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Original article

Beyond the safety assessment of drug-mediated changes in the QT interval… what's next?

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ABSTRACT

Assessing drug-induced changes (particularly prolongation) in the QT interval has been the major preoccupation of safety pharmacology since its inception, under the assumption that QT widening represents a surrogate biomarker for torsades de pointes (TdeP) liability. While evidence of changes in QT remains a bane to the development of novel therapeutic agents, non-clinical and clinical methods have been developed (with a certain amount of validation) to limit this potential liability of a new chemical entity (NCE). Because of the associated withdrawal of numerous drugs from clinical use, determining whether or not a drug development candidate exhibits a TdeP liability has been the motivation in the implementation of discussions between 'pharmaceutical companies', academicians, clinicians and regulatory authorities worldwide that has led to the development of the ICHS7A and ICHS7B guidance documents (Anon, 2001, 2005). Simultaneously, it has resulted in the firm establishment of safety pharmacology as a standalone discipline within the drug development scheme (Pugsley et al., 2008).

As far as TdeP liability is concerned, QT widening remains the most poignant issue, in that QT widening in humans is immediately regarded as a cause for concern, yet QT widening in preclinical models (and indeed in man) is not a quantitative predictor of TdeP liability (and indeed may not even be a qualitative predictor by itself (Pugsley et al., 2008).

The present focused issue of the journal returns to safety pharmacology, and contains papers arising from the 8th annual SPS Meeting that was held in Madison, WI in 2008. Indeed, so many papers have arisen from the meeting that this issue of the *Journal* is only part 1. Part 2 will be published as the next issue of the *Journal*. Some topics which have been addressed include whether an assessment method for drugs that produce a shortened QT interval is needed, what the role of the slow component of the delayed rectifier K current (I_{Ks}) should be in a safety assessment and whether safety pharmacology endpoints can or should be added to repeat dose Toxicology studies.

1. Drug-induced short QT syndrome — is pre-clinical assessment needed and are there any validated pre-clinical methods available?

The well-known drug-unrelated short QT syndrome (SQTS) is a newly characterized arrhythmogenic (inherited genetic) disease associated with an *abrogated* QT interval due to an *accelerated* rate of cardiac repolarization (see review by Shah, 2009). The clinical diagnostic criteria remain to be firmly established, but it was originally suggested, based upon clinical data at the time, that a QTc<300 ms represents an appropriate diagnostic 'cut-off' point (Cerrone, Noujaim, & Jalife, 2006). As has transpired with long QT (and torsades de pointes), there is now an ongoing clinical effort to outline clinical diagnostic criteria for changes in the QT/QTc associated with SQTS (Viskin, 2009). Clinical QT population data suggest that QT/QTc intervals at or below 360–370 ms could be classified as 'short', could be indicative of some variant of SQTS and may present a cardiac liability to the patient (Gussak et al., 2000; Bjerregaard & Gussak, 2005; Morita et al., 2008; Patel and Antzelevitch, 2008; Viskin, 2009). The reason why this is relevant to safety pharmacology is that if SQTS is a relevant medical condition then *drug-induced* QT shortening is likely to be a safety issue (hitherto unrecognized).

At least 3 distinct single point genetic mutations in repolarizing cardiac K^+ currents have been recognized and linked to SQTS. These 'gain of function' mutations occur for the rapid (I_{Kr} or KCNH2 gene) and slow (I_{Ks} or KCNQ1 gene) components of the delayed rectifier (I_K) current as well as the inward rectifier (I_{K1} orKCNJ2 gene) current and

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mediate changes in cardiac repolarization processes (Gussak et al., 2000; Bjerregaard & Gussak, 2005; Patel and Antzelevitch, 2008). The changes include a shortened atrial and ventricular action potential duration (APD) and altered morphology (peaked) of the ventricular T-wave resulting in an abbreviated QT interval on the EKG (Cerrone et al., 2006). Note that 'loss of function' mutations in cardiac L-type calcium channels (CACNA1C or the pore-forming $Ca_v1.2$ α-subunit and CACNB2b the $Ca_v1.2\beta$ subunit) have also been identified as contributing to SQTS (Patel and Antzelevitch, 2008). Thus, (congenital) SQTS patients experience a range of symptoms that include palpitations, syncope, a high prevalence of atrial fibrillation and increased risk of sudden cardiac death (Gussak et al., 2000).

In contrast, a literature on drug-induced QT shortening and its relevance to safety pharmacology is virtually absent. Consequently, there needs to be a push to develop and validate methods for detecting drug-induced QT shortening and link the readout to a quantitative assessment of proarrhythmia liability (Lu et al., 2008; Towart et al., 2009-this issue). This will require elaboration of species sensitivity, and underlying electrophysiological mechanisms.

