Ivabradine for the prevention of inappropriate shocks due to sinus tachycardia in patients with an implanted cardioverter defibrillator

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Aims

Ivabradine is a specific blocker of the pacemaker current (If) used to decrease the sinus rate. Several clinical trials have shown that it is beneficial, with or without concomitant beta-blocker therapy, in patients with stable angina or heart failure. We sought to take advantage of ivabradine’s ability to decrease the maximal obtainable sinus rate in order to prevent inappropriate shocks due to sinus tachycardia in patients with an implanted cardioverter defibrillator (ICD).

Methods and results

Prospective open-label series including all our patients with an implanted ICD who, during the course of 2010–2011, received ivabradine with the only purpose of preventing inappropriate ICD shocks for sinus tachycardia. These are patients who received one or more inappropriate shocks for sinus tachycardia or were conceived to be at very high risk for developing such complication. Our series includes five patients who received ivabradine (5–10 mg/day) in addition to their usual beta-blocker therapy. During a follow-up of 14 months no inappropriate shocks due to sinus tachycardia were recorded.

Conclusion

It is sensible to recommend ivabradine for the prevention of inappropriate ICD shocks due to sinus tachycardia in carefully selected patients.

Keywords

Ivabradine • Inappropriate shocks • Implantable cardioverter defibrillator • Sinus tachycardia

Introduction

Ivabradine is a specific blocker of the pacemaker current (If) used to decrease the sinus rate.1 Unlike other negative chronotrophic agents (e.g. beta-blockers, calcium blockers) it does not have negative inotropic or vasodilating effects1 and does not influence intracardiac conduction.2 Several clinical trials have shown that it is beneficial, with or without concomitant beta-blocker therapy, in patients with stable angina3–6 or heart failure.7 Furthermore, ivabradine has also been successfully used for the ‘off-label’ treatment of inappropriate sinus tachycardia8 and for heart rate slowing before cardiac imaging.9

We sought to take advantage of ivabradine’s ability to decrease the maximal obtainable sinus rate in order to prevent inappropriate shocks due to sinus tachycardia in patients with an implanted cardioverter defibrillator (ICD).

Methods

This is a prospective, non-randomized, open-label series including all our patients with an implanted ICD who, during the course of 2010–2011, received ivabradine with the only purpose of preventing inappropriate ICD shocks for sinus tachycardia. These are patients who received one or more inappropriate shocks for sinus tachycardia or were conceived to be at very high risk for developing such complication. In all but one (see below) this was a direct result of the fact that their ICD was programmed with a relatively slow ventricular tachycardia (VT)-detection rate, as mandated by previously detected spontaneous sustained monomorphic VT.

All patients received ivabradine (at doses of 5–10 mg/day) on top of maximally tolerated beta-blockers. An exercise test was performed 1 week later. The patients were then followed with the same doses of ivabradine and beta-blockers used at the time of the exercise test for a minimum of 9 months. Follow-up included ICD interrogation.

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ICD for VT recurrence. Two years after the implantation he was treated appropriately several times by the ICD following one episode of sustained monomorphic VT. Over a period 2 years he was hospitalized with monomorphic VT below the ICD’s detection rate, eventually terminated with DC shock. An attempted radiofrequency ablation somewhere else failed to abolish the VT and led to pericardial effusion. He was discharged with a very low VT detection rate (125/min) and a drug regimen including bisoprolol 10 mg/day. Following hospital discharge, however, the dose of the beta-blocker was reduced because of profound weakness. A week later he was admitted to our institution, this time due to a series of ICD shocks triggered by sinus tachycardia. The patient declined further VT ablation attempts. Ivabradine was started at this point in order to prevent further inappropriate shocks from sinus tachycardia above the (very low) VT detection rate. During a follow up of 14 months, while being treated with ivabradine (10 mg a day) and bisoprolol (5 mg a day) there were no further inappropriate ICD shocks. Implantable cardioverter defibrillator interrogation revealed several events of monomorphic VT that have been treated successfully with anti-tachycardia pacing by the device.

