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Disopyramide: Although potentially life-threatening in the setting of long QT, could it be life-saving in short QT syndrome?

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Approximately eight years ago (February, 1998), the antihistamine terfenadine (Seldane) was taken off the US market because of the death of 7 individuals concomitantly administered the antifungal ketoconazole, a CYP3A inhibitor, or the macrolide antibiotic erythromycin, an inhibitor of the rapidly activating delayed rectifier channel current, I_{Kr}. Among the effects attributed to terfenadine was its ability to block the I_{Kr} channel, via inhibition of the α subunit of the I_{Kr} channel, encoded by the human ether à gogo-related gene (HERG) [1,2]. Blockade of I_{Kr} prolongs the cardiac ventricular action potential, resulting in a prolongation of the QT interval in the ECG, which in some individuals is accompanied by the development of a life-threatening polymorphic ventricular tachycardia known as Torsade de Pointes (TdP). The withdrawal of terfenadine was followed by the withdrawal of 4 additional agents (sertindole, astemizole, grepafloxacin and cisapride) in rapid succession, for similar reasons. Such drug-induced reactions are referred to as acquired forms of the long QT syndrome (LQTS), to distinguish them from the congenital or inherited forms (LQT2) that develop secondary to genetic mutations. A genetic predisposition to acquired LQTS has also been demonstrated in recent years [3].

These findings prompted the Unites States Food and Drug Administration (FDA) to require testing of all drugs for such undesirable side-effects. A number of Class IA and Class III antiarrhythmic drugs have been identified among the group of agents capable of prolonging the QT interval and inducing TdP; included among them are quinidine and disopyramide [4, 5]. Like other Class 1A and III antiarrhythmic agents, disopyramide is used with caution, particularly in individuals predisposed to LQTS [6,7]. The work by McPate and co-workers in this issue of JMCC [8] shows that the effects of disopyramide which can be life-threatening in the setting of LQTS, may be life-saving in Short QT Syndrome (SQTS).

Unlike QT prolongation, abbreviation of the QT interval was not considered to pose an arrhythmic risk until the publication by Gussak et al. [9] identifying this phenotype as a new clinical entity associated with an arrhythmic burden. The familial nature of the disease was further delineated by Gaita et al. in 2003 [10]. Since its discovery in 2000, families displaying short QT intervals associated with atrial and ventricular tachycardia and fibrillation, have been identified in Brazil, Finland, Germany, Spain, the Netherlands, France, Turkey, Italy and the United States. Over 40 patients with short QT syndrome (SQTS) have been reported to date. Giustetto et al. [11] reviewed the clinical profile of 27 patients with SQTS and found syncope in 40% and cardiac arrest in 26%. The diagnosis had been made in young adults, children as well as infants as young as 3 month of age, suggesting that it may account for some cases of Sudden Infant Death Syndrome (SIDS).

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The definition of SQTS is still in a state of flux. While the syndrome appears to be a primary electrical disease characterized by an abnormally short QT interval and a propensity to atrial and/or ventricular tachycardia and fibrillation [12,13], the appropriate cut-off for QT interval in SQTS is not clearly delimited. In cases published thus far, reported QT intervals are ≤320 ms. Because rate-adaptation of the QT interval is abnormal in SQTS patients, the QT interval may appear normal at fast heart rates when a Bazzett's or other correction is applied, but turn out to be abnormally short during slow heart rates [10]. A relatively shallow QT-RR relationship is also observed in patients with idiopathic ventricular fibrillation (IVF) [14]. Moreover, Viskin and co-workers have reported that short QT intervals (QTc of ≤360 for males and ≤370 for females) are commonly observed in patients with idiopathic ventricular fibrillation (IVF) [15]. Abbreviation of cellular action potential duration leads to abbreviation of atrial and ventricular refractory periods, which combined with flattening of the refractory period/ heart rate relationship, increases ventricular vulnerability to VT/ VF. Clinical observations of a prolonged Tpeak-Tend interval and direct measurements in an *in vitro* model of SQTS suggest that augmented transmural dispersion of repolarization [16] underlies the substrate for the development of VT/VF. A recent study has also proposed the hypothesis that differences in repolarization time between Purkinje fibers and ventricular myocardium contribute to the substrate and/or trigger for the development of VT/VF [17].