Because of the paucity of information regarding drug-induced QT shortening, there likely remains a genuine concern within the Medical/Scientific and Regulatory communities about the safety of drugs that shorten the QT interval (Shah, in press). Indeed, current links between drug-induced QT shortening and proarrhythmia are primarily based merely on *hypothetical* considerations (Shah & Hondeghem, 2005) rather than on data-driven non-clinical model validation and clinical experience. Nevertheless, drug-induced QT shortening has recently been included in the product label for the recently-approved triazole anticonvulsant drug rufinamide (BANZEL®). Rufinamide is approved for use in Lennox–Gastaut syndrome (a severe form of epilepsy in children) and partial-onset seizures in adults and adolescents (BANZEL® Package Insert, 2008; Ferrie & Patel, 2009; Shah, in press). The label for the drug states "BANZEL® is contraindicated in patients with familial short QT syndrome. These patients should not be treated with BANZEL®. Formal cardiac ECG studies demonstrated shortening of the QT interval (up to 20 ms) with BANZEL® treatment. Caution should be used when administering BANZEL® with other drugs that shorten the QT interval" (BANZEL® Package Insert, 2008). Rufinamide did not reduce the QT interval below 300 ms in formal clinical cardiac QT studies ('thorough QT') and no ventricular arrhythmias or SCD have been observed (BANZEL® Package Insert, 2008; Shah, in press), yet the product label also includes the statement "Non-clinical data also indicate that QT shortening is associated with ventricular fibrillation". Unfortunately, the literature describing the non-clinical effect has not been published (to date) so it is difficult to know what non-clinical safety model(s) were used to assess QT shortening that revealed the proarrhythmia. What is known from the literature is that rufinamide prolongs the inactivation kinetics of the neuronal Na channel (McLean et al., 2005), reduces repetitive firing of action potentials from neurons which results from Na channel and contributes to a plausible potential mechanism of action in non-clinical seizure models (Rogawski, 2006) and clinical efficacy. Thus, a drug has acquired a liability product label in the absence of any published validation of the methods used to detect the liability. Indeed, although safety efforts have ensured that strategies have been developed to detect potassium channel blocking activity, QT prolongation and proarrhythmia as part of an integrated risk assessment for TdeP liability for a NCE, the possibility of proarrhythmia via QT shortening has only recently received attention from the safety pharmacological methods community (Lu et al., 2008).

Although a number of drugs apparently 'shorten' the QT interval, each effect has not been rigorously investigated or mechanistically characterized and importantly, the rhythm consequences in humans are unknown (contrast this with the situation for drug-induced QT prolongation). Thus, while work progresses apace to examine the genetic aspects of heritable SQTS, the pathology and risk potential imposed in humans resulting from *drug-induced* shortening of the QT interval remain a relatively neglected area of research. This needs to change.

A recent set of reviews that discuss the cardiac I_{Ks} current include overviews of drugs with characterized mechanisms of molecular pharmacological action that appear to result in QT shortening (mechanisms additional to Na channel blockade). Such mechanisms include I_{KATP} activation (levcromakalim), I_{Kr} activation (mallotoxin) and I_{Ks} activation (L-364,373) (Lu et al., 2008; Towart et al., 2009-this issue). Note that Towart et al. (2009-this issue) also provide data describing highly potent and selective ('pure') I_{Ks} blockers (e.g., JNJ-282, IC_{50} 1.1 nM) that produce both adrenergic- and pause-dependent TdP (Towart et al., 2009-this issue). While no validated non-clinical methods have been developed to assess drug-induced QT shortening and its possible proarrhythmia liability, application of guiding principles used to assess QT prolongation may be applied (Pugsley, Authier, & Curtis, 2008; Towart et al., 2009-this issue).

2. Should drug-mediated blockade of I_{Ks} and other CV parameters be routinely evaluated in non-clinical safety pharmacology studies?

I_{Ks} expression in animal species has an electrophysiological signature that is most comparable to humans in the dog and rabbit (Jost, Papp, & Varro, 2007). While the physiological role of I_{Ks} is now better established (delayed due to a lack of selective blockers), it remains an essentially 'overlooked' current because of its reduced role in 'normal' human ventricular repolarization processes. Because I_{Ks} activates slowly at positive membrane potentials, limited current flows during the plateau of the action potential and it is perceived to have a limited role regarding the effects on the QT interval. However, under conditions in which there may be a prolongation of the APD in the ventricle, activation of I_{Ks} is thought to limit this prolongation and hence provide some safety aspect to this process (Jost et al., 2005, 2007). If an NCE in development blocks I_{Ks}, in addition to I_{Kr}, there is likelihood for a diminution in 'repolarization reserve' of the ventricle (Roden, 2006) and hence a potential increased risk for arrhythmia susceptibility (Curtis, 2006). This is why it has been suggested that I_{Ks} blocking activity be routinely evaluated in preclinical safety pharmacology examination (Lu et al., 2008; Pugsley et al., 2008).

If one looks back through the literature there appears to have been a number of drugs empirically determined to be relatively selective blockers of I_{Ks} (such as chromanol 293B and HMR1556) and many more (amiodarone, bepridil, imipramine, mibefradil, propafenone and thiopentone) having ancillary I_{Ks} blocking activity in addition to the primary molecular action (Jost et al., 2007; Towart et al., 2009). Chromanol 293B was the first relatively selective blocker of I_{Ks} (Jost et al., 2007; Towart et al., 2009-this issue). In a review on I_{Ks}, Towart et al. (2009-this issue) emphasized that diverse compounds can affect I_{Ks} and recommend the use of *in vitro* and *in vivo* pre-clinical methods to evaluate NCE activity on the consequences of I_{Ks} blockade. The blockade of I_{Ks} may prolong ventricular repolarization and hence prolong the QT interval, but the extent depends on how much repolarization reserve is present (determined by the co-availability of I_{Kr} and I_{Ks}). Additionally, however, the TdeP liability associated with I_{Ks} blockade is classified as being adrenergic-dependent, in contrast to TdeP liability associated with blockade of I_{Kr} (which is pause-dependent, whereby the probability of likelihood increases during sleep or bradycardia) (Towart et al., 2009-this issue). Cheng and Incardona (2009) have recently attempted to assess the proarrhythmic potential of repolarization reserve using isolated rabbit and guinea pig hearts as a first step to begin validation of a pre-clinical model of TdeP.

Thus, the issue for those involved in drug safety is whether it is a cause for concern in the drug safety screening process that there is no validated method for determining the proarrhythmic liability of a drug that has off-target effects on I_{Ks}? From an integrated risk assessment perspective the answer should be 'yes' — a gap in the proarrhythmic liability testing exists, as discussed by Lu et al. (2008) and Towart et al.