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The thorough QT study: Let's be precise

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In 1990, Monahan et al. [1] published a report linking terfenadine, the first non-sedating antihistamine, to QT prolongation and torsade de pointes (TdP) ventricular tachycardia [1]. The event that led to this connection being noted was a syncopal episode leading to a motor vehicle accident in a middle-aged woman taking terfenadine and ketaconazole, a drug that inhibited the metabolism of the antihistamine. While it was well known that quinidine and other antiarrhythmic drugs were associated with TdP, the revelation that two non-cardiac drugs could interact to cause a life-threatening interaction initiated a chain of events that has had profound consequences for the pharmaceutical industry. Apart from sounding the death knell for a billion-dollar drug (terfenadine), the US Food and Drug Administration demanded that all new drugs should undergo an extensive evaluation for any torsadegenic potential. This has greatly increased the cost of developing new agents.

While the precise requirements for satisfying regulators continue to evolve, at present in the European Union [2] and the United States [3] all new molecules must be evaluated for their effects on repolarization using pre-clinical and clinical approaches. In the pre-clinical setting, each drug is tested in an *in vitro* assay for evidence of inhibition of the human ether-a-go-go-related gene (hERG) associated potassium channel. The conductance of this channel largely determines the duration of cardiac repolarization in the resting state, i.e. at slow heart rates and in the absence of sympathetic nervous system stimulation.

Unfortunately, this critically important channel has a structure that can be compared to a garbage can, and many small molecules are capable of becoming lodged in its pore and inhibiting the passage of potassium ions. Drugs that block 50% of the current flow at concentrations near those likely to be achieved *in vivo* are considered to be higher risk for QT prolongation and TdP, although the interpretation of these results is complicated by a number of uncertainties. Drugs that achieve 20% hERG blockade at very low concentrations may be hazardous in subjects with a compromised repolarization reserve; the exact amount of non-protein bound free drug available to block the channel may vary with the health of the individual; some drugs, such as pentamidine, do not block the channel *per se* but interfere with the movement of functional channel protein to the cell membrane [4, 5]. Drugs such as verapamil and ranolazine are potent hERG blockers, but their balancing effects on inward currents offset the risk for TdP. These considerations by themselves prevent regulators from relying on a simple *in vitro* approach to screening new agents for pro-arrhythmic potential.

The clinical evaluation of the TdP risk for new drugs relies on a 'Thorough QT (TQT) study'. This approach, outlined in intentionally vague language in the ICH E14 guidance, requires the serial measurement of the QT interval in the presence of a placebo, the candidate drug, and a positive control [6]. The purpose of the positive control, usually a 400 mg dose of the weak-QT prolonging drug moxifloxacin, is to ensure that the assay is sufficiently sensitive to reliably detect a 5 ms increase in rate-corrected QT (QTc), meaning that the lower-bound of the 90% confidence interval (CI) should be above 5 ms [7]. If the mean maximum placebo corrected QTc on a drug is increased by 5 ms or more, or if the 95% CI exceeds 10 ms, the study is deemed positive for a 'regulatory concern' of QT prolongation. Thus, a TQT study can falsely 'fail' if it does not demonstrate sensitivity in picking up a > 5 ms increase

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in QTc on moxifloxacin [8], or if it lacks specificity, and the on-drug QTc prolongs by as little as 4 ms with a 95% CI of 11 ms.

Maximizing the precision of the QTc measurement is imperative, because any increase in variability will result in a wider CI. The cost of a 'false--positive' TQT is the need for further studies that add millions to the drug development [6].

The present issue of *Cardiology Journal* contains an important contribution to the science of measuring QTc precisely [9]. Darpo et al. [9] describe an automated method for QTc analysis that appears significantly more precise than standard methods when applied to two TQTs. From the standpoint of the pharmaceutical industry, increasing the precision of QTc measures is highly desirable for at least two reasons: 1. It allows for TQT to be performed in fewer subjects at considerable cost savings, as well-proven by Malik et al. [10]; 2. Greater precision reduces the likelihood of a TQT failing due to inadequate sensitivity or specificity.

So the introduction of automated methods may save the pharmaceutical industry money, but what are the implications for public safety? Measuring the QTc is the only accepted clinical approach, at present, for predicting which drugs pose a risk of TdP. Yet it is widely acknowledged that the extent of QTc prolongation is neither particularly sensitive nor specific for predicting TdP [11]. Improved techniques for assessing the presence of depressed repolarization reserve in individuals are sorely needed. Particularly promising are methods assessing the beat-to-beat variability in the duration of the QT interval [12, 13] or changes in T wave morphology [14], either spontaneous or on drug. The success of such approaches likely depends on the ability to precisely measure the QT interval in thousands, or preferably hundreds of thousands, of beats. We hope that the methods described by Darpo et al. [9] will be exploited to develop such new approaches in order to achieve the proper goal of identifying and quantifying the torsadegenic potential of new drugs.

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References

1. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Torsades de pointes occurring in association with terfenadine use. JAMA, 1990; 264: 2788–2790.
2. http://www.ema.europa.eu/docs/en_GB/document_library/ /Scientific_guideline/2009/09/WC500002879.pdf.
3. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ /ucm129357.pdf.
4. Dennis A, Wang L, Wan X, Ficker E. hERG channel trafficking: Novel targets in drug-induced long QT syndrome. Biochem Soc Trans, 2007; 35 (Part 5): 1060–1063.
5. Cubeddu LX. Iatrogenic QT abnormalities and fatal arrhythmias: Mechanisms and clinical significance. Curr Cardiol Rev, 2009; 5: 166–176.
6. Shah RR. Drugs, QT interval prolongation and ICH E14: The need to get it right. Drug Saf, 2005; 28: 115–125.
7. Malik M, Garnett CE, Zhang J. Thorough QT studies: Questions and quandaries. Drug Saf, 2010; 33: 1–14.
8. Morganroth J, Lepor H, Hill LA, Volinn W, Hoel G. Effects of the selective alpha-1 adrenoceptor antagonist silodosin on ECGs of healthy men in a randomized, doubleblind, placebo and moxifloxacin controlled study. Clin Pharmacol Ther, 2010; 87: 609–613.
9. Darpo B, Fossa AA, Couderc JP et al. Improving the precision of QT measurements. Cardiol J, 2011; 18: 401–410.
10. Malik M, Hnatkova K, Batchvarov V, Gang Y, Smetana P, Camm AJ. Sample size, power calculations, and their implications for the cost of thorough studies of drug induced QT interval prolongation. Pacing Clin Electrophysiol, 2004; 27: 1659–1669.
11. Hondeghem LM. Thorough QT/QTc not so thorough: Removes torsadogenic predictors from the T-wave, incriminates safe drugs, and misses profibrillatory drugs. J Cardiovasc Electrophysiol, 2006; 17: 337–340.
12. Thomsen MB, Verduyn SC, Stengl M et al. Increased short-term variability of repolarization predicts d-sotalol-induced torsades de pointes in dogs. Circulation, 2004; 110: 2453–2459.
13. Hinterseer M, Thomsen MB, Beckmann BM et al. Beat-to-beat variability of QT intervals is increased in patients with drug--induced long-QT syndrome: A case control pilot study. Eur Heart J, 2008; 29: 185–190.
14. Couderc JP, Xia X, Peterson DR et al. T-wave morphology abnormalities in benign, potent, and arrhythmogenic I(kr) inhibition. Heart Rhythm, 2011 [Epub ahead of print].