A novel genetic modifier for clarithromycin-related cardiac arrhythmia risk?

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A number of drugs in clinical use, including some antimicrobial agents, are associated with prolongation of the QT interval and the associated ventricular arrhythmia *torsades de pointes* (TdP) [Vandenberg *et al.* 2001; Yap and Camm, 2003; Bril *et al.* 2010]. Although typically the incidence of TdP with particular drugs is low, the potential hazard is high as TdP either (usually) spontaneously resolves into sinus rhythm or degenerates into potentially fatal ventricular fibrillation. Consequently, to maximize safety in both drug development and in the use of existing drugs, it is important to establish factors that may exacerbate QT-interval prolongation and liability towards TdP with drugs.

Some macrolide antibiotics have been associated with TdP [Bril *et al.* 2010; Shaffer *et al.* 2002]. Clarithromycin is one such drug [e.g. Gysel *et al.* 2013; Vieweg *et al.* 2013]. A recent paper in this journal reported major risk factors from the evaluation of 21 case reports of TdP associated with clarithromycin use [Vieweg *et al.* 2013]. These included female sex (the majority of identified cases were in women), old age and the presence of heart disease [Vieweg *et al.* 2013]. Some patients received other QT interval-prolonging drugs and/or presented with hypokalaemia, and three patients had evidence of congenital long QT syndrome [Vieweg *et al.* 2013]. These factors are concordant with known risk factors for drug-induced QT prolongation and TdP [Vandenberg *et al.* 2001; Yap and Camm, 2003; Bril *et al.* 2010]. In this letter, we wish to highlight a potential novel modifier of QT prolongation with clarithromycin, on the basis of a recent *in vitro* investigation of the drug's actions [Du *et al.* 2013].

Most drugs associated with QT-interval prolongation and TdP share a common action of

pharmacological inhibition of the cardiac rapid delayed rectifier potassium current (I_{Kr}), which plays an important role in regulating ventricular electrical repolarization [Vandenberg *et al.* 2001; Yap and Camm, 2003; Hancox *et al.* 2008]. The pore-forming subunit of I_{Kr} channels is encoded by the *human ether-à-go-go related gene* (*hERG*) and recombinant hERG channels are widely used to evaluate the propensity of drugs to inhibit I_{Kr} [Vandenberg *et al.* 2001; Yap and Camm, 2003; Hancox *et al.* 2008]. Clarithromycin is known to produce pharmacological inhibition of hERG [Vieweg *et al.* 2013]. In addition, the potency of clarithromycin inhibition of hERG has been shown to be enhanced by a mutation to the *KCNE2* gene found in a patient with clarithromycin-induced QT prolongation and TdP [Abbott *et al.* 1999]. The *KCNE2* protein can complex with hERG and is a putative molecular partner for hERG in forming I_{Kr} channels [Abbott *et al.* 1999]. The Q9E *KCNE2* mutation increases the potency of clarithromycin's action on hERG [Abbott *et al.* 1999], thereby exacerbating delayed ventricular repolarization with the drug. We have investigated whether a related protein, *KCNE1*, can modify hERG pharmacology and our results in respect of clarithromycin suggest that it can [Du *et al.* 2013].

KCNE1 is a small transmembrane protein most well known as a molecular partner of *KCNQ1* to form ' I_{Ks} ' potassium channels in the heart, with loss-of-function *KCNE1* mutations responsible for the LQT5 form of congenital long QT syndrome [Modell and Lehmann, 2006]. However, *KCNE1* appears also able to complex with hERG and thereby has potential to influence I_{Kr} [McDonald *et al.* 1997; Du *et al.* 2013]. We investigated the effects of two *KCNE1* mutations (A8V and D76N, respectively in the N and C termini) and one polymorphism (D85N in the

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C terminus) on the sensitivity of the hERG current to pharmacological blockade [Du *et al.* 2013]. Clarithromycin sensitivity of hERG was measured through patch-clamp recordings from hERG co-expressed with wild-type or variant KCNE1 in human embryonic kidney (HEK293) cells [Du *et al.* 2013]. The half-maximal inhibitory concentration (IC₅₀) for hERG current inhibition with A8V KCNE1 co-expression was raised nearly two-fold compared with that of wild-type KCNE1 ($80.26 \pm 9.20 \mu\text{M}$ versus $40.85 \pm 4.39 \mu\text{M}$, respectively), whilst both D76N and D85N KCNE1 showed lower IC₅₀ values ($14.81 \pm 6.76 \mu\text{M}$ and $27.48 \pm 6.77 \mu\text{M}$, respectively) [Du *et al.* 2013]. Thus, two KCNE1 variants conferred increased sensitivity to clarithromycin upon hERG, whilst one resulted in decreased sensitivity to the drug [Du *et al.* 2013].

The significance of these findings is that it is possible that individual variation in KCNE1 could feasibly influence cardiac sensitivity to clarithromycin through influencing sensitivity of I_{Kr}/hERG to pharmacological blockade (additional to any effect of KCNE1 variation on the I_{Ks} channel, which itself may influence net available repolarizing potassium current). A recent candidate gene survey found the D85N KCNE1 polymorphism in 8.6% of drug-induced long QT syndrome cases, compared with less than 2% of controls [Kaab *et al.* 2012], with other smaller studies also providing evidence of an association [Paulussen *et al.* 2004; Lin *et al.* 2012]. This association underscores the potential value of genetic screening in drug-induced long QT syndrome/TdP, whilst our recent data on clarithromycin highlight a potential new mechanism for individual variation in clarithromycin sensitivity [Du *et al.* 2013].

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Conflict of interest statement

None declared.

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