BJP BRITISH JOURNAL OF PHARMACOLOGY
BPS BRITISH PHARMACOLOGICAL SOCIETY

BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2010.00980.x
www.brjpharmacol.org

COMMENTARY

A new preclinical biomarker for risk of Torsades de Pointes: drug-induced reduction of the cardiac electromechanical window

Hugo M Vargas

Department of Investigative Toxicology, Amgen Inc., Thousand Oaks, CA, USA

Correspondence
Hugo M. Vargas, Investigative Toxicology, Amgen Inc., Thousand Oaks, CA 91320, USA.
E-mail: hvargas@amgen.com

Keywords
cardiac repolarization; QT interval; drug-induced QT prolongation; proarrhythmia; Torsades de Pointes; ventricular dysfunction; electromechanical window

Received
29 June 2010
Accepted
16 July 2010

Evaluation of new therapeutic agents for their potential to cause QT interval prolongation and drug-induced ventricular arrhythmia, like Torsades de Pointes (TdP), is a critical activity during drug development. The QT interval has been used as a surrogate biomarker to assess ventricular repolarization effects caused by drug-induced blockade of cardiac repolarizing currents, mainly I_{Kr}, but is imperfect in predicting proarrhythmia. Evidence suggests that left ventricular mechanical dysfunction may also contribute to ventricular arrhythmias; thus, electrical and mechanical alterations may have a role in drug-induced TdP. The electromechanical window (EMw) represents the time difference between the end of electrical systole (i.e. the QT interval) and the completion of ventricular relaxation (i.e. the $QLVP_{end}$ interval), and appears to be a new potential biomarker for TdP risk. A reduction in the EMw (to negative values) has now been shown to be associated with the onset of TdP in an anaesthetized dog model of long QT1 syndrome. Therefore, the EMw represents a novel indicator of TdP risk that may add predictive value beyond assay of drug-induced QT interval prolongation.

LINKED ARTICLE

This article is a commentary on van der Linde *et al.*, pp. 1444–1454 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2010.00934.x

Abbreviations

EMw, electromechanical window; hERG, human *Ether-a-go-go* Related Gene; I_{Ks}, slowly activating potassium membrane current; I_{Kr}, rapidly activating potassium membrane current; LVP, left ventricular pressure; QT interval, time between Q and T waveforms; TdP, Torsade de Pointes

Some drug-induced arrhythmias, like polymorphic ventricular tachycardia or Torsades de Pointes (TdP), have been associated with prolongation of the QT interval (Roden, 2004). Consequently, assessment of new therapeutic agents for their potential to delay ventricular repolarization is a primary safety focus during non-clinical and clinical drug development (Anon, 2005a,b). Most drugs known to cause long QT syndrome do so by preferentially blocking the rapidly activating delayed rectifier potassium current I_{Kr} (Sanguinetti *et al.*, 1995). The human *Ether-a-go-go* Related Gene (hERG) encodes the pore-forming α-subunit of I_{Kr}, a K^+ current with a critical role in ventricular repolarization. During non-clinical testing, it is common to use a variety of *in vitro* (e.g. hERG channel function assay), *ex vivo* (e.g. isolated heart or Purkinje fibres or myocytes from various species) and *in vivo* animal models (e.g. anaesthetized or conscious preparations) to assess the ability of a new candidate drug to cause QT prolongation (Pollard *et al.*, 2010). While the QT interval is a straightforward parameter to measure in animal models and humans, and there is a mechanistic link to hERG channel function and blockade (Wallis, 2010), the QT end point is not a reliable predictor of TdP risk, because some agents that inhibit hERG/I_{Kr} current or prolong the QT interval are not associated with TdP, such as verapamil and

amiodarone (Roden, 2004). Furthermore, the QT interval is an imperfect biomarker of proarrhythmic risk because it is highly variable due to normal variations in heart rate and autonomic tone (Fossa, 2008); thus, drug-induced changes in the QT (or heart rate-corrected QT) interval may not accurately reflect or quantify TdP risk. As a result, a variety of specialized assays have emerged, like the atrioventricular (AV)-blocked rabbit heart and the ventricular wedge preparation, and complex animal models with remodelled hearts, such as AV-blocked dogs, as additional approaches to study drug-induced dispersion of repolarization, beat to beat instability and TdP risk in normal and diseased myocardium, to augment risk evaluation beyond QT interval prolongation (Lee *et al.*, 2010).

