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SHORT COMMUNICATION

Ivabradine in Postural Orthostatic Tachycardia Syndrome: Preliminary Experience in Children

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Abstract
Objective Ivabradine is a selective and specific inhibitor of the I(f) current in the sinoatrial and atrioventricular nodes. It decreases heart rate and myocardial oxygen consumption at rest and during exercise. It is used in adults for management of heart failure and angina, but promising results have been obtained in postural orthostatic tachycardia syndrome (POTS). There is little experience of ivabradine in childhood, although it is used on a compassionate basis. Our aim was to review our experience of ivabradine in a retrospective evaluation of pediatric patients with POTS.
Methods We evaluated all patients younger than 18 years for whom ivabradine had been prescribed for this indication, from February 2008 to June 2014.
Results Twenty-two patients were identified (15 female). Median age was 14.5 years (11–17 years). The ivabradine dosage after up-titration was 0.1 mg/kg per dose twice daily. In 15 (68%) symptoms improved. Ivabradine was suspended in five, but only in one for worsening of symptoms. There was a reduction in heart rate on resting electrocardiogram (EKG) from a mean (standard deviation) of 82.5 (13.6) bpm to a mean of 71 (16.5) bpm ($p = 0.007$). No patient had increased duration of QTc ($p = 0.44$). One (4.5%) experienced phosphenes.
Conclusions From this initial experience, ivabradine is safe in patients younger than 18 years with POTS. We observed improvement of symptoms in 68% and phosphenes in less than 5%. Further studies are needed to assess the safety in a randomized control setting.

Key Points

Ivabradine is safe in the pediatric population.

Ivabradine improves symptoms in patients with postural orthostatic tachycardia syndrome.

1 Introduction

Ivabradine is a selective and specific inhibitor of the I(f) current in the sinoatrial node and atrioventricular node. The I(f) current controls the spontaneous electrical pacemaker activity in the sinoatrial node. Ivabradine decreases the heart rate and thereby the myocardial oxygen consumption at rest and during exercise. It is used in the adult population for management of heart failure and angina [1, 2]. Ivabradine has also been used in patients with postural orthostatic tachycardia syndrome (POTS), showing good results in improving symptoms [3, 4].

Whereas ivabradine is used in the adult population, little is known about it in the pediatric population. Recently, Bonnet et al. [5] published a multicenter study establishing the efficacy of ivabradine in reducing heart rate in children with dilated cardiomyopathy. The aim of this descriptive retrospective study was to review the efficacy and safety of ivabradine in children with POTS. This was an observational study and no attempt was made to influence the

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management of the patients or the clinicians' decision-making. The patients had all been prescribed the drug on a compassionate basis by their clinician and after potential benefits and side effects had been discussed with them and their parents.

2 Methods

We evaluated patients younger than 18 years in our institution for whom ivabradine had been prescribed, from February 2008 to June 2014. We used our institutional pharmacy database. We ascertained the indication for starting the medication and in particular those where POTS was specified. POTS was defined as a sustained heart rate increase of 30 bpm or increase of heart rate to 120 bpm within the first 10 min of orthostasis associated with symptoms of orthostatic intolerance and without significant orthostatic hypotension [6]. Gender, weight, age at commencement, dose at commencement and after up-titration, reason for discontinuation, follow-up, days of treatment, medication prior to starting ivabradine, and medications with ivabradine, outcome (improvement, worsening of symptoms), heart rate and QTc at baseline and at follow-up were evaluated. Heart rate and electrocardiogram (EKG) were recorded before starting ivabradine and at follow-up.

2.1 Statistical Analysis

Normally distributed data were described with the mean and standard deviation (SD), whereas non-parametric data were described with median and range. Student's independent *t* test was used as appropriate. A statistically significant level was set at $p < 0.05$.

3 Results

From the pharmacy database, ivabradine was prescribed to 28 children < 18 years; POTS was the indication to start ivabradine in 22. Their demographics are shown in Table 1.

All patients included in this study had adopted non-pharmacological therapies (e.g., increase in salt and fluid intake, counter pressure maneuvers, avoidance of precipitating factors). One (4.5%) had hypermobility syndrome and three (13.6%) confirmed Ehlers–Danlos syndrome. A tilt test was performed in all of these 22 patients.

