

REVIEW

Key clinical considerations for demonstrating the utility of preclinical models to predict clinical drug-induced torsades de pointes

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While the QT/QTc interval is currently the best available clinical surrogate for the development of drug-induced torsades de pointes, it is overall an imperfect biomarker. In addition to low specificity for predicting arrhythmias, other issues relevant to using QT as a biomarker include (1) an apparent dissociation, for some drugs (for example, amiodarone, sodium pentobarbital, ranolazine) between QT/QTc interval prolongation and TdP risk, (2) Lack of clarity regarding what determines the relationship between QTc prolongation and TdP risk for an individual drug, (3) QT measurement issues, including effects of heart rate and autonomic perturbations, (4) the significant circadian changes to the QT/QTc interval and (5) concerns that the development, regulatory and commercial implications of finding even a mild QT prolongation effect during clinical development has significant impact the pharmaceutical discovery pipeline. These issues would be significantly reduced, clinical development simplified and marketing approval for some drugs might be accelerated if there were a battery of preclinical tests that could reliably predict a drug's propensity to cause TdP in humans, even in the presence of QTc interval prolongation. This approach is challenging and for it to be acceptable to pharmaceutical developers, the scientific community and regulators, it would need to be scientifically well validated. A very high-negative predictive value demonstrated in a wide range of drugs with different ionic effects would be critical. This manuscript explores the issues surrounding the use of QT as a clinical biomarker and potential approaches for validating preclinical assays for this purpose against clinical data sets.

British Journal of Pharmacology (2008) **154**, 1544–1549; doi:10.1038/bjp.2008.222; published online 9 June 2008

Keywords: torsades de pointes; drugs; QT; QTc; hERG; cardiac electrophysiology; biomarker; VT

Abbreviations: hERG, ether-a-go-go related gene; I_{Ca} , inward calcium current; I_{Kr} , rapidly activating component of delayed rectifier potassium current; I_{Ks} , slowly activating component of the delayed rectifier potassium current; I_{Na} , late inward sodium current; ms, milliseconds; TdP, torsades de pointes

Introduction

Prolongation of the QT interval has recently received significant regulatory scrutiny as a biomarker for the risk of development of drug-induced torsades de pointes (TdP), culminating in 2005 with the finalization of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance document E14 (Sager *et al.*, 2005; Darpo *et al.*, 2006). The clear need for regulatory guidance stemmed from the finding that a number of drugs (for example, terfenadine, cisapride, erythromycin, droperidol and bepridil) (Torsades, 2007; <http://www.torsades.org>) caused TdP resulting in mortality, including occasionally young individuals without heart disease. Increases in the QT interval and/or the development of TdP are the most

common reason for pharmaceutical agents to be withdrawn from the market or to have significant restrictions placed upon their clinical labelling and use (Roden, 2004). Because TdP is only very rarely observed during clinical development of non-antiarrhythmic drugs, the use of a surrogate biomarker to identify such a risk before a medication is approved is appropriate.

ICH E14 requires that drugs undergo testing of their effects on cardiac repolarization using a 'Thorough QT/QTc Study', typically performed in healthy volunteers. The guidance defines the boundary of minimum changes in the QT/QTc interval (the placebo-adjusted change in QTC upper one-sided 95% confidence interval <10ms) that result in regulatory concern, and the need for the collection of additional data during Phases II and/or III of drug development. However, although the focus on the QT interval represents the current state of clinical science and it is the best available clinical surrogate for TdP, the QT interval is overall an imperfect biomarker. It is recognized that even

