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Single centre experience of ivabradine in postural orthostatic tachycardia syndrome

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Aims Postural orthostatic tachycardia syndrome (POTS) is associated with tachycardia on orthostasis. Patients frequently report palpitations, presyncope, and fatigue. Conventional therapy is effective in less than 60%. Case reports suggest ivabradine (a selective sinus node blocker, with no effect on blood pressure) may alleviate POTS-related symptoms. This is a retrospective case-series.

Methods and results Postural orthostatic tachycardia syndrome patients prescribed ivabradine were identified from the pharmacy database. Case notes were reviewed and participants completed a symptom assessment tool. Twenty-two patients were identified. Data were available from 20. Eight patients reported reduced tachycardia and fatigue and four reported only reduced tachycardia. The most common reason for discontinuing ivabradine was lack of efficacy ($n = 6$). Five patients reported side-effects resulting in two discontinuing treatment.

Conclusion This retrospective case series indicates that 60% of patients treated with ivabradine report a symptomatic improvement. A randomized controlled trial accessing the efficacy of ivabradine in POTS is indicated, particularly in patients resistant to, or intolerant of, conventional therapy.

Keywords Postural orthostatic tachycardia syndrome • Ivabradine • Fatigue

Introduction

Postural orthostatic tachycardia syndrome (POTS) is defined as a condition where the heart rate (HR) increases ≥30 bpm or is sustained ≥120 bpm within 10 min of sustained orthostasis.[1] It is associated with a diverse range of symptoms including palpitations, presyncope, syncope, and profound fatigue.[2] Treating POTS-related symptoms remains challenging and results are unsatisfactory. No single approach is universally effective.[3]

A wide range of pharmacological treatments has been used in POTS with approaches including increasing intravascular volume with fludrocortisone, increasing peripheral vasoconstriction with agents such as midodrine, and suppressing HR with beta-blockers or calcium channel blockers. Conventional therapies, however, are often poorly tolerated due to side-effects, such as supine hypertension or orthostatic hypotension.

Clinicians frequently find that a treatment that is effective in one patient may have no effect in others and there is limited evidence to predict response.[2] Cross-sectional studies fail to demonstrate a clear superiority of one agent over the others. Beta-blockers, fludrocortisone, midodrine, and selective serotonin reuptake inhibitors are partially effective in 40–60% by patients reports.[2] Effective treatment is, therefore, often only found through trial and error, a lengthy and frustrating process for patients.

Recent case reports have described a dramatic improvement in HR and POTS-related symptoms with ivabradine.[4,5] Ivabradine is a selective sinus node blocker, reducing firing rate without affecting blood pressure. Here, for the first time, we report a case series of POTS patients treated with ivabradine.

Methods

All patients had been seen in a tertiary cardiovascular investigation unit (Falls and Syncope Service, Newcastle upon Tyne, UK). Search of the hospital pharmacy database identified all POTS patients prescribed ivabradine. A self-reporting symptom assessment tool was developed

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locally to explore patients' experiences of ivabradine, specifically their perceptions of efficacy, changes in symptoms, and side-effects. A copy of this tool and a pre-paid envelope were sent to all patients who were currently taking, or had previously taken, ivabradine for POTS. To maximise the response rate, those who had not replied by 6 weeks were sent a reminder. Further information was obtained by review of patients' case notes.

Statistical analysis

Normally distributed data are described with the mean and standard deviation, whereas non-parametric data are described with the median and (IQR or range). Comparison of two binary, categorical groups were performed with Pearson's χ^2 test, or Fisher's exact test if the assumptions of expected cell counts were violated. Two normally distributed groups of continuous data were compared with Student's independent *t*-test. A statistically significant level was set at 0.05.

Ethical considerations

On attending the cardiovascular investigation unit, all patients provide consent to data storage for service development, audit, and research purposes. Data from all patients who provide written, informed consent were added to a clinic database, which has full Caldicott approval.

Results

Twenty-two patients had been prescribed ivabradine for POTS since January 2008 (the first occasion ivabradine was prescribed by our department) to date. Recruitment, response rate, and loss to follow-up are summarized in *Figure 1*. Ivabradine had been prescribed for the sole purpose of treating POTS. None of the patients had a history of ischaemic heart disease.