All 22 had an echocardiogram to exclude cardiac structural abnormalities. Twenty-four hour Holter monitoring was performed in 17 of the 22 patients (77%) showing no arrhythmia. Fourteen of the 22 patients (63.6%) were on at least one other medication for POTS prior to the introduction of ivabradine (Table 2). In four of 22 (18%), ivabradine was added to one other drug: fludrocortisone in two patients and midodrine in two patients.

Ivabradine was prescribed at the initial dosage of 5 mg/day in two divided doses. It was titrated up to 15 mg/day according to the control of symptoms.

Ivabradine was up-titrated in 11 patients (50%). Mean (SD) dose of ivabradine after up-titration was 9.5 (4.1) mg, corresponding to 0.1 mg/kg/dose twice a day. EKGs after commencing ivabradine were available for retrospective analysis in 19 patients.

3.1 Follow-Up and Outcome

Median follow-up was 4.6 (0.9–17) months. Six patients were followed up for less than 3 months. In four of them, ivabradine was discontinued: two for complete resolution of symptoms, one for worsening of the symptoms of syncope and palpitation (after 55 days). In one patient,

Table 1 Demographics and the clinician's stated indications for starting ivabradine

POTS	22 patients
Gender	Female 15, male 7
Age at commencement, median (range) and mean (SD)	14.5 (11–17) years, 14.8 (1.6) years
Dose after up-titration mean (SD), absolute and per kg	9.5 (4.1) mg, 0.1 mg/kg
Follow-up median (range)	4.6 (0.9–17) months
Duration of treatment median (range)	3.7 (0.9–17) months
EKG available for retrospective analysis (number of patients)	19
Holter 24-h monitoring (number of patients)	17
Echocardiogram (number of patients)	22
Tilt test (number of patients)	22
Baseline heart rate, mean (SD)	82.5 (13.6) bpm
Baseline QTc, mean (SD)	397.6 (20.2) ms

EKG electrocardiogram, *POTS* postural orthostatic tachycardia syndrome, *SD* standard deviation

Table 2 Medications taken prior to starting ivabradine. Some were discontinued when it was started

Number of medications prior to ivabradine	Medication	Number of patients
1	Fludrocortisone	7
	Beta-blocker	2
	Midodrine	4
	Sodium supplement	0
2	Fludrocortisone	1
	Beta-blocker	0
	Midodrine	0
	Sodium supplement	1

Table 3 Follow-up (total patients, $n = 22$)

	Number of patients	Ivabradine discontinued
Follow-up < 3 month	6	4
Follow-up > 3 months	16	1

Table 4 Evaluation of symptoms after starting ivabradine

	Improvement	Unchanged	Deterioration
22 patients	15 (68%)	6 (27%)	1 (4.5%)

ivabradine was discontinued for no change in symptoms (after 30 days).

Sixteen patients were followed up for more than 3 months: in one ivabradine was discontinued for no improvement in symptoms (after 14.5 months) (Table 3).

In 15 patients (68%), the symptoms improved according to the treating clinician: reduced syncopal episodes and resolution of symptoms (Table 4).

3.2 Side Effects

One patient (4.5%) experienced mild phosphenes (flashing lights). The ivabradine dosage was slightly reduced, from 10 to 7.5 mg/day, with improvement of the symptoms. No patient experienced symptomatic bradycardia.

3.3 Electrocardiograms

EKGs were retrospectively available for analysis in 19 of the 22 patients (86%) after starting ivabradine. Changes to heart rate and QTc are shown in Table 5.

Table 5 Changes to heart rate and QTc on starting ivabradine

	Baseline, mean (SD)	Follow-up, mean (SD)	*p*
Heart rate (bpm)	82.5 (13.6)	71.3 (16.5)	< 0.05
QTc (ms)	397.6 (20.2)	398.7 (29.1)	0.44

SD standard deviation

None of the patients had an abnormal QTc interval when on ivabradine. There was a reduction in heart rate on resting EKG, from a mean (SD) of 82.5 (13.6) bpm to a mean of 71.3 (16.5) bpm ($p = 0.007$). None of the patients developed symptomatic bradycardia.