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Received 3 March 2008; revised 12 May 2008; accepted 13 May 2008; published online 9 June 2008

though it has moderate sensitivity for identifying TdP risk, the specificity is rather low. For example, Bednar *et al.* (2001) performed a literature review of all reported non-cardiac drug cases of TdP that they identified ($n = 116$) and showed that 92.2% of cases had a QTc above 500 ms. The analyses may have been confounded by the possibility that many reporters may not have considered a polymorphic VT occurring without marked QT prolongation to be TdP. In addition, most patients with QTc > 500 ms will not develop TdP, and although it was not possible to measure specificity in this study, it is clearly limited. In contrast, no drug has been convincingly shown to cause TdP, which does not have a central tendency effect to prolong the QT interval. Other issues relevant to using QT as a biomarker include (1) an apparent dissociation, for some drugs, between QT interval prolongation and TdP risk, (2) lack of clarity regarding what determines the relationship between QT prolongation and TdP risk for an individual drug and (3) QT measurement issues, including the proclivity for the QT interval to be significantly affected by changes in heart rate and autonomic influences. Recently, concerns have been expressed that the development, regulatory and commercial implications of finding even a modest QT prolongation effect during clinical development has had a significant negative impact on the discovery pipeline (Pink Sheet, 2005). Some companies, to reduce these potential issues, are commonly terminating the early development of compounds with relatively weak effects on the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) encoded by the ether-a-go-go-related gene (hERG) before the clinical role of the agent can be assessed and its effects on targets are examined (Pink Sheet, 2005).

These issues would be significantly reduced, clinical development simplified and marketing approval for some drugs might be accelerated if there were a battery of preclinical tests that could reliably predict a drug's propensity to cause TdP in humans, irrespective of the presence of QT interval prolongation. In order for this approach to be acceptable to drug developers, the scientific community and regulators, it would need to be scientifically well validated. This would include a test (or more likely a battery of tests) that has high positive and negative predictive power to determine if a drug is proarrhythmic.

This paper discusses the issues surrounding the use of QT as a clinical biomarker and potential approaches for validating preclinical assays against clinical data sets. The emphasis is on the clinical approach to validating preclinical models for the assessment of TdP risk. The specifics of the preclinical tests are addressed by other articles in this symposium.

Specific issues regarding QT as a biomarker

Once a drug is shown to prolong the QT interval, it is difficult during the drug development process to prove the absence of possible clinical risk. Many drugs that cause TdP may have a frequency of significantly less than one in several thousand people (in the case of cisapride, the frequency of TdP adverse events during post marketing was in the range of 1 per 110 000 prescriptions (mean three per patient

(Malik and Camm, 2001) and thus, except for antiarrhythmic agents (with a TdP incidence of up to about 4%), it is not expected that this arrhythmia will be observed during clinical development, despite a real risk and thus its absence prior to marketing approval is not indicative of an absence of risk. It can often take years of post-marketing data to clearly determine the presence of TdP (as well as other adverse events). In the case of cisapride, approximately 30 million prescriptions were written in the United States (FDA, 2000) and in the case of terfenadine, the risk was clearly demonstrated after 100 million prescriptions. Only after large numbers of patients are exposed who are receiving other drugs and have heart disease and altered pathophysiologic states, can proarrhythmia risk be fully excluded from a clinical standpoint.

The finding of a clinical QT signal during development can result in the need for intensive ECG monitoring during Phases II and III with large increases in development costs and possible delays in regulatory approval and a competitive disadvantage if warnings are placed into the label. A large-scale outcome study may be required and the drug may be restricted to a second-line indication. Regulatory approval may be delayed until additional studies can be performed (for example, ziprasidone) (Zygmunt *et al.*, 2001), with resulting commercial implications. As a result, some companies are not moving drugs into clinical development if their hERG IC_{50} to expected therapeutic human drug concentration is more than around 1:200. This has the potential to limit the development of drugs that could have important therapeutic uses and good benefit/risk ratio. The validation of preclinical tests that can reliably differentiate between drugs with preclinical 'QT' signals (for example, an effect on hERG) and their proclivity to cause TdP would be advantageous, if it would reduce the development burden and result in more drugs moving from discovery to development.

