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Efficacy of ivabradine in four patients with inappropriate sinus tachycardia: A three month-long experience based on electrocardiographic, Holter monitoring, exercise tolerance and quality of life assessments

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Abstract

Background: *Inappropriate sinus tachycardia (IST) is an uncommon disorder characterized by an exaggerated heart rate (HR). It is mostly treated with β-blockers or verapamil leaving the sinus node modulation for refractory cases. Ivabradine, a pure HR lowering agent, has proven anti-anginal efficiency linked to the I_f current inhibition. We conducted a small prospective experience investigating its efficacy in IST.*

Methods: *Four women exhibiting sinus rhythm with a resting HR ≥ 100 bpm and an average HR ≥ 90 bpm (Holter monitoring) were followed for three months. Structural heart disease and other causes of tachycardia were discarded. Electrocardiographic, Holter monitoring, exercise tolerance and quality of life determinations were performed. Ivabradine was initiated at 5 mg (bid) and increased to 7.5 mg (bid) after one week.*

Results: *All patients (mean age 33.7 years) presented a typical history of effort intolerance, palpitations and tachycardia. Resting HR (bpm) was decreased: 106.5 ± 3 to 88.5 ± 2 (week 1), to 77.0 ± 3 (week 2) and to 73.7 ± 13 (month 3). Reductions (Holter monitoring) of the maximum, average and minimum HR (beats) were: 152.0 ± 19 to 128.5 ± 18; 96.0 ± 1.4 to 73 ± 3.2 and 63.2 ± 6 to 48.2 ± 3. Total exercise time was amplified (555 ± 99 to 679 ± 90 s) and quality of life improved.*

Conclusions: *IST causes an elevated HR and its control is the treatment objective. If future data confirm our results, ivabradine could be used for this purpose. More information is necessary in order to define its role: initial option, second step (β-blockers non-responders or intolerants) or combined (refractory cases).* (Cardiol J 2010; 17, 2: 166–171)

Key words: inappropriate sinus tachycardia, ivabradine

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Introduction

Inappropriate sinus tachycardia (IST) is an uncommon form of tachyarrhythmia characterized by an exaggerated resting heart rate (HR) and/or an increased HR response to a minimal effort [1]. Its aetiology remains not well established but it has been attributed to an augmentation in the intrinsic sinus rate, associated with a beta-adrenergic hypersensitivity and a marked depressed response to the vagal reflex [2, 3]. In addition, IST has been linked to an eventual immunoregulatory dysfunction caused by anti-beta receptor antibodies [4]. This entity is defined as a nonparoxysmal tachyarrhythmia with a resting daytime HR higher than 100 beats per minute (bpm) or an average heart rate higher than 90 bpm in a 24 hours Holter monitoring with a preserved P wave morphology [1]. IST is found more often in women (4:1). Its clinical features vary from transitory episodes of palpitations to an incessant tachycardia. In this setting, patients may present dyspnoea, fatigue, thoracic pain or even syncope [5, 6]. Its standard therapy includes a beta-blocker agent or verapamil leaving the modulation of the sinus node for refractory cases [5, 7, 8].

Ivabradine is a selective inhibitor of the I_f current that contributes to the sinus node automaticity. This means it can reduce HR without disturbing the inotropic state [9]. Its effectiveness as an anti-anginal agent is well established [10–12] but its utility in the specific field of IST has not been previously investigated. Isolated experiences suggest that ivabradine may have a beneficial effect in this context [13–16].

We present a very small prospective experience with four patients suffering from IST who were treated with ivabradine. A three month-long follow-up was conducted implementing electrocardiographic, Holter monitoring, exercise tolerance and quality of life assessments. To the best of our knowledge, this is the first prospective experience evaluating the efficacy of ivabradine in patients with IST.

Methods

Objective

We wanted to investigate the chronotropic effects of ivabradine in patients fulfilling the criteria of IST. For this purpose, we followed the same diagnostic requirements used to assess the prevalence of this disorder in the OPERA study [1]. Our four patients exhibited sinus rhythm with a resting HR ≥ 100 bpm in both supine or sitting position and an average HR ≥ 90 bpm in a 24 hours Holter monitoring [1].