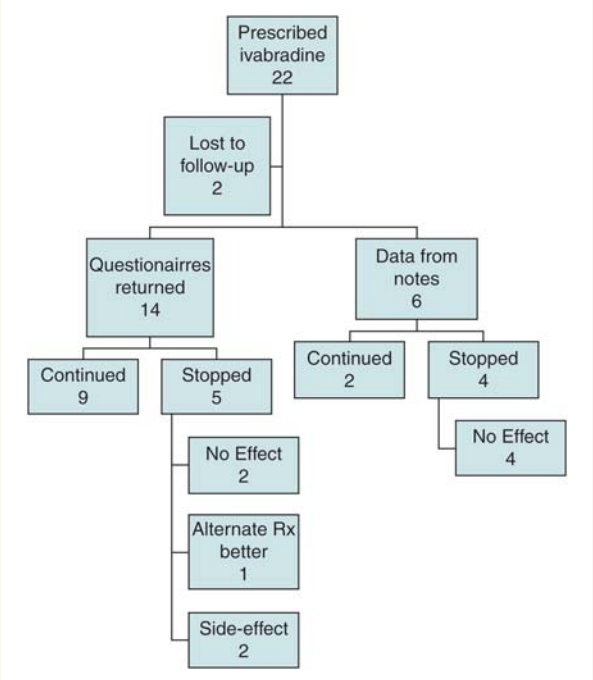

Figure 1 Recruitment, response rate, and loss to follow-up.

In keeping with previous studies, there was female predominance (females: males = 5:1). Mean age for all POTS patients was 35 ± 9.9 years. Although patients who returned the questionnaire tended to be older (mean age 36 ± 11 vs. 27 ± 9), this was not statistically significant ($P = 0.28$). There were no statistical differences between those patients currently taking ivabradine and those who had stopped (*Table 1*).

All patients had tried at least one other treatment for POTS prior to taking ivabradine, most commonly a beta-blocker (*Table 2*). Patients were initially prescribed ivabradine 2.5 mg once daily in the morning. During subsequent clinic visits, the dose was titrated according to symptoms.

Fourteen patients returned the symptom assessment tool. Case notes of the remaining eight were reviewed; four had discontinued ivabradine due to lack of efficacy; two were taking ivabradine at their last clinic appointment and had symptomatic improvement. Two patients were lost to follow-up. All 20 patients for whom data were available were included in this analysis. At the time of data analysis, 11 (55%) patients continued to use ivabradine, the median duration of treatment was 25 weeks (range 7–113), median daily dose 5 mg (range 2.5–15) taken in one or two divided doses (*Figure 2*). The percentage of patients using ivabradine was higher in the group ($n = 14$) that returned the symptom assessment tool compared with the group that did not reply ($n = 6$), but this was not statistically significant (64 vs. 33%, respectively, $P = 0.39$). All those who continued to take ivabradine (55% of POTS patients) reported fewer episodes of palpitations and tachycardia. Eight (44% of those who tolerated ivabradine) reported a reduction in fatigue. Improvement in fatigue was reported exclusively in those who had reported reduced tachycardia. Three patients took fludrocortisone and one took midodrine in conjunction with ivabradine. The most commonly cited reason for discontinuing ivabradine was no improvement in symptoms at maximum dose ($n = 6$). Five patients reported side-effects (*Table 3*), resulting in two patients discontinuing treatment, one of whom reported a reduction in HR but increased fatigue. Two patients reported visual abnormalities; phosphenes.

Table 1 Demographics of patients' currently taking ivabradine and those who are not

	Patients taking ivabradine	Patients who had stopped ivabradine	*P*-value
N	11	8	
Age (mean ± SD)	38.5 ± 10.7	30.3 ± 8.01	0.09
Male:female	11:0	4:4	0.28
Weeks since diagnosis, median (range)	55 (22–142)	59 (27–38)	0.78
Number of weeks taking ivabradine, median (range)	25 (7–113)	15 (1–111)	0.16
Number of patients reporting adverse effects	3	2	

Table 2 **Medication patients had taken for Postural orthostatic tachycardia syndrome-related symptoms before ivabradine was prescribed. (All patients had tried conservative measures before pharmacological therapy, and all were advised to continue conservative measures while taking ivabradine)**