Dissociation between QT prolongation and arrhythmia risk

A major issue in relying on QT as a biomarker is that there can be a significant dissociation between QT interval prolongation and the development of TdP for an individual drug. Drugs that specifically block the rapidly activating component of I_{Kr} have been associated with a clear relationship between drug dose, the degree of I_{Kr} blockade, and the development of QT prolongation and TdP. Examples would include dofetilide and sotalolol. However, the situation can be significantly more complex when multiple ionic channels are blocked, and it has been suggested that block of the late inward sodium current (I_{Na}) may actually protect from the development of TdP despite a drugs' ability to reduce I_{Kr} (Belardinelli *et al.*, 2003, 2005). In addition, inhibition of the L-type calcium inward current may also be protective. Dissociation between QT and TdP effects has been shown in the canine model of AV nodal block. Although amiodarone has been shown to prolong the QTc interval by 70 ms in this model and the specific I_{Kr} blocker almokalant by 75 ms, the occurrence of TdP was 0% with

amiodarone in this particular study, but approximately 64% with almokalant using similar investigative techniques (Belardinelli *et al.*, 2003). It has been suggested that in addition to prolongation of the QT interval and action potential duration, critical features of drugs that cause TdP are early delayed after depolarizations and increased dispersion of ventricular repolarization (Belardinelli *et al.*, 2003). Frequency-dependent effects upon repolarization may also be important (Sager *et al.*, 1993a, b; Hondeghem, 2005).

Importantly, this dissociation between QT prolongation and TdP has also been observed in humans. For example, sodium pentobarbital significantly prolongs the QT interval but is not associated with TdP. Sodium pentobarbital inhibits I_{Kr} , the slowly activating component of the delayed rectifier potassium current (I_{Ks}) and the I_{Na} ; is not associated with early after depolarizations; and reduces transmural dispersion. In the case of amiodarone, the incidence of TdP is clinically rare, despite marked QT effects. In some patients, the QTc interval exceeds 650 ms without clinical events, and QT monitoring is not routinely performed in patients receiving amiodarone. Amiodarone also inhibits multiple ionic currents including I_{Kr} , I_{Ks} , and peak and late I_{Na} , as well as the inward calcium current (I_{Ca}), and is not associated with early after depolarizations or transmural dispersion in animal studies (Antzelevitch, 2004a). Recent experimental data using ATX-II to increase the late I_{Na} current and blockers of late I_{Na} have suggested that block of this current may provide protection against TdP, even in the setting of drug-reduced I_{Kr} blockade (Belardinelli *et al.*, 2003, 2005). Ranolazine has been shown to be devoid of proarrhythmia in a number of preclinical models, including the AV-blocked dog, transmural dispersion, the TRLad model 1 and the ATX-II model of increased late I_{Na} (Antzelevitch, 2004b, c; Wu *et al.*, 2004), and it has been hypothesized that inhibition of the late I_{Na} current counterbalances the TdP effects of I_{Kr} blockade. Clinically, the mean QTc increase by ranolazine is about 6 ms and in 5% of the population with the highest plasma concentrations, the prolongation of QTc is at least 15 ms (Ranexa, 2006). Although clinical proarrhythmia has not been observed to date, the drug only recently initiated marketing in the United States and significant post-marketing data will accrue over the next several years.

Verapamil has not generally been associated with significant QT effects during oral dosing, although QT prolongation has been shown with intravenous administration (De Cicco, 1999). However, the agent is not associated with TdP, and although it potently inhibits I_{Kr} , it also inhibits I_{Ca} . It is hypothesized that this block of the inward calcium current protects against the development of TdP. Thus, it is clear that for some drugs, there is an important dissociation between I_{Kr} blockade, QT prolongation and the development of TdP. Premature discontinuation of sodium pentobarbital, verapamil and amiodarone during the drug discovery processes, because of hERG effects, would have curtailed the availability of important pharmacologic agents.

Further evidence of this dissociation comes from the Ziprasidone 054 Study performed by Pfizer Pharmaceuticals (FDA, 2006) in which the anti-psychotic agents ziprasidone, risperidone, olanzapine, quetiapine, thioridazine and haloperidol were compared. Ziprasidone prolonged the QTc

interval by 15 ms, thioridazine by approximately 30 ms and haloperidol prolonged by approximately 7 ms. The QT prolongation with risperidone, olanzapine and quetiapine were in the 5-ms or less range. However, the only two drugs that have been clearly associated with clinical TdP are thioridazine and haloperidol, and whereas the increase in the QTc interval with thioridazine was robust, it was only marginal with haloperidol. Ziprasidone, which prolonged the QTc interval by approximately 15 ms, has not clearly been associated with the development of TdP recently. Thus, the development, validation and acceptance of preclinical tests that accurately predict the development of TdP in humans could meaningfully impact drug development.

