Adjunctive ivabradine in combination with amiodarone: A novel therapy for pediatric congenital junctional ectopic tachycardia

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BACKGROUND Treatment of congenital junctional ectopic tachycardia (JET) is often challenging. In the majority of patients affected, a combination of ≥2 antiarrhythmic drugs is required for JET control.

OBJECTIVE The purpose of this study was to assess the efficacy and safety of adjunctive ivabradine therapy for pediatric congenital JET.

METHODS Since January 2015, 5 consecutive patients aged 10 days to 3.5 years (median 8 weeks) were treated with adjunctive ivabradine for congenital JET. All patients had previously undergone antiarrhythmic therapy with unsatisfactory control of JET. Ivabradine was administered orally at an initial dosage of 0.05–0.1 mg/kg/d divided into 2 single doses and was increased up to 0.28 mg/kg/d if necessary.

RESULTS In all 5 patients, ivabradine proved to be successful in controlling JET. Complete suppression of JET and conversion into sinus rhythm were achieved in 4 of 5 patients. The remaining patient had effective heart rate control with persistent slow JET. Mean heart rate was reduced by 31% compared to pre-ivabradine ($P = .03$) as assessed by 24-hour Holter monitoring. Echocardiography revealed improvement of left ventricular function in all 3 patients with previously impaired left ventricular function. No significant side effects of ivabradine were encountered during median follow-up of 135 days (range 37–203 days).

CONCLUSION In our group of patients with congenital JET, adjunctive treatment with ivabradine resulted in effective and safe rhythm/heart rate control and therefore may be recommended early in the course of this rare inborn tachyarrhythmia.

KEYWORDS Children; Ivabradine; Congenital junctional ectopic tachycardia; Arrhythmia

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Introduction

In pediatric patients, junctional ectopic tachycardia (JET) most often occurs after surgical repair of congenital heart defects and usually self-limiting.[1,2] Nonpostoperative congenital JET is rare and is associated with high morbidity and mortality. In a recent retrospective multicenter study, patients <6 months of age presented with faster heart rates in JET. These infants had a higher risk for incessant tachycardia and a fatal outcome.[3] Control of heart rate and/or conversion to sinus rhythm by antiarrhythmic medication is of paramount importance but often is challenging, requiring ≥2 antiarrhythmic drugs, with amiodarone being used most frequently.[3,4] Permanent cure of JET can be achieved by catheter ablation of the tachycardia substrate in selected patients. However, the risk of AV block is significant, with reports as high as 18%.[3]

Ivabradine is a novel bradycardic agent that reduces heart rate by selective inhibition of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. These channels conduct a mixed sodium–potassium inward current.[5] Activation of HCN channels leads to diastolic myocardial depolarization, thereby creating the pacemaker current of the conduction system and controlling the rate of spontaneous activity of sinoatrial myocytes.[5] Expression of HCN channels is ubiquitous in the cardiac conduction system with the highest levels in the sinoatrial node.[5–7] Ivabradine has been recommended for the treatment of stable angina and

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Table 1 Patient characteristics

	Patient no.				
	1	2	3	4	5
Sex	Female	Male	Female	Male	Female
Age at diagnosis (weeks)	8	14	14	0	0
Age at start with ivabradine	8 weeks	3 years 6 months	2 years 1 month	10 days	17 days
Weight (kg)	4.2	14.5	9.8	2.17	3.5
Length (cm)	51	94	75	48	52
Antiarrhythmic medication before ivabradine (mg/kg/d)	Amiodarone (10)	Amiodarone (10) Digoxin (0.002)	Amiodarone (5) Digoxin (0.004) Flecainide (2.5)	Amiodarone (10)	Amiodarone (10)
Antiarrhythmic medication with ivabradine (mg/kg/d)	Ivabradine (0.24) Amiodarone (10)	Ivabradine (0.22) Amiodarone (5)	Ivabradine (0.2) Amiodarone (5) Digoxin (0.004) Flecainide (2.5)	Ivabradine (0.12) Amiodarone (7) Propranolol (3)	Ivabradine (0.28) Amiodarone (10) Propranolol (4)
Inotropic support	No	No	No	Yes	Yes
Mean HR before ivabradine (Holter; bpm)	171	105	137	143	NE
Mean HR with ivabradine (Holter; bpm)	96	82	97	110	137
HR on surface ECG before ivabradine (bpm)	210	118	117	210	210
HR on surface ECG with ivabradine (bpm)	118	77	132	119	136
FS before ivabradine (%)	17	39*	38*	25	11
FS with ivabradine (%)	32	39	33	46	25
Heart rhythm at discharge from hospital	SR	SR	JR/JET	SR	JR/SR
Success of ivabradine treatment at last follow-up	Total	Total	Partial	Total	Total

FS = fractional shortening; HR = heart rate; JR = junctional rhythm; NE = not examined; SR = sinus rhythm.

*FS at diagnosis was 20% in patient 2 and 24% in patient 3.

heart failure in adult patients[8–10] because it reduces heart rate in sinus tachycardia.[11] It also proved to cause rate-dependent increase of A-H interval and slowed ventricular rate in patients with atrial fibrillation (AF) without depression of cardiac contractility.[12] In children, its use for treatment of supraventricular tachyarrhythmias has not yet been established. To the best of our knowledge, treatment of tachyarrhythmias with ivabradine in children has only been described in 1 patient with focal left atrial tachycardia[13] and in another patient with congenital JET.[14]

According to the electrophysiologic properties of ivabradine, the purpose of this study was to prospectively assess the efficacy and safety of ivabradine as an adjunctive agent in infants and toddlers with congenital JET.

Methods

Patients

Since January 2015, 5 consecutive patients were treated with adjunctive ivabradine therapy in combination with amiodarone for congenital JET in our institution. In each of the patients, diagnosis of JET was established according to standard ECG criteria as previously described.[4] All patients suffered from recurrent or permanent JET despite antiarrhythmic medication (Table 1 and Figure 1).

The study was approved by the Institutional Review Board of the Göttingen Heart Center and fully complies with the Declaration of Helsinki. Off-label use of ivabradine and the potential side effects of the medication were discussed in detail with the parents, and informed consent was obtained before therapy was initiated.

Clinical assessment

Before starting ivabradine, all 5 patients underwent detailed cardiologic workup, including 12-lead ECG and 2-dimensional (2D) transthoracic echocardiography. Twenty-four–hour Holter monitoring could be obtained in 4 of 5 patients before ivabradine administration. The remaining patient (no. 5) was in critical condition immediately after delivery and required repeated cardiopulmonary resuscitation as well as high-dose inotropic support because of hemodynamically instable JET. After amiodarone infusion failed to control JET, the patient was immediately started on ivabradine as add-on antiarrhythmic therapy.

Ivabradine protocol

Ivabradine was administered at an initial dose of 0.05–0.1 mg/kg/d divided in 2 equal doses under continuous ECG and blood pressure monitoring. All patients were admitted to the pediatric cardiac intensive care unit before starting ivabradine. If ECG and Holter monitoring did not show any significant reduction of heart rate (aim $<10\%$ vs before ivabradine) and patients tolerated ivabradine well, dosage was increased in daily steps of 0.05 mg/kg/d up to 0.28 mg/kg/d. Routine diagnostic procedures included daily ECG and 2D echocardiography, Holter monitoring every 48 hours, and daily laboratory tests including electrolytes and serum creatinine level.