Have you suffered from tachycardia episodes in recent weeks?	_____
Have you suffered from palpitation episodes in recent weeks?	_____
Have you suffered a disproportionate fatigue during a routine effort in recent weeks?	_____
Have you suffered from thoracic pain episodes in recent weeks?	_____
Have you suffered from dizziness episodes in recent weeks?	_____
Have you had the sensation of being permanently tired in recent weeks?	_____

Figure 1. Quality of life questionnaire. The questionnaire was answered assigning a number (from 1 to 5) to each question (baseline and three month follow-up). Frequency of symptoms was described according to the following scale (points): No symptoms — 1; Occasional occurrence — 2; Repeated occurrence — 3; Frequent occurrence — 4; Very frequent occurrence — 5.

Patients

The studied patients were four female outpatients referred to our cardiology unit by their family doctors during 2008. All four presented a typical history of marked effort intolerance, early fatigue or dyspnoea, palpitations and exaggerated tachycardia. No previous treatment (beta-blocker agents or verapamil) had been administered to these patients.

Structural cardiac disease was ruled out (normal echocardiogram) and other causes of accelerated HR like anaemia, hyperthyroidism, diabetes, orthostatic hypotension, drugs, etc., were also discarded. After the confirmation of the diagnosis (Holter monitoring), a fatigue-limited treadmill exercise tolerance test (ETT) using the standard Bruce protocol was performed. In addition, the subjective impact of the disease was addressed by a short quality of life questionnaire which was specifically designed for this purpose (Fig. 1).

Ivabradine was provided by the hospital pharmacy. The study was approved by the local bioethical committee and all patients gave their informed consent.

Methodology

Our study was a prospective follow up of three months and ivabradine was started at an initial daily dose of 5 mg bid. This was increased to 7.5 mg bid after the first week and continued until the end

Table 1. Changes in heart rate over a three month follow-up.

Visit	HR [bpm]	Range HR [bpm]	95% CI	Variation (%)
Baseline	106.5±3	103–110	101.55–111.4	
Week 1	88.5±2	87–91	85.45–91.55	–16.9±2.7
Week 2	77.0±3	74–80	71.49–82.51	–27.7±3.8
Week 3	79.7±3	77–84	74.82–84.68	–25.0±5.0
Week 4	77.5±7	67–82	66.05–87.95	–27.7±5.6
Month 2	74.0±7	64–79	63.29–85.71	–30.1±5.5
Month 3	73.7±13	55–85	52.83–94.67	–30.9±11.4

CI — confidence interval; HR — heart rate

Table 2. Changes in heart rate assessed by Holter monitoring.

Determination	Value [bpm]	Range [bpm]	95% CI	Variation (%)
Baseline maximum HR	152.0±19	127–168	122.0–182.0	
Month 3 maximum HR	128.5±18	106–150	99.17–157.8	–15.5±4.6
Baseline minimum HR	63.2±6	57–69	54.21–72.29	
Month 3 minimum HR	48.2±3	46–52	44.07–52.43	–23.1±9.9
Baseline average HR	96.0±1	95–98	93.7–98.2	
Month 3 average HR	73.0±3	69–77	67.8–78.2	–23.9±3.6

CI — confidence interval; HR — heart rate

of the follow-up. Patients were evaluated at weeks 1, 2, 3 and 4 and during the second and third months. At the end of the third month, a new evaluation was made repeating the Holter monitoring, the ETT and the quality of life questionnaire. Data is presented as mean values ± standard deviation (SD) and two sided 95% confidence interval (CI); variation is expressed as percentage (%). CI is included in the tables in spite of the reduced sample size.

Results

The mean age of our four patients was 33.7 years (21 to 44) and all were Caucasian. None of them were smokers and their mean heights and weights were 161 ± 2.6 cm and 60 ± 9.7 kg, respectively. Mean left ventricular ejection fraction and left ventricular diastolic diameter were normal: 69.2% (65–72) and 45.2 mm (38–53), respectively.