4 Discussion

This is the first observational study to describe the use of ivabradine in patients under 18 years of age with POTS. The study was retrospective and purely descriptive, with no attempt made to influence the patients' management. The data should therefore be regarded as preliminary, but as it is the first documentation of a group of pediatric patients with POTS receiving ivabradine, it is important to report initial outcome and side effects. In this group, just over two-thirds reported improvement of symptoms. The dosage was 0.1 mg/kg twice a day. Side effects were rare, with less than 5% developing temporary and mild phosphenes that did not warrant suspension of the drug; the symptom resolved on reducing the dose. There were no concerning side effects.

Ivabradine is a promising and relatively new drug. It is a selective inhibitor of the I(f) current that contributes to sinus node automaticity. The mechanism of action has been studied in detail in isolated rabbit sinoatrial node cells [7]. Ivabradine was approved by the European Medicines Agency in 2005, and it is the first clinically approved drug that targets the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. The therapeutic indications in the adult population are the symptomatic treatment of chronic stable angina in patients intolerant to, or inadequately controlled by, beta-blockers and whose heart rate exceeds 60 bpm in sinus rhythm and heart failure [1, 8–13]. The European Society of Cardiology guidelines on heart failure suggest considering ivabradine to reduce the risk of hospitalization due to heart failure in patients in sinus rhythm with an ejection fraction of $\leq 35\%$, heart rate remaining at ≥ 70 bpm, and persisting symptoms [New York Heart Association (NYHA) class II–IV] despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), angiotensin

converting enzyme inhibitor or angiotensin receptor blocker, and a mineralocorticoid receptor agonist [2, 14, 15].

Off-label indications are POTS, inappropriate sinus tachycardia and heart rate reduction before computed tomography (CT) coronary angiography [16].

There is emerging evidence of the use of ivabradine in POTS. All the studies published are retrospective or case reports. Sutton et al. [4] reported marked benefit or complete resolution of symptoms in 72% of patients, and ivabradine was well tolerated. McDonald et al. [3] concluded that 60% of patients reported a symptomatic improvement; the drug was well tolerated. The most common reason for discontinuing ivabradine was lack of efficacy. Five of 22 patients reported side effects, leading to discontinuation in two patients. Khan et al. [17] reported a case of a 44-year-old woman with POTS and dual chamber pacemaker implanted because of intermittent complete heart block. Ivabradine was successfully used to lower heart rate. There was no evidence of POTS on repeat investigation; the pacemaker check showed a maximum heart rate of 120 bpm, and the 24-h tape showed appropriate heart rate response. There was symptomatic benefit [17].

Until recently, very little was known about ivabradine in the pediatric population. Case reports have reported ivabradine being used to treat junctional ectopic tachycardia [18] and cardiomyopathy induced by inappropriate sinus tachycardia [19]. Recently, Bonnet et al. [5] published a randomized, double-blind, placebo-controlled study. They evaluated 116 children with dilated cardiomyopathy. During a 1-year follow-up, there was a reduction in heart rate and an increase in left ventricular ejection fraction and clinical status [5].

In our retrospective observational series, we report that ivabradine is well-tolerated and safe in patients younger than 18 years with POTS. One developed mild and dose-dependent phosphenes. This visual disturbance (flashing lights) is due to ivabradine interaction with the HCN1 isoform expressed in the retinal photoreceptor. The transient change in visual sensation was observed in about 15% of adult patients following initial treatment with ivabradine [20]. It has been shown that it typically resolves during treatment [21].

As with the previous studies published in the adult population in POTS, we observed 68% improvement of the symptoms.

4.1 Limitations

This is a preliminary and observational retrospective study of a small number of children prescribed ivabradine on a compassionate basis for POTS. It was purely descriptive and not randomized or blinded. Widespread implications must therefore be guarded until such time as a randomized controlled trial is published for this indication. With these caveats, at the dose used, it does appear to be safe and have some efficacy in children with POTS. As this was an observational study, there was no attempt to influence patient management. The tilt test and Holter 24-h recordings were not repeated on ivabradine to confirm reduction in heart rate.

5 Conclusions

From our limited preliminary experience, ivabradine appears to be a safe treatment for patients under 18 years of age with POTS. There is an improvement of symptoms in over two-thirds of our patients, a low incidence of phosphenes, and no other obvious side effects. Further studies are needed to assess the efficacy and the safety of this drug in a randomized controlled setting for this indication.

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Compliance with Ethical Standards

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Conflict of interest Grazia Delle Donne, Ferran Rosés Noguer, Jan Till, Tushar Salukhe, Sanjay K. Prasad and Piers E. F. Daubeney declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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