The minimal amount of QT prolongation that is safe is controversial, and appears to be, in part, drug specific. Specific block of I_{Kr} may be associated with a different degree of risk, for a certain amount of QT prolongation, than drugs that also block inward calcium channels or late I_{Na} . Thus, in using QT as a biomarker, the degree of increase in the mean QT interval (that is, central tendency) may not accurately predict risk. In addition, the variability around the QT effect on central tendency and the degree of 'outliers' with exaggerated QT responses may also be important.

Effect of heart rate changes on QTc

It has been observed that increases in the heart rate, because of imperfections in the QT heart rate correction formula commonly used in humans, may result in an increase in the QTc interval that does not represent an actual prolongation in ventricular repolarization. The commonly utilized correction formula (for example, Bazett) overcorrect the QT interval at heart rates >60 b.p.m., and, thus, it is hypothesized that small drug-induced increases (either by direct or indirect mechanisms) in the heart rate, without direct effects on ventricular repolarization, can result in the increase of QTc. This issue may impact the development and labelling of any drug that increases the heart rate, including β -adrenergic agents and systemic vasodilators.

The use of QT as a biomarker is also impacted by the relative difficulty in measuring small changes in this parameter in patients with significant heart disease. Although highly reproducible measurements are readily obtainable in healthy volunteers, there is an increased variability in patients with abnormal baseline ECGs and underlying heart disease, which affects variability, accuracy and precision of the measurements. This is compensated for, in part, by focusing during later stage development on 'outliers' with large categorized changes instead of central tendency.

Validation of preclinical models: overview and assay sensitivity

The appropriate goal for validation for a preclinical assay strategy is not to solely predict human QT prolongation but to determine the risk of TdP-type proarrhythmia development, because this is the key clinical question. This is a

challenging endeavour. Because proarrhythmic complications can be fatal, the models will need to have very high sensitivity and have a very low false-negative rate to exclude TdP risks for drugs when interacting with the altered physiologic substrate commonly found in patients, including heart disease, hypokalemia, polypharmacy, altered metabolism resulting in high plasma levels, hypomagnesaemia, congestive heart failure, altered ionic channel number or properties, individuals with reduced repolarization reserve (Roden, 2006) and others. To what degree the outcome of the tests are probabilistic (Malik and Camm, 2001) or approach certainty will be a critical issue that requires in-depth discussion. Clearly, to gain scientific and regulatory acceptability for using a preclinical testing methodology for decision-making purposes and because of the intrinsic safety issues, sensitivity must take precedence over specificity. The testing evaluation methodology must prospectively pre-define statistical margins of 'acceptable' assay sensitivity. Ideally, the scientific methodology and the definition of end points and margins will be developed in coordination with international regulators. Regulatory input will help to proactively identify issues and increase the likelihood of wider acceptance of the results, if they are 'positive' and to best address the regional regulatory differences that currently exist in the confidence in preclinical data.

Assay evaluation

It is highly unlikely that a single preclinical model will have sufficient predictive power for this purpose, and for practical purposes, defining a relatively limited number of assays for prospective evaluation is preferable to a large assay battery. Other articles in this symposium will focus on the specific tests. The individual assays should be widely available in a number of laboratories, validated and be able to be performed meeting Good Laboratory Practice guidelines. To maximize the scientific rigour, the evaluation should be prospective, blinded, randomized and reproducibility should be tested utilizing at least two different laboratories for each individual assay. It may be important to include an *in vivo* model to permit elucidation of the effects of any reflex phenomenon.

Drugs to be evaluated

A relatively large number of drugs will likely need to be studied to define the sensitivity and specificity with sufficiently narrow confidence intervals and to test drugs with divergent ionic mechanisms. Currently, the drugs associated with TdP all block I_{kr} or reduce trafficking of I_{kr} -related proteins. However, it is likely that drugs working through other ionic mechanisms (for example, I_{Ks} or I_{Na}) will be identified, given the diversity of ion channel genetic defects that can cause the long QT syndrome and TdP (Roden, 2006). It is important that this be considered when designing the testing methodology.

