

hERG potassium channel inhibition by ivabradine may contribute to QT prolongation and risk of Torsades de Pointes

by

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Ivabradine is the first and only specific bradycardic agent in current clinical use. It reduces heart rate through slowing diastolic depolarization in the sinoatrial node by inhibition of ionic current carried by the HCN ion channel family [Rushworth *et al.*, 2011]. Results from the BEAUTIFUL study showed that ivabradine may reduce coronary artery disease (CAD) outcomes in a subset of patients with baseline heart rates of 70 beats min⁻¹ or greater [Fox *et al.*, 2008] and may also improve left ventricular ejection fraction and reverse deleterious ventricular remodelling [Ceconi *et al.*, 2011]. The drug has been approved for use in Europe for some time and in April of 2015, the US Food and Drugs Administration (FDA) granted approval for the use of ivabradine to decrease hospitalization from heart failure [FDA, 2015]. Under this approval, ivabradine is indicated for individuals with stable heart failure and a heart rate of 70 beats min⁻¹ or more, who are already in receipt of β -blocker therapy [FDA, 2015].

Although ivabradine has been considered to have a good cardiac safety profile [Camm & Lau, 2003; Savelieva & Camm, 2006], recent evidence has highlighted that some qualification is necessary in this regard. Thus, a meta-analysis of clinical trial data has reported an increased relative risk of atrial fibrillation in patients receiving ivabradine [Martin *et al.*, 2014]. Also, in the SIGNIFY trial, which focused on patients with stable CAD without clinical heart failure and with a heart rate of 70 beats min⁻¹ or more, ivabradine did not improve patient outcomes [Fox *et al.*, 2014]. Indeed, in a subset of patients with activity-limiting angina, ivabradine was associated with an increase in the primary end-point of the trial: the composite of death from non-fatal myocardial infarction or cardiovascular causes [Fox *et al.*, 2014].

A year ago, ivabradine was added to the “CredibleMeds” database of clinically used drugs that are associated with prolongation of the QT interval of the ECG and with *Torsades de Pointes* (TdP) arrhythmia [Anon, 2014]. Ivabradine was classed as a drug with a ‘conditional risk’ of TdP, with the CredibleMeds update saying that “There is substantial evidence that ivabradine is associated with TdP when taken with other

medicines that prolong the QT interval, diuretics or drugs that block the metabolic breakdown of ivabradine, or electrolyte abnormalities (low potassium or low magnesium), which may be induced by co-administration of diuretics" [Anon, 2014]. Publicly accessible information on the European database of suspected drug reaction reports shows that 24 individual cases of TdP associated with ivabradine have been reported by health-care professionals, up to March 2015 [Anon, 2015]. Two recently published case-reports also highlight an association between ivabradine use and TdP in a setting of concomitant drug use. One of these cases involved a 68 yr old male treated with ivabradine for paroxysmal sinus tachycardia, who developed TdP when additionally given azithromycin for acute sinusitis [Cocco & Jerie, 2015]. The second case involved an elderly (80 yr old) female who was given ivabradine together with ranolazine and diltiazem for the treatment of unstable angina [Mittal, 2014]. She developed a slow junctional rate, prolongation of the rate-corrected QT (QT_c) interval and transient TdP. The authors of the latter study highlighted that the patient had no electrolyte abnormalities, but that ivabradine and ranolazine share the same metabolic pathway (CYP 3A) with diltiazem [Mittal, 2014].

When ivabradine was administered intravenously (0.2 mg kg⁻¹) to 14 patients (12 males, 2 females) with normal baseline electrophysiology, it was reported to lead to a heart rate reduction of 13-14 beats min⁻¹ (at 0.5 and 1 hr following administration) and to prolong the QT interval, without changes in PR or QRS intervals [Camm & Lau, 2003]. However, when QT interval values were corrected for heart rate (QT_c) [in that study](#), no change in QT_c interval was seen with ivabradine. These findings may be interpreted as suggestive that the role of ivabradine in TdP arising with drug co-administration is indirect rather than direct, either/both through inducing bradycardia or through impairment of metabolism of other drugs with a QT interval prolonging propensity. However, on the basis of recent data from our laboratories [Melgari *et al*, 2015], we suggest that ivabradine itself has the potential for *direct* effects on ventricular repolarization. Virtually all drugs associated with TdP act as pharmacological inhibitors

of *hERG* (*human Ether-à-go-go-Related Gene*) potassium channels, which mediate the cardiac rapid delayed rectifier potassium current (I_{Kr}) [Sanguinetti & Tristani-Firouzi, 2006]. We have recently demonstrated that ivabradine inhibits *hERG* channels with a potency that is similar to that reported for HCN4, the predominant HCN channel isoform in the sinoatrial node [Melgari *et al*, 2015]. Moreover, we found that concentrations of ivabradine between 100 and 500 nM prolonged the duration of monophasic action potentials recorded from both the left ventricular apex and base of perfused, paced guinea-pig hearts, whilst effective refractory period was prolonged and maximal restitution slope for basal action potentials was steepened [Melgari *et al*, 2015]. On the basis of the concentration-dependence of these effects, we suggest that at low therapeutic concentrations, ivabradine normally has a small propensity to impair ventricular repolarization directly, but at higher concentrations or with tissue accumulation, it may contribute to delayed repolarization [Melgari *et al*, 2015]. A similar argument can be made for co-administration of ivabradine with drugs that impair its metabolism (thus resulting in increased plasma ivabradine levels), or that themselves act on *hERG*, in which event synergistic effects of the combination of drugs on *hERG* and repolarization might occur. [The ability of ivabradine to inhibit *hERG* has subsequently been verified independently \[Lees-Miller *et al*, 2015\]](#). Furthermore, another distinct study has provided evidence that effects of ivabradine on repolarization may be augmented when other potassium currents are also reduced and so 'repolarization reserve' is impaired [Koncz *et al.*, 2011]. Thus, whilst it is already recognized that, due to its bradycardic action, ivabradine should not be co-administered with QT prolonging agents [Savelieva & Camm, 2006], we suggest that an additional important reason for such caution is the drug's potential to interact with *hERG* and thereby directly influence ventricular repolarization.

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Disclosures None declared

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