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ORIGINAL ARTICLE

Ivabradine in patients with inappropriate sinus tachycardia

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Abstract Inappropriate sinus tachycardia (IST) is characterized by paroxysmal tachycardia originating in the sinus nodal area. IST predominately affects young, female patients. Current antiarrhythmic drug treatment (ß-blockers, calcium antagonists), frequently complicated by side effects, is often not successful. Ivabradine, approved for angina pectoris, selectively reduces heart rate by blocking the "funny current" in the sinus node. We therefore evaluated the effect of ivabradine in patients with symptomatic IST. Ten female patients (median age 32.5 years, range 12–57) suffering from symptomatic IST who had either failed (n=8) or refused (n=2) conventional therapy were analyzed. Symptoms included palpitations, pre-syncope, syncope, dyspnea, and exercise intolerance. After obtaining informed consent for individual off-label therapy, patients were treated with ivabradine (5–7.5 mg bid) in addition to beta-blocker therapy (n=3) or as mono- therapy (n=7). Therapy was monitored by 72-h Holter ECG and a symptoms questionnaire. Ivabradine significantly reduced maximum and mean heart rate (baseline, maximal heart rate 176±45/min, mean heart rate 84±11/min; ivabradine, maximal heart rate 137±36/min, mean HR 74±8/min, both $p<0.05$, all values as mean ± SD). Minimum heart rate was not significantly changed. Three patients reported transient phosphene-like phenomena without discontinuation of ivabradine while on therapy. IST-associated symptoms were ameliorated (3 pts) or suppressed (5 pts) in all eight patients who could be contacted after a mean follow-up of 16±9 months. Ivabradine appears effective and safe in patients with symptomatic inappropriate sinus tachycardia.

Keywords Ivabradine · Inappropriate sinus tachycardia · IST · I_f blocker

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Introduction

Inappropriate sinus tachycardia (IST) is an uncommon form of atrial tachycardia characterized by inappropriately rapid depolarizations in the sinus nodal region. Main clinical characteristics include a resting heart rate exceeding 90–100 beats per minute (bpm), an inappropriate heart rate increase upon physical activity, and/or paroxysmal tachy-

cardia without changes in P wave morphology compared to sinus rhythm. Typical signs for IST on 24-h Holter monitoring are a mean heart rate or resting daytime heart rate exceeding 95 bpm or an increase in heart rate of more than 25–30 bpm upon changing position from supine to upright (Castellanos et al. 1998). IST predominately affects females under the age of 50 years. A wide range of symptoms may include palpitations, pre-syncope, syncope, dyspnea upon exertion, and exercise intolerance but also "extra-cardiac" complaints like headache, abdominal pain, anxiety, and depression. The diagnosis is usually based on the abovementioned features, an association of tachycardias with symptoms and exclusion of other forms of supraventricular tachycardia.

Available treatment options include beta-blockers, calcium channel blockers, and antiarrhythmic drugs, and in drug-refractory cases, catheter-based ablation of parts of the sinus nodal region (Marrouche et al. 2002). These are often not sufficient to render patients asymptomatic.

Ivabradine is a novel antiarrhythmic drug that selectively reduces heart rate by blocking the "funny current" (I_f) in a dose-depended manner, thus inhibiting the diastolic depolarization in sinus nodal cells by (Bucchi et al. 2002; Camm and Lau 2003). Ivabradine does not alter blood pressure (Joannides et al. 2006), myocardial contractility (Manz et al. 2003), intracardiac conduction, or ventricular repolarization when given in dosages that lower heart rate (Camm and Lau 2003). Although the drug so far has been approved only for stable angina pectoris (Borer et al. 2003), its mechanism of action suggests that ivabradine could be effective in patients with IST. Case reports suggest a beneficial effect of ivabradine on IST (Khan et al. 2009). Here, we report our experience with ivabradine to reduce heart rate, improve symptoms, and suppress tachycardic episodes in patients suffering from IST.

Methods

Ten female patients (median age 32.5 years, range 12–57) suffering from IST who had either failed conventional antiarrhythmic drug therapy (beta-blocker, calcium channel antagonist, or class Ic antiarrhythmic drugs) for symptomatic IST (n=8) or who refused conventional drug therapy (n=2) were enrolled at the Department of Cardiology and Angiology, Hospital of University of Münster and the Department of Medicine 1, Ludwig-Maximilians-Universität Munich (Table 1).