Resting HR (sitting position) was significantly reduced after the first week using a daily dose of 5 mg bid (106.5 ± 3 to 88.5 ± 2 bpm). A significant reduction was observed after the second week, having increased the dose to 7.5 mg bid (88.5 ± 2 to 77.0 ± 3 bpm). Subsequently, HR remained stable until the end of the follow-up (77.0 ± 3 to 73.7 ± ± 13 bpm). Considering the baseline HR, ivabradine induced a dramatic reduction at three months follow-up (106.5 ± 3 to 73.7 ± 13 bpm; Table 1). On the other hand, a slight increase of blood pressure measurements (baseline-three month) was observed: 112 ± 12.6 to 120 ± 11.5 mm Hg for systolic blood pressure and from 67.5 ± 9 to 70 ± 8 mm Hg for diastolic blood pressure.

The benefit of the therapy was also confirmed in the 24 hours Holter monitoring, where the reduction of the HR (maximum, average and minimum) was evident (Table 2). Maximum and average HR significantly decreased (152.0 ± 19 to 128.5 ± 18 and 96.0 ± 1.4 to 73 ± 3.2 beats, respectively). Minimum HR was also reduced and ivabradine did not provoke excessive bradycardia (63.2 ± 6 to 48.2 ± 3 beats).

In addition, treatment with ivabradine was accompanied by an increased effort tolerance which was demonstrated as longer total exercise time (time to fatigue: 555 ± 99 to 679 ± 90 s) and a greater intensity of effort (10.68 ± 1.9 to 13.15 ± ± 1.7 METS). These positive changes were obtained departing from a lower baseline HR and reaching a lower peak exercise HR too. According to this, a reduction in the maximal theoretic heart rate (age-predicted maximal heart rate) was observed (Table 3).

Table 3. Changes in exercise tolerance test criteria.

Exercise treadmill test	Value	Range	95% CI	Variation (%)
Baseline pre-test HR [bpm]	114.8 ± 10	103–127	99.03–130.5	
Month 3 pre-test HR [bpm]	98.7 ± 13	85–112	77.67–119.8	–14.13 ± 6
Baseline time of exercise [s]	555 ± 99	450–690	396–713	
Month 3 time of exercise [s]	679 ± 90	571–780	535–823	24.6 ± 24
Baseline effort developed [METS]	10.68 ± 1.9	9.2–13.5	7.62–13.73	
Month 3 effort developed [METS]	13.15 ± 1.7	11.0–15.2	10.39–15.91	24.5 ± 17
Baseline highest HR [bpm]	178.5 ± 15	162–193	154.1–202.9	
Month 3 highest HR [bpm]	165.0 ± 25	134–187	124.8–205.1	–7.8 ± 8
Baseline MTHR (%)	93.5 ± 6	87–100	84.4–102.5	
Month 3 MTHR (%)	87.2 ± 13	69–100	66.3–108.2	–7.04 ± 9

CI — confidence interval; HR — heart rate; MTHR — maximal theoretic heart rate (age-predicted maximal heart rate)

The subjective perception of the disorder was also improved (13.25 ± 0.9 to 9.25 ± 2.7 points; Fig. 1) and no side effects from the use of ivabradine were detected.

Discussion

IST is a diagnosis of exclusion and it is necessary to rule out other causes of sinus tachycardia before considering whether it is present. This disorder was initially thought to be rare, but its prevalence in the general population seems to be higher than other arrhythmias such as Wolf-Parkinson-White syndrome or ectopic atrial tachycardia. This point was addressed in 604 patients (aged 40 to 59) belonging to the OPERA study (Oulu Project Elucidating Risk of Atherosclerosis) where IST was detected in seven subjects (1.16%). The prognosis of IST appears to be benign since none of the 11 subjects (seven OPERA patients and four extra cases) who attended a mean follow up of 6 ± 2.4 years developed any clinical or echocardiographic evidence of deterioration, although the elevated HR was maintained [1].

This inappropriately high HR is responsible for the clinical manifestations of the disease. Its reduction is the objective of the treatment. Until now, it has been mostly treated with beta-blocker agents or verapamil leaving the modulation of the sinus node for refractory cases [5, 7, 8].

Selective inhibition of the I_f current confers on ivabradine the ability to reduce HR without compromising myocardial contractility. Ivabradine has a dose-dependent effect on both resting HR and HR during exercise, something which has greater significance at a higher HR [9].