### Case 1

A 68-year-old man with an old myocardial infarction was implanted an ICD following one episode of sustained monomorphic VT. Over a period 2 years he was treated appropriately several times by the ICD for VT recurrence. Two years after the implantation he was implanted cardioverter defibrillator shocks due to sinus tachycardia are described in Table 1. During a follow up of 9–14 months no inappropriate shocks occurred. Two demonstrative cases are described in detail.

### Case 2

A 28-year-old man underwent an implantation of a single-chamber ICD (in a different medical centre) because of hypertrophic cardiomyopathy and multiple episodes of non-sustained VT (NSVT). Eight years later he presented to our institution after receiving a series of ICD shocks. Interrogation of the ICD revealed episodes of NSVT at a slow VT zone (all patients had more than one VT detection zone programmed) based on previously documented spontaneous VT.

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**Table 1** Details of patients treated with ivabradine for the prevention of inappropriate shocks

<table>
<thead>
<tr>
<th>Case no. (gender/age)</th>
<th>ICD indication</th>
<th>VT detection rate (b.p.m.)</th>
<th>Ivabradine indication</th>
<th>Heart rate-lowering medications</th>
<th>Ivabradine dosage (with ivabradine)</th>
<th>ΔmaxHRmin, VT detection rate (follow-up period since ivabradine initiation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M/68)</td>
<td>Ischaemic CMP (secondary prevention)</td>
<td>125</td>
<td>Inappropriate shock due to sinus tachycardia</td>
<td>Bisoprolol—5 mg/day</td>
<td>10 mg/day</td>
<td>NC</td>
</tr>
<tr>
<td>2 (M/28)</td>
<td>Hypertrophic CMP</td>
<td>188c</td>
<td>VT detection ≈ sinus tachycardia rate $^d$</td>
<td>Metoprolol—300 mg/day</td>
<td>10 mg/day</td>
<td>68</td>
</tr>
<tr>
<td>3 (M/64)</td>
<td>Ischaemic CMP (secondary prevention)</td>
<td>100</td>
<td>VT detection ≈ sinus tachycardia rate $^d$</td>
<td>Bisoprolol—10 mg/day</td>
<td>10 mg/day</td>
<td>30</td>
</tr>
<tr>
<td>4 (M/79)</td>
<td>Ischaemic CMP (secondary prevention)</td>
<td>140</td>
<td>VT detection ≈ sinus tachycardia rate $^d$</td>
<td>Carvedilol—25 mg/day</td>
<td>5 mg/day</td>
<td>40</td>
</tr>
<tr>
<td>5 (M/66)</td>
<td>Ischaemic CMP (primary prevention)</td>
<td>140</td>
<td>VT detection ≈ sinus tachycardia rate $^d$</td>
<td>Bisoprolol—2.5 mg/day</td>
<td>10 mg/day</td>
<td>20</td>
</tr>
</tbody>
</table>

ATP, anti-tachycardia pacing; CMP, cardiomyopathy; HR, heart rate; ICD, implantable cardioverter defibrillator; NC, not capable of performing a treadmill-based exercise test (Parkinson’s disease); VT, ventricular tachycardia.

$^a$The slowest VT zone (all patients had more than one VT detection zone programmed) based on previously documented spontaneous VT.

$^b$The relatively slow VT detection rate of 188/min was mandated by the special programming required to prevent QRS double-counting during non-sustained VT.

$^c$Ventricular tachycardia detection rate $\approx$ sinus tachycardia rate signifies that the recorded or expected maximal sinus tachycardia was within 20 b.p.m. of the VT detection rate.