All patients gave informed consent to an individualized off-label drug therapy with ivabradine. All analyses were

Table 1 Clinical characteristics and results of the follow-up interview of the patients

Patient	Age	Ivabradine daily dose (mg)	FU (months)	Previous therapy	Concomitant therapy	Effect of therapy	Adverse side effects
#1	39	10	26	Previous ablation attempt, beta-blocker, calcium antagonist, propafenone	Bisoprolol 5 mg, verapamil 160 mg	Marked improvement of palpitations and symptoms	Transient phosphenes
#2	57	10	–	Beta-blocker	Metoprolol 47.5 mg	Discontinued ivabradine due to non-cardiac disease	
#3	56	15	27	Beta-blocker	–	Complete suppression of tachycardia attacks and symptoms	Transient phosphenes
#4	38	10	27	Beta-blocker	–	Marked improvement of palpitations and symptoms	Transient phosphenes
#5	27	15	–	Previous ablation attempt, dual chamber pacemaker, beta-blocker	Bisoprolol 10 mg	NA	NA
#6	18	15	16	Beta-blocker	–	Complete suppression of tachycardia attacks and symptoms	None
#7	18	10	10	No	–	Complete suppression of tachycardia attacks and symptoms	None
#8	12	10	8	Beta-blocker	–	Slight improvement of palpitations and symptoms	None
#9	22	10	8	No	–	Complete suppression of tachycardia attacks and symptoms	None
#10	45	10	6	Beta-blocker	–	Complete suppression of tachycardia attacks and symptoms	None

done on this group of patients in accordance with the principles of good clinical practice and the Declaration of Helsinki. The ethics committee of the University of Münster approved of the judgment of the authors that the patients summarized in this report were not enrolled in a pharmacological study. Other forms of supraventricular tachycardia had been excluded by analysis of 12-lead ECG recordings during tachycardia (n=10). Blood count, electrolytes, and TSH were within normal limits. In three patients with un-equivocal diagnosis after clinical and ECG evaluation, an invasive electrophysiological study was performed which identified no sign of another form of supraventricular tachycardia. Physical examination, history, and transthoracic echocardiography showed normal left ventricular function without evidence for structural heart disease in all patients. In one patient, a catheter ablation in the sinus nodal area and an implantation of a dual chamber pacemaker was performed at another hospital in addition to beta-blocker therapy without clinical success. In another patient, an ablation in the sinus nodal area did not suppress IST.

We administered ivabradine (5–7.5 mg bid orally) as an off-label therapy in addition to a beta-blocker therapy (n=3) or as mono-therapy (n=7). The effect of therapy was analyzed in 72-h Holter ECGs before and during the initial phase of the therapy. To verify the therapeutic effect of the off-label intervention, we also contacted the patients by telephone to assess symptoms after a mean follow-up of 16±9 months.

Results

Ivabradine significantly reduced maximum and mean heart rate (max. HR 176±45/min at baseline, 137±36/min on ivabradine; mean HR 84±11/min vs. 74±8/min, both $p<0.05$, all values as mean ± SD). Minimum heart rate was not significantly changed (Fig. 1). No side effects requiring ivabradine discontinuation, especially Bradycardia-related symptoms, were noted. Discrete phosphene-like phenomena were initially reported by three patients. These resolved during the first 2 months of therapy while ivabradine was continued. IST-associated symptoms were considerably ameliorated (3 pts) or completely relieved (5 pts) in all of the patients who could be contacted for a telephone interview after a mean follow-up duration of 16±9 months (range 6–27 months; Table 1).

Discussion

Here, we report on our combined experience with ivabradine therapy for the treatment of symptomatic inappropriate sinus tachycardia. The drug, applied on an individual basis as off-label therapy, was well-tolerated and ameliorated (3/8) or suppressed (5/8) tachycardia-related symptoms after a mean follow-up duration of 16±9 (range 6–27) months. Ivabradine alone or in combination with beta-blocker therapy appears a promising therapeutic option in patients with symptomatic IST.