Ivabradine has proven anti-ischemic efficacy compared to a placebo [10], atenolol [11] or amlodipine [12]. Its effectiveness comparative to atenolol was revealed in a double-blind randomized study (the INITIATIVE trial) in patients with chronic stable angina. This involved 939 patients randomized to either 5 mg bid of ivabradine or 50 mg od of atenolol. At four weeks, both agents were increased (if tolerated) to 7.5 mg bid and 100 mg od respectively. Ivabradine reduced resting HR in a way comparable with atenolol and at four weeks, resulted non-inferior in all primary and secondary end-points (time to onset of angina, time to limiting angina and time to onset of 1 mm ST-segment depression) [11]. In another double-blind study, ivabradine (7.5 mg bid) was compared with amlodipine (10 mg od) in patients with stable angina. A significant reduction in HR was observed in the ivabradine group (at rest and during exercise), something which did not happen in the amlodipine group. A non-significant difference between the two groups was detected in the primary end-point (change in total exercise duration at three months) and both agents exhibited a similar improvement in terms of the frequency of anginal episodes [12]. In a further double-blind trial, 889 patients with stable angina treated with atenolol (50 mg/day) were randomized to receive ivabradine 5 mg bid for two months and then augmented to 7.5 mg bid for a supplementary two months or a placebo. Primary end-point was change in total exercise duration at four months and the ivabradine group had better results. Ivabradine in combination with atenolol was well tolerated and an additional reduction of HR was observed (at rest and during exercise). Only 1.1% of patients were removed due to sinus bradycardia in the ivabradine group [17].

Published information concerning the use of ivabradine as a pure HR lowering agent in patients not suffering from chronic stable angina has been, until now, very limited. It was successfully used in a female patient (aged 21) with postural orthostatic tachycardia syndrome in the context of a chronic fatigue syndrome [13]. The same success was observed in another woman with postural orthostatic tachycardia syndrome (aged 44) with a dual chamber pacemaker [14]. The favorable effect of ivabradine was also reported in two female patients (ages 29 and 30) with IST but intolerant to beta-blockers (fatigue and hypotension) [15, 16]. In the first case, the average 24 hours HR was reduced from 101 bpm to 76 bpm using 15 mg daily of ivabradine [15]. In the second case, resting HR was decreased from 100 bpm to 63 bpm with the same dose [16]. In addition, ivabradine was satisfactorily used in 26 heart transplant recipients with permanent sinus tachycardia secondary to cardiac denervation. Resting HR was lowered from 106.3 ± 9.1 to 82.2 ± 6.3 bpm after three weeks of treatment (5 mg bid) [18].

Generally, beta-blockers are prescribed as the first choice in the therapy of IST. But despite their efficacy, their potential side effects could represent a limitation (fatigue, induced hypotension, bronchospasm, reduced libido, etc) [19]. If beta-blockers are not well tolerated, verapamil is usually the second option, but its chronotrophic control tends to be more modest. On the other hand, sinus node modulation is an effective (though invasive) procedure which is reserved for unmanageable cases [5, 7, 8].

In our modest study, ivabradine exhibited a dose-dependent effect on both resting HR and HR during exercise. In consequence, our patients were able to develop a higher effort tolerance. The subjective perception of the disease was attenuated and ivabradine was well tolerated (no side effects).

Taking this into account, it seems reasonable to assume that ivabradine may have a therapeutic role for IST. One possibility is to use it as a valid initial choice or as an alternative to beta-blockers for non-responders or those who are intolerant. We should also consider a possible combination with a beta-blocker agent as a previous step in order to avoid an invasive modulation of the sinus node.

To the best of our knowledge, this is the first prospective experience evaluating the chronotrophic efficacy of ivabradine in this setting. Although this is a very limited study, we believe that ivabradine could be an effective and safe therapeutic choice for patients with IST. A larger study is needed to clarify its role.

Conclusions

IST is a relatively uncommon disorder that causes an elevated HR. Accordingly, chronotrophic control is the objective of the treatment. In our very limited experience, ivabradine has proved to be an effective and safe way of reducing HR in patients with IST. So, if future data confirms our results, it is highly likely that ivabradine will be of use for this purpose. More information is needed in order to define its role: initial therapy, second step (beta-blockers non-responders or intolerants) or as a combination of both in more severe cases.

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