Number of medications previously taken for POTS-related symptoms	Medications taken (in some case, multiple medication may have been taken at one time)	Number of patients
One ($n = 11$)	Beta-blocker	5
	Midodrine	2
	Fludrocortisone	2
	Calcium channel blocker	1
	Beta-blocker	3
	Midodrine	
Two ($n = 6$)	Beta-blocker	1
	Calcium channel blocker	
	Beta-blocker	1
	Fludrocortisone	
	Midodrine	1
	fludrocortisone	
Three ($n = 4$)	Beta-blocker	2
	Calcium channel blocker	
	Fludrocortisone	
	Beta-blocker	2
	Midodrine	
	Fludrocortisone	

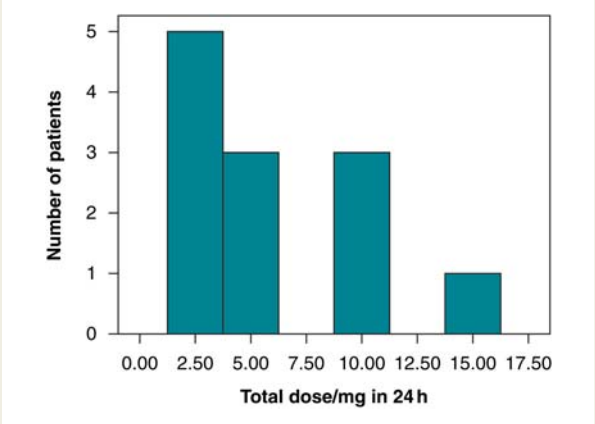

Figure 2 Dose of ivabradine.

Discussion

This is the first case series to describe the use of ivabradine in the management of POTS. We demonstrate that ivabradine can reduce the symptoms and patient perceived tachycardia in 55% of POTS patients, an efficacy comparable with other therapies.[3]

Table 3 **Reported adverse effects**

Adverse effect	Number of patients reporting adverse effect	Number of patients discontinuing ivabradine due to adverse effect
Light sensitivity	2	0
Headache	1	0
Dizziness	2	1
Nauseas	1	0
Increased fatigue	1	1

These findings are in keeping with two recent case series reporting clinical improvements in patients with inappropriate sinus tachycardia treated with ivabradine.[6,7]

In addition to cardiovascular symptoms, it is recognized that fatigue affects 55–75% of POTS patients.[2,8,9] It is therefore noteworthy that 70% of patients continuing to use ivabradine report reduced fatigue. Interestingly, only patients reporting decreased tachycardia reported a reduction in fatigue severity.

We believe that ivabradine has advantages over other therapies used POTS. Ivabradine does not cause unwanted decreases in blood pressure or supine hypertension (common problems with traditional therapy). However, it should also be stressed that, like most conventional therapy, ivabradine is not licensed for the treatment of POTS.

Two patients discontinued ivabradine due to side-effects (*Table 3*). In clinical trials, transient enhanced brightness in a limited area of the visual field, phosphenes, were reported by 14.5% of patients.[10] In our case series, two patients experienced visual symptoms which, in both cases, resolved during treatment. It is the standard practice of our unit to counsel patients regarding this common adverse effect.

When used in angina (the licensed indication), the usual starting dose is 5 mg twice a day (2.5 mg bd in the elderly). It is, therefore, interesting that the majority of patients who continued to take ivabradine found 2.5 mg od effective. Anecdotal reports from POTS patients suggest that they often have a better response to low doses of multiple medications rather than higher doses of a single agent.[3] Four patients took ivabradine in conjunction with midodrine or fludrocortisone. Fludrocortisone and midodrine have peripheral effects, increasing intravascular volume and peripheral vasoconstriction, respectively. It is possible that combined with ivabradine, these drugs offer benefit over further rate control. Ivabradine has been used in conjunction with beta-blockers in ischaemic heart disease. However, calcium channel blockers increase plasma concentration of ivabradine and concomitant use should be avoided.[11]

One limitation of the study is its retrospective design. Although retrospective recall of subjective symptoms usually guides therapy in clinical practice, prospective longitudinal studies formally quantifying patient's symptoms and the efficacy of ivabradine are needed. Few POTS treatments have been evaluated in controlled trials and well-designed studies comparing the efficacy of placebo,

conventional therapeutic approaches and ivabradine are needed to develop best practice.

In summary, this case series is encouraging but not conclusive. Ivabradine appears to control POTS-related symptoms with an efficacy similar to conventional treatment. Further systematic collection of objective data or controls is needed to establish the true efficacy of ivabradine over placebo and pharmacological agents used in the management of POTS.

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