$^d$ΔmaxHRmin, VT detection rate is the difference between the programmed VT detection rate and the maximal sinus tachycardia during symptom limited exercise testing.
rate of 140/min. Erroneous QRS double-counting during VT caused the ICD to classify these events as ventricular fibrillation (VF) and deliver an inappropriate shock (Figure 1). Importantly, QRS double-counting was never present during sinus rhythm. To prevent further inappropriate shocks, the ventricular refractory period was prolonged, using a value of 157 ms based on the spurious ‘R–R’ interval recorded during double-counting. As a consequence of the selected ventricular refractory period, the VT zone had to be set for 188/min to allow for a sufficient ‘alert period’ in case of recurrent VT. Prior to hospital discharge, VF was induced and appropriate detection and termination by the device was demonstrated. However, in spite of treatment with high doses of beta-blockers (metoprolol 300 mg/day), sinus tachycardia within the range of his programmed VT zone was recorded during exercise testing. In order to prevent inappropriate shocks, this time due to sinus tachycardia, ivabradine was added to his treatment. Repeated symptom-limited exercise tests showed a maximal sinus rate of 120. During a follow-up of 14 months no further events were recorded. Additional cases (cases 3–5) are shown in Table 1.

**Discussion**

Inappropriate ICD shocks occur in 10–25% of patients after ICD implantation.\(^\text{10–14}\) Shocks cause pain, anxiety, and frank fear, and have been shown to reduce quality of life.\(^\text{15–18}\) In one survey,\(^\text{15}\) 5% of patients indicated they would rather be without an ICD because of fear from shock delivery. Furthermore, inappropriate shocks may induce VT or VF\(^\text{10}\) and be fatal if recurrent.\(^\text{19–21}\) Whether by this mechanism or others, inappropriate shocks...
have been associated with increased mortality in some (albeit not all) studies.\textsuperscript{13}

The most common cause of inappropriate shocks is supraventricular tachycardia, including primarily atrial fibrillation but also sinus tachycardia.\textsuperscript{11,13} Methods to prevent inappropriate shocks due to sinus tachycardia include ICD discrimination algorithms, programming the lowest VT zone to a rate as high as possible and treatment with heart rate-lowering drugs. Unfortunately, in some patients ICD algorithms and programming are inadequate and drugs are contra-indicated or not tolerated at the high dosages required. The $I_f$ channel blocker ivabradine may be of benefit in these cases as it lowers heart rate without the side effects of other heart rate-lowering drugs such as beta-blockers or calcium channel blockers.\textsuperscript{1,2}

As described in the cases above, patients who may benefit from ivabradine for this indication include two groups: (i) patients with an ICD programmed to detect VT at low rates: these patients most typically have extensive scars from previous myocardial infarction and/or treatment with antiarrhythmic drugs that slow the VT rate. This mandates programming of the lowest VT zone to a low heart rate that may overlap with the sinus rate achievable during stress, exposing the patient to the risk of inappropriate shocks. In case VT ablation is unsuccessful, contra-indicated or unacceptable by the patient, ivabradine may be of use. A low VT detection rate may also be needed with special ICD programming (e.g. in cases of QRS double-counting, as in case 2). (ii) Patients likely to reach high sinus rates: these patients are most frequently young and physically active. If the lowest VT zone needs to be programmed to $<200$ min, they also may be at risk of inappropriate shocks because during physical activity their sinus rate might approach this level. Young patients are often reluctant to take beta-blockers and ivabradine may prove to be a suitable alternative.

We demonstrated appropriate blockade of sinus node acceleration during exercise test with ivabradine prior to hospital discharge. The maximal sinus tachycardia achieved during an exercise test is an imperfect (at best) surrogate for the maximal achievable sinus tachycardia in real life. Nevertheless, the absence of adverse events with the use of ivabradine for the prevention of inappropriate shocks during a mean follow-up period of 12 months is rewarding.

Of note, the effect of ivabradine on the defibrillation threshold has not been thoroughly evaluated. Although this should be kept in mind while prescribing ivabradine to a patient with an ICD, it should also be remembered that systematic defibrillation threshold testing is controversial.\textsuperscript{22}

In our series, most patients had ischaemic cardiomyopathy with low left ventricular ejection fraction. In view of the proven beneficial role of ivabradine for patients with angina and heart failure,\textsuperscript{3–7} it will be practically impossible to conduct randomized studies of this drug for the prevention of inappropriate ICD shocks. We believe it is sensible to recommend ivabradine for the prevention of inappropriate ICD shocks due to sinus tachycardia in carefully selected patients.

\textbf{Conflict of interest:} none declared.

\textbf{References}