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Could ivabradine be a new treatment for the short QT syndrome?

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The short QT syndrome (SQTS) is a rare condition involving accelerated ventricular repolarization, abbreviated rate-corrected (QTc) QT intervals on the electrocardiogram (ECG), poor rate adaptation of the QT interval, and an increased risk of atrial and ventricular arrhythmias and of sudden cardiac death.[1-3] In patients with genetic forms of SQTS, thus far gain-of-function mutations have been found in three potassium ion channel genes: \( \text{KCNH2} \) (responsible for \( \text{hERG} \) potassium channels that mediate the rapid delayed rectifier current, \( I_{Kr} \); \( \text{KCNQ1} \) (responsible for the \( \alpha \) subunit of channels mediating the slow delayed rectifier current, \( I_{Ks} \)); \( \text{KCNJ2} \) (which encodes Kir2.1 channels that carry inwardly rectifying K\(^+\) current).[1-3] Mutations to these genes are respectively responsible for SQT1, SQT2 and SQT3 variants of the syndrome. Loss-of-function mutations in both pore-forming (\( \text{CACNA1C}, \text{SQT4} \)) and accessory (\( \text{CACNB2b}, \text{SQT5}; \text{CACND2D1}, \text{SQT6} \)) subunits of L-type Ca channels have also been identified.[1-3] Treatment of the condition frequently involves the use of implantable cardioverter devices (ICDs), which protect against potentially fatal ventricular arrhythmias. Adjunct pharmacotherapy can be useful in delaying repolarization and decreasing arrhythmia risk. However, Class III drugs such as sotalol are ineffective in SQTS patients with \( \text{KCNH2} \) mutations that reduce affinity of the drug for the \( \text{hERG} \) channel. Current SQTS antiarrhythmic pharmacotherapy predominantly involves use of the Class Ia antiarrhythmic agent (hydro)quinidine.[1-3]

There is at present no mammalian model that accurately reproduces a clinically identified SQTS genotype. Investigations of the mechanisms underlying arrhythmogenesis in the syndrome have therefore relied either on computer modelling[4] or the use of isolated hearts or tissue preparations to which pharmacological activators of potassium channels are applied; these induce an increase in repolarizing K\(^+\) current, if not through the precise mechanisms of identified SQTS mutations.[5, 6] The \( \text{K}_{\text{ATP}} \) channel opener pinacidil has been used with perfused left ventricular wedge and whole heart preparations to help identify arrhythmia substrate(s) in the condition.[5] In the canine wedge preparation, pinacidil has been shown to abbreviate ventricular repolarization and exacerbate transmural dispersion of repolarization.[5] In perfused rabbit hearts pinacidil abbreviates repolarization, increases dispersion of repolarization and shortens the effective refractory period (ERP).[7] These changes are broadly similar to those predicted from computer modelling of SQTS mutations.[4] Increased transmural dispersion of repolarization and abbreviated ERP
increase vulnerability to re-entrant arrhythmia. Consistent with patient data, quinidine has been shown to be effective in the pinacidil-treated, intact perfused hearts at countering increased arrhythmia susceptibility, delaying repolarization and ERP, and prolonging post-repolarization refractoriness (PRR).[1-3, 7] Pinacidil-treated, intact, paced rabbit hearts have also been used to pursue additional potential pharmacological treatments, with recent work showing prolongation of QT interval and of ERP and suppression of VF by both ranolazine and vernakalant.[8] In a new report in this volume of the journal, Frommeyer and colleagues have now employed the pinacidil-treated whole rabbit heart SQTS model, to demonstrate a potentially beneficial role for ivabradine in the SQTS.[9]

Ivabradine was developed as a specific bradycardic agent, with clinical applications in coronary artery disease and heart failure.[10] It acts to slow the spontaneous action potential firing rate of the sinoatrial node (SAN), via inhibition hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels that underpin the “funny” current, If, which participates in generating diastolic depolarisation.[10] The specificity of the drug for HCN channels enables a bradycardic effect without the concomitant negative inotropy that can occur with β blockers.[10] Recently, however, two independent reports have demonstrated that ivabradine inhibits hERG potassium channels over a concentration range which overlaps that for inhibition of If and HCN4, the dominant HCN isoform in the SAN.[11, 12] Moreover, in perfused, paced guinea-pig hearts ivabradine has been seen to prolong monophasic action potential duration and ERP at submicromolar concentrations that are relevant to the clinical concentration range.[11] Whilst such actions might be undesirable against a background of normal repolarization, a logical question that arises is whether they might be beneficial in a pathological setting of abbreviated ventricular repolarization? In their paper, Frommeyer and colleagues answer this question using ECG and monophasic ventricular AP recordings from perfused rabbit hearts.[9] The hearts were electrically paced following destruction of the AV node. In the absence of pinacidil, application of ivabradine concentrations between 1 and 5 μmol/L did not significantly prolong QT interval or monophasic AP duration (APD, measured at 90% repolarization), though at 5 μmol/L an increase of ERP was observed. The reason for the lack of overtly prolonged repolarization is unclear; though, as the authors comment, this may reflect the sample size used. However, repolarization-delay became marked when ivabradine (5 μmol/L) was applied after pinacidil
(1 μmol/L). As expected, APD90, QT interval and ERP were abbreviated by pinacidil; they were subsequently lengthened, across a range of cycle lengths, by ivabradine. The extension of ERP exceeded that of APD90, resulting in an increase in PRR. Importantly, whilst pinacidil led to increased vulnerability to induction of ventricular fibrillation by programmed ventricular stimulation, ivabradine markedly suppressed this inducibility. To summarise: under the conditions of this study, ivabradine showed clear antiarrhythmic effects in the pinacidil SQTS model.

The findings in this paper are important in two respects: first, they provide further evidence that ivabradine can exert clear electrophysiological actions that are independent of If/HCN channel inhibition; second, they provide proof-of-concept that, at least under the conditions of this study, ivabradine is antiarrhythmic against abbreviated ventricular repolarization. So, could the drug be beneficial in clinical SQTS? Possibly, yes, though further preclinical work is likely needed first. In particular, it would be useful to verify that submicromolar ivabradine concentrations closer to the clinical range produce similar effects to those seen here.

Second, as the authors themselves note, one of the main SQT1 hERG mutations (N588K-hERG) significantly reduces the ability of ivabradine to block the channel[11] and so the drug is unlikely to be effective in forms of SQT1 in which hERG channel inactivation is markedly impaired. Third, the paced preparation used in this study eliminates the bradycardic effect of ivabradine on the sinoatrial node and this would not be the case in the clinical setting. The significance of this point is that some forms of SQTS are themselves associated with bradycardia. For instance, one study has reported that up to 75% of SQT2 cases and 9% of non-SQT2 cases also show sick sinus syndrome/bradycardia.[3] Ivabradine would be expected to exacerbate these and so should be avoided in such cases. Also, as has been commented by others,[1] heterogeneity of repolarization and abnormality of the QT-RR relationship are likely to be greatest at slow rates, and this may facilitate susceptibility to tachyarrhythmia. Thus, if ivabradine were to be pursued further as a potential treatment for the SQTS, it may be important to establish whether or not the drug’s prolongation of PRR would suffice to offset any increased vulnerability associated with drug-induced bradycardia.
DISCLOSURE

None.

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