Genetic screening has identified 3 genes linked to SQTS. A missense mutation in which arginine at position 588 of HERG is replaced by lysine (N588K) has been found in three separate families [18,19]. KCNH2 (HERG) encodes the α subunit of the potassium channel responsible for I_{Kr} [20]. Soon after the discovery of this first hereditary form of short QT syndrome (SQT1), a sporadic case involving a mutation in KCNQ1 (SQT2) [21] and two other cases involving related patients carrying mutations in KCNJ2 (SQT3) [22] were identified. Whereas SQT1 is linked to a gain of function in I_{Kr}, SQT2 involves a gain of function in the slowly activating delayed rectifier current, I_{Ks}, and SQT3 is caused by a gain of function in the inward rectifier potassium current, I_{K1}. These currents all contribute to phase 3 repolarization in atria and ventricles. As a consequence, each of the channel mutations has the potential to abbreviate the ventricular and atrial action potential.

In SQT2, the gain of function of I_{Kr} is caused by loss of inactivation of the channels within the voltage range of the action potential [17,18], whereas in LQT2 it is due to a negative shift in the voltage dependence of activation [21] and in LQT3 the gain of function is secondary to a reduction in inward rectification of I_{K1} due to disruption of binding of polyamines [22].

Pharmacological testing of Class III antiarrhythmic agents such as sotalol and dofetilide (E4031) to correct the gain of function of I_{Kr} revealed that the N588K mutation decreased the affinity of the channel for these drugs such that the IC_{50} values were increased to concentrations outside the therapeutic range [23]. Biophysical analysis revealed that N588K mutation induced a +90 mV shift in the voltage-dependence of inactivation of the HERG channel [17,18]. It therefore came as no surprise that drugs such as sotalol and dofetilide, which have a higher affinity for channels in the inactivated state, failed to block the N588K HERG channel effectively. Because of its propensity to block open channels and its ability to block I_{Ks}, quinidine was thought to be a better choice to suppress the augmented repolarizing current. Quinidine proved more effective both in *in vitro* expression studies as well as in patients. Quinidine (1 g/day) significantly prolonged the QT interval, steepened the QT/HR (heart rate) relationship and prevented induction of VT/VF [24]. When expressed in HEK293 cells, N588K-HERG decreased the affinity of quinidine for the channel to a lesser degree than observed with the Class III antiarrhythmic agents. Whereas the IC_{50} for sotalol was increased 20-fold, the IC_{50} for quinidine was increased by only 5.8-fold [24]. These results suggest that drugs favoring open channel block of HERG are better candidates for suppression of the gain of function produced by N588K.

The work presented by McPate and colleagues [8] in this issue of JMCC provides a further test of this hypothesis. Previous studies have shown that I_{HERG} inactivation plays little role in the inhibition of the current by disopyramide [7]. McPate et al. evaluated the action of disopyramide in Chinese Hamster Ovary (CHO) cells expressing WT-HERG and N588K-HERG. Unlike previous studies, they conducted their experiments at a physiological temperature (37°C). In addition, they contrasted the response of disopyramide with that of E-4031, a selective I_{Kr} blocker and quinidine, another Class IA antiarrhythmic agent. The presence of the N588K mutation only slightly attenuated I_{HERG} blockade by disopyramide (1.5-fold increase of IC_{50}), compared to quinidine (3.5 fold increase of IC_{50}) and the Class III antiarrhythmic drug E-4031 (11.5-fold increase of IC_{50}). These findings indicate that of the various drugs studied to date, disopyramide is the one least affected by the N588K HERG mutation, presumably because of its limited dependence on the inactivated state of the channel for the development of block.

Disopyramide is associated with QT prolongation as well as prolongation of the refractory period in the atria and ventricles of normal individuals and these findings provide a rational basis for its evaluation as a treatment for SQT1. It is noteworthy that disopyramide has anticholinergic properties that may be of further benefit, especially in suppressing atrial arrhythmias. The results also provide support for the hypothesis that open state block (open channel block) of the I_{Kr} channel is an important criteria to consider in the search for pharmacologic therapy of N588K-mediated SQT1.

Because of the high risk of VT/VF and sudden cardiac death, an implantable cardioverter defibrillator (ICD) remains first line treatment for SQTS. However, ICD therapy is not without problems as the characteristic high amplitude T waves can cause oversensing, leading to double counting of the R and T waves, and inappropriate shock therapy. Frequent adjustments of ICD sensitivity are needed and ICD therapy may not be available or suitable for any number of reasons [25,26]. The need for a pharmacological approach to therapy is undeniable in these cases as well as in those in which frequent appropriate shocks are delivered.

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