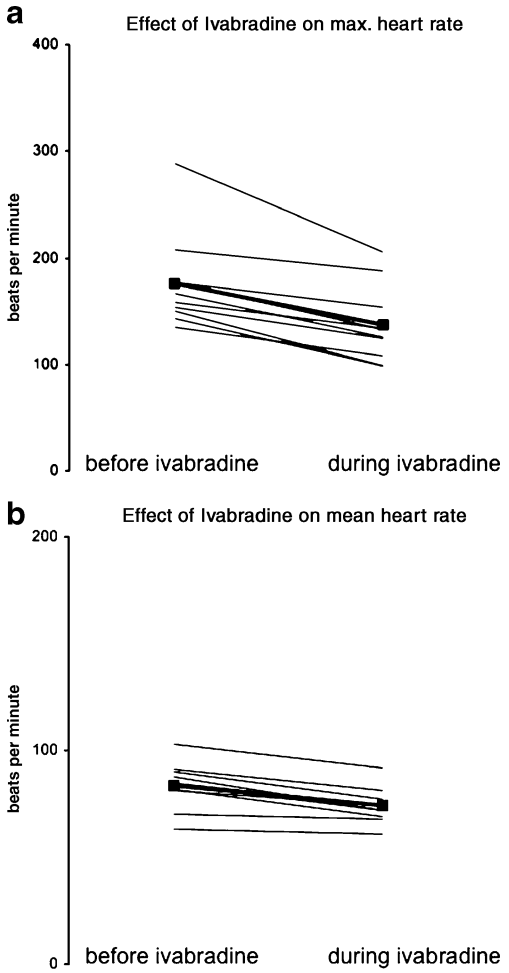

Fig. 1 Maximum (**a**) and mean (**b**) heart rates before and during ivabradine therapy in the patients. *Thin lines* show heart rates from individual patients, *thick line* shows mean values (two-sided $p<0.05$)

Several underlying mechanisms causing IST have been proposed. An intrinsic abnormality of the sinus node characterized by a high intrinsic heart rate, depressed efferent cardiovagal reflexes, and beta-adrenergic hypersensitivity have been suggested by a study in six female patients undergoing autonomic function tests (Morillo et al. 1994). An autonomic imbalance of the heart manifests as increased sympathetic tone either directly or via sympathetic receptor hypersensitivity or blunted parasympathetic tone was found in other studies in patients with IST. Even a subtle systemic autonomic dysregulation may cause IST (Shen et al. 2001). A considerable overlap of the clinical symptoms of IST with clinical features of patients suffering from postural orthostatic tachycardia syndrome is known (Grubb 2008).

Irrespective of the mechanism that causes IST in an individual patient, the "final common pathway" is thought to be an inadequate increase in sinus nodal heart rate which occurs in paroxysms that may be triggered by different autonomic constellations. The effect of ivabradine in this series of patients suggests that ivabradine may modulate this "final common pathway" and thereby suppress inadequate increase in heart rate. Of note, this "modulation" of inadequate sinus nodal function occurred without symptomatic or measurable bradycardia possibly due to ivabradine's action as an open channel blocker with a more pronounced effect at higher heart rates. Bradycardia was not noted, although three patients were treated with the combination of a ß-blocker and ivabradine. This combination treatment appears safe in IST, similar to its safety in post myocardial infarction patients with reduced left ventricular function (Fox et al. 2008). The rate of symptomatic hypotension, which often compromises the use of ß-blockers in young females, might be lower using this combination treatment because a relative reduction in ß-blocker dosage is possible. Compared to available data concerning adverse reactions to ivabradine, we observed a relatively high incidence of phosphenes after administration of ivabradine, possibly due to the relatively young age of the patients reported in this series.

Limitations

The patients studied here represent a highly symptomatic and selected group of patients suffering from IST sufficiently to desire individualized off-label therapy. Further studies comparing conventional therapies with I_f current blockade using ivabradine in a larger group of patients are warranted. A placebo-like effect while receiving ivabradine as a kind of "last resort" therapy cannot be excluded, especially in patients who previously underwent multiple treatment regimens. The cause for the high incidence of phosphenes is not known, yet these complaints were self-limiting in all cases and did not lead to a termination of the ivabradine therapy. These limitations, notwithstanding ivabradine, appear as safe and effective treatment option for patients with symptomatic IST.

Conclusions

Selective blockade of the I_f current by ivabradine, which contributes to the pacemaker activity in the sinus node, appears an effective and safe treatment option in this group of patients with inappropriate sinus tachycardia refractory to other therapies.

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