricular function. After four months follow-up to date, this therapy continues to show satisfactory results in terms of clinical conditions and control of JET. Provided therapies step by step are summarized in Figure 3.

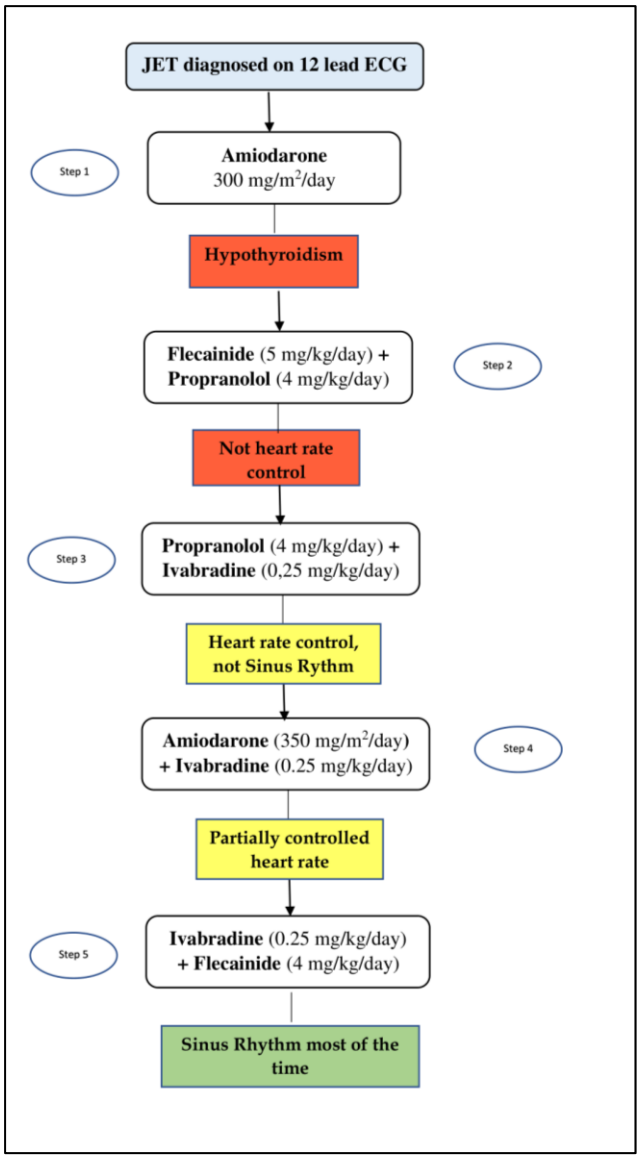

Figure 3- Congenital Junctional Ectopic Tachycardia (CJET) management in our case, step by step.

Discussion

CJET is tachyarrhythmia that can occurs in infants with a structurally normal heart and without previous cardiac surgery. In normal sinus rhythm, spontaneous depolarization of the sinus node results in propagation of electrical signal through the atrium. Conduction of the electrical signal occurs through the AV node to the ventricle via the bundle branches and His-Purkinje system. In JET, spontaneous depolarization occurs in the AV node and conducts to the ventricle. There may or may not be conduction of the signal retrograde into the atrium. A postulated mechanism of enhanced automaticity would explain why it is unresponsive to adenosine and Direct Current cardioversion, emphasizing the automatic rather than reentrant nature of this tachycardia [1].

Medical management is a challenge for most patients who typically require two or more antiarrhythmics for adequate tachycardia control [1-2].

Amiodarone, given intravenous or orally according to severity of symptoms, is therefore recommended as the first line therapy for JET. In case of unsatisfactory response, a combined therapy with Digoxin, Beta-blocking agent or Flecainide is recommended [3].

Amiodarone has been associated with toxicity involving the lungs, thyroid gland, liver, eyes, skin, and nerves. The frequency of most adverse effects is related to dosage and duration of treatment. Therefore, physicians must use the lowest possible dosage of Amiodarone and, if possible, discontinue treatment if adverse effects occur [4].

The addition of a second drug may help reduce the dose of Amiodarone and its potential long-term toxicity [5-6].
Beta-blockers, Digoxin and Flecainide are the preferred agents in Amiodarone combination therapy [1-3,7-9].
The combination of Flecainide and Propranolol has also been described as an effective alternative therapy for CJET [10].
Nevertheless, complete control of this arrhythmia is still a challenge.
Ivabradine is a novel, pure rate-lowering drug that acts by inhibiting the cardiac pacemaker I(f) current underlying the normal pacemaker function of the sinus node [11].
It has been used extensively to decrease sinus rate in the treatment of cardiac failure [12-13] and recently, it has also been reported to successfully treat JET in children with rapid rate control and establishment of sinus rhythm [14-16].
This could be explained by that these pacemaker currents are also present in the AV node and His-Purkinje cells of the cardiac conduction system, as well as in immature ventricular myocardium. I(f) current is a sodium current and flows through channels made up of tetramers of HCN channel proteins. Four isoforms (HCN1–4) of these channel proteins have been cloned, with HCN4 being the predominant isoform in the sinus node and HCN3 in the AV node (5.5- fold greater than ventricular myocardium) based on a mouse reporter gene model [17].
In this paper we conducted literature research about the use of Ivabradine in postoperative and Congenital JET. Databases of PubMed and Google Scholar were used with keywords as follows: "Junctional Ectopic Tachycardia", "children", "Ivabradine". We excluded paper as they were reviews, adult studies (>18 years), guidelines, commentaries, morbidity/mortality report, case-series already reported in another paper included. A final set of 11 articles were suitable for the scope of our review (Table 1).
As shown in Table 1, the use of Ivabradine in the treatment of JET, alone or in combination with other antiarrhythmics, has been described by several authors. [14,16,18-25].