In this issue of the *British Journal of Pharmacology*, van der Linde *et al.* (2010) describe a cardiovascular study in the anaesthetized dog that evaluated a new end point, the cardiac electromechanical window (EMw), and its potential value as a proarrhythmia biomarker for TdP. The EMw represents the time difference between the QT interval (or the duration of electrical systole) and the duration of a left ventricular pressure (LVP) cycle or the $QLVP_{end}$ interval (measured from Q wave onset to the end of the LVP signal; Figure 1). In their study, alterations in the EMw were assessed at normal heart rate (rest) and after various interventions (cardiac pacing, atropine, elevation or reduction in body temperature) to assess the relationship between QT and $QLVP_{end}$ at various heart rates. In addition, the magnitude and direction of change in the EMw were examined following administration of a QT interval prolonging agent alone (HMR1556, an I_{Ks} blocker), and in combination with isoprenaline (β-adrenoceptor agonist), a positive inotrope/chronotrope that shortens the $QLVP_{end}$ interval. The authors demonstrated in untreated anaesthetized dogs with a resting heart rate (~80 beats per minute) that the EMw has a positive magnitude because the $QLVP_{end}$ duration is longer than the QT interval, and that the EMw remained relatively positive (>0 ms) when the heart rate was elevated by pacing, vagal blockade or isoprenaline challenge. In contrast with the QT interval, which varied with body temperature in this study, the EMw was relatively uninfluenced by body temperature, and remained positive, that is, $QLVP_{end}$ > QT. Of great interest to proarrhythmia risk evaluation was the finding that delayed cardiac repolarization (QT prolongation) induced by HMR1556 shortened the EMw (28 ms) relative to the baseline value (87 ms), and when a bolus dose of isoprenaline was given afterwards, the EMw became negative (–109 ms; QT > $QLVP_{end}$) and TdP was observed in all animals. However, no TdP was observed in dogs at

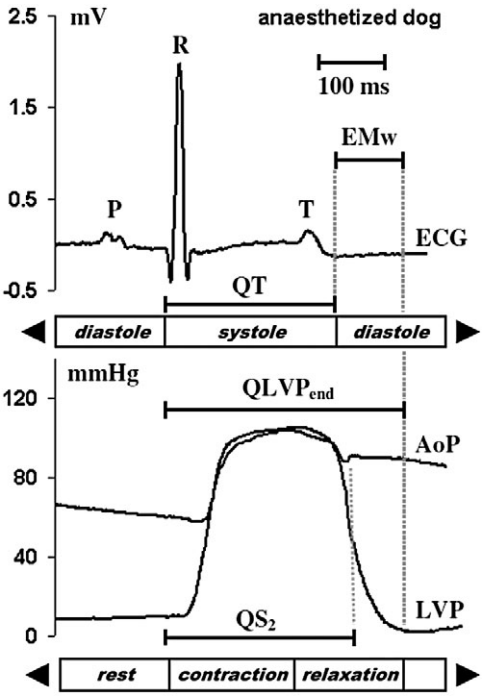

Figure 1

The cardiac electromechanical window (EMw). The relationship between the electrocardiogram (upper) and aortic (AoP) and left ventricular pressure (LVP) curves (lower) are depicted. The time difference between the QT interval duration (electrical systolic) and its associated ventricular contraction-relaxation cycle ($QLVP_{end}$) is the EMw. (Figure modified from van der Linde *et al.*, 2010, with permission).

baseline, or following maximal I_{Ks} blockade following HMR1556; thus, the emergence of TdP following cardiac β-adrenoceptor activation suggests that alterations in ventricular mechanics may have been arrhythmogenic. Given that the dogs used in the study were normal and presumably healthy in regard to cardiac electrical activity, structure and function, the reduction in the EMw prior to the onset of TdP implies that assessment of electromechanical events may be a predictor of ventricular arrhythmia beyond prolongation of the QT interval.