Table 1- Use of Ivabradine in Pediatric JET – review of the literature

Author	Number of patients (N); Gender	Type of JET	Antiarrhythmic medication before Ivabradine	Treatment with Ivabradine	Outcome, Response to Ivabradine	Antiarrhythmic medication with Ivabradine	Adverse reactions
Al-Ghamdi et al. [14]	N=1; F	Congenital	Flecainide , Sotalol, Procainamide, Amiodarone	2.5 mg once daily	SR, HR control	None	None
Dieks et al. [18]	N=5; 2M,3F	Congenital	Amiodarone n=5 Flecainide n= 1 Digoxin n=2	0.05–0.1 mg/kg increased up to 0.28 mg/ kg/d.	HR control n=5 SR n=3 JR/JET n=1 JR/SR n=1	Amiodarone n=5 Propranolol, Amiodarone n=2 Digoxina, Amiodarone, Flecainide n=1	None
Ergul et al. [16]	N=3; 2M,1F	Congenital	Flecainide, Amiodarone, Digoxine n=1 Flecainide, Amiodarone and Propranolol n=2	0.1 mg/kg/day	HR control n=3 SR n=2 JR/SR n=1	Amiodarone n=1 Amiodarone, Propranolol, Flecainide n=2	None
Kothari et al. [15]	N=2; 1M, 1F	Congenital	Amiodarone, Propranolol, Flecainide n=2	0.5 mg/kg/dose	SR, HR control	Amiodarone, Propranolol, Flecainide n=2	None
Rios et al. [19]	N=2; 2M	Congenital	Amiodarone, Flecainide, Propranolol n=1 Propanolol, Amiodarone n=1	0.05/mg/kg/d ose	HR control n=2 SR/TN n=2	Amiodarone n=2	None
Khan et al. [20]	N=7 (6 JET); 5M,2F	Postoperative	Amiodarone n=7	0.05 mg/kg/dose	SR n=4 HR control with persistent slow JET n=1	Amiodarone	None
Krishna et al. [21]	N=8; 4M,4F	Postoperative	Amiodarone n=1 Overdrive pacing n=5	0.05 mg/kg/d ose twice daily	SR, HR control n=8	Amiodarone n=1	Bradycardia
Kumar et al. [22]	N=2; 1M,1F	Postoperative	Amiodarone, Esmolol n=1	0.1 mg/kg/day	SR n=2	It is not clear whether ivabradine was used as a single or adjunctive treatment	N/S
Kumar* et al. [23]	N=5; 3M,2F	Postoperative	Amiodarone, Esmolol n=5	0.1-0.2 mg/kg/d twice daily	SR, HR control n=5	Amiodarone n=2	None
Sahu et al. [24]	N=1; F	Postoperative	Magnesium sulfate, Digoxin, Amiodarone	0.05 mg/kg twice daily	SR, HR control	None	None
Sharma et al. [25]	N=4; 2M,2F	Postoperative	Magnesium n=4	0.1-0.2 mg/kg/dose	SR, HR control n=4	None	Bradycardia

F: Female; M: male; SR: Sinus Rhythm; HR: Heart rate, TN: Nodal Tachycardia; JR: Junctional Rhythm; N/S: Not Specified; JET: Junctional Ectopic Tachycardia.
*Twenty patients had postoperative JET. Among these, five infants, aged seven to twelve months, had refractory JET and were treated with Ivabradine.

Except for some findings of bradycardia, Ivabradine is generally well tolerated and led in in the greatest number of cases to good heart rate control and restoration of sinus rhythm.
When focusing on congenital JET, we found five papers describing the use of Ivabradina.
Dieks et al., basing on the outcomes observed in five patients, proposed the use of Ivabradine associated with other antiarrhythmic agents such as Amiodarone in children with CJET [18].
Al-Ghamdi et al. described a case of CJET in a three-year-old girl who converted to sinus rhythm after a second oral dose of Ivabradine [14].
Ergul et al. reported three infants with medically refractory congenital JET despite multiple antiarrhythmics (Amiodarone and Flecainide combined with either Propranolol or Digoxin), and quickly converted to sinus rhythm with an ivabradine treatment [16]. The authors however pointed that using Ivabradine as a monotherapy may not be as effective as in combination therapy.

Kothari et al. reported two siblings with CJET unsatisfactory controlled with multiple drugs including Propranolol, Flecainide, and Amiodarone and dramatically converted to sinus rhythm after the first dose of Ivabradine [15].

Rios et al. described the cases of two patients affected by congenital JET with inadequate response to other antiarrhythmic medications [19]; treatment with Ivabradine, showed a brilliant clinical response.

Although the combination of Ivabradine with other antiarrhythmic agents has already been described, Ivabradine in association with Flecainide alone, as reported here, is indeed new and this may be the first report of this combination therapy for infants with CJET.

Conclusion

The present study suggests that a combination of Ivabradine and Flecainide is an alternative effective therapy for CJET with a satisfactory efficacy/tolerability ratio in patients resistant to the conventional antiarrhythmics association.

Further studies on a larger patients' group are imperative to understand the efficacy and safety of this new drug combination.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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