Alterations in left ventricular dysfunction have been recognized to be a predictor of sudden cardiac death in humans, so it is likely that complex electrophysiological and mechanical interactions may contribute to or underlie the occurrence of drug-induced arrhythmia (Fabritz, 2007; Kirchhof *et al.*, 2008). Earlier, work from Gallacher *et al.* (2007) demonstrated that in an anaesthetized dog model of drug-induced long QT1 syndrome, left ventricular systolic aftercontractions preceded the onset of TdP following isoprenaline challenge, which the authors surmised might be an indication of a role for abnormal calcium homeostasis having a role in TdP onset

in this model. The current experimental findings of van der Linde *et al.* (2010) expand this work and demonstrate that electrical and mechanical changes associated with drug-induced TdP are manifested as negative changes in the EMw, which reinforces the notion that ventricular electromechanical interactions may conspire to induce TdP, and can be modelled in this assay system.

While this EMw end point is relatively straightforward to measure and appears to be a more stable and reliable index of proarrhythmic risk in comparison to QT interval, this work is limited, and needs to be studied further and confirmed by others. In the future, it will be important to study agents known to prolong the heart rate corrected QT interval and induce TdP in humans, especially hERG/I_{Kr} blockers, to evaluate their overall effect on the magnitude and direction of the EMw, and the overall performance and predictive value of this novel end point in the anaesthetized dog assay. It might also be valuable to evaluate the EMw end point in conscious animals, with invasive or non-invasive LVP assessment methods, to see if this biomarker responds in the same manner in unanaesthetized animals, or if the anaesthetized animal is a more sensitive model. Clinical evidence has identified left ventricular dysfunction in patients with long QT syndrome (De Ferrari and Schwartz, 2009; Huagaa *et al.*, 2009), so future scientific investigations on the EMw end point in non-clinical studies will further our understanding of this new biomarker, and its possible value in the evaluation of new drugs for TdP risk.

Conflict of interest

The author is an employee of Amgen, Inc, a biopharmaceutical company.

References

Anon. (2005a). ICH S7B. The nonclinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals. Available at: http://www.ich.org (accessed 19 August 2010).

Anon. (2005b). ICH E14. The clinical evaluation of the QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Available at: http://www.ich.org (accessed 19 August 2010).

De Ferrari GM, Schwartz PJ (2009). Long QT syndrome, a purely mechanical disease? Not anymore. Eur Heart J 30: 253–255.

Fabritz L (2007). Drug-induced Torsades de Pointes – A form of mechano-electric feedback? Cardiovasc Res 76: 202–203.

Fossa AA (2008). The impact of varying autonomic states on the dynamic beat-to-beat QT-RR and QT-TQ interval relationships. Br J Pharmacol 154: 1508–1515.

Gallacher DJ, Van de Water A, van der Linde H, Hermans AN, Lu HR, Towart R *et al.* (2007). In vivo mechanisms precipitating Torsades de Pointes in a canine model of drug-induced long-QT1 syndrome. Cardiovasc Res 76: 247–256.

Huagaa KH, Edvardsen T, Leren TP, Gran JM, Simseth OA, Amlie JP (2009). Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high risk individuals with long QT syndrome. Eur Heart J 30: 330–337.

Kirchhof P, Fortmuller L, Waldeyer C, Breithardt G, Fabritz L (2008). Drugs that interact with cardiac electro-mechanics: old and new targets for treatment. Prog Biophys Mol Biol 98: 497–512.

Lee N, Authier S, Pugsley MK, Curtis MJ (2010). The continuing evolution of Torsades de Pointes liability testing methods: is there an end in sight? Toxicol Appl Pharmacol 243: 146–153.

van der Linde HJ, Van Deuren B, Somers Y, Loenders B, Towart R, Gallacher DJ (2010). The electro-mechanical window: a risk marker for Torsade de Pointes in a canine model of drug induced arrhythmias. Br J Pharmacol 161: 1444–1454.

Pollard CE, Abi Gerges N, Bridgland-Taylor MH, Easter A, Hammond TG, Valentin JP (2010). An introduction to QT interval prolongation and non-clinical approaches to assessing and reducing risk. Br J Pharmacol 159: 12–21.

Roden DM (2004). Drug-induced prolongation of the QT interval. Engl J Med 350: 1013–1022.

Sanguinetti MC, Jiang C, Curran ME, Keating MT (1995). A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. Cell 81: 299–307.

Wallis RM (2010). Integrated risk assessment and predictive value to humans of non-clinical repolarization assays. Br J Pharmacol 159: 115–121.