The preclinical assays should be able to detect TdP risks for drugs with only a relatively small effect to prolong repolarization and a low, but real, risk of TdP, to rigorously test the methodology's sensitivity and demonstrate that the tests can detect a drug's proarrhythmic risk, despite only a relatively mild risk. Thus, test agents need to include drugs with limited QT prolongation effects and a known TdP risk. To determine specificity, drugs with QT effects but without TdP associations also should be studied. Additionally, drugs with a wide range of electrophysiologic actions (for example, potassium, sodium, calcium and mixed ion channel effects) should be evaluated so that the results are widely applicable, and the sensitivity of the assays can be assured for drugs with a wide range of electrophysiologic actions. Drugs that are devoid of preclinical effects on hERG and repolarization, but that increase the heart rate (through direct and indirect mechanisms) should be included, because they may increase the QTc interval without actual changes in ventricular repolarization (alfuzosin may be such an example).

Even though there are a number of drugs whose association with TdP is clear (for example, cisapride, terfenadine, grepafloxacin, sertindole, terodiline, astemizole and moxifloxacin), it is likely that a larger cohort of test agents will be necessary. Recently, a number of drugs are being approved by regulatory authorities (for example, ranolazine, vardenafil and ziprasidone) that do have small amounts of QTc prolongation and determining if these drugs are associated with a real clinical TdP risk will be important to determine assay sensitivity. This assessment will have to be based on post-marketing data and represents a challenge, because for many drugs with small or modest QT effects, it is difficult to know if the relatively small number of episodes of TdP observed during post-marketing surveillance actually represents a TdP risk or simply the background incidence of TdP in the patient population. It is very difficult to know what the background incidence of non-drug-related TdP is. In a prospective hospital-based Swedish study, an incidence of 3.3 cases per million individuals over a 28-day study period was observed (equating to an annual incidence of 4/100 000 individuals) (Darpo, 2001). Of the 14 individuals with TdP in this study, about 50% may have been drug-induced (d,l-sotalol was given to six, antidepressants to two, and an unspecified antibiotic and cisapride to one patient each), yielding a possible incidence as high as 2/100 000 individuals per year. Although this figure seems markedly high, it is also appreciated that post-marketing surveillance is associated by considerable underreporting. Post-marketing surveillance has shown a TdP-reporting rate with moxifloxacin of 1 per 1–2 million cases (Camm, 2005), which may not be higher than the background rate. Of course, the incidence of TdP with a drug, which has a TdP proclivity, is also affected by the inherent arrhythmia risk of the patient population being studied. Clearly, additional studies examining the background non-drug-induced incidence of TdP are indicated.

Post-marketing data also create challenges in interpretation, because it is often confounded by the difficulties of collecting detailed information on the index cases and having incomplete data, including the use of concomitant medications and details of changing pathophysiologic states

of the patients. Occasionally, it is not possible to determine if the arrhythmia is actually TdP, because sufficient documentation may not be available. Nevertheless, post-marketing data have been critical, despite these limitations, in identifying drugs with a clear risk of TdP. Some have advocated using sudden death instead of TdP to identify risk, although other mechanisms might account for sudden death events. One potential approach for adjudicating if drugs with unclear data are proarrhythmic is for an expert panel to review the post-marketing data in a blinded fashion and to determine the propensity of individual drugs to cause TdP, keeping in mind the background incidence of this phenomenon. Another approach is to focus not on TdP but sudden cardiac death because if a drug causes TdP, it should increase the sudden death rate and this is more easily defined and measured. However, a high background incidence of sudden death in the study population could mask a significant drug-induced contribution if the study population was not sufficiently robust.

Another approach that may be considered is to perform pharmacoepidemiologic studies. A recent study used this approach to evaluate erythromycin and CYP3A inhibitors, and found a clear association between erythromycin and co-administration with CYP3A inhibitors, and the development of sudden death (Harris and Leon-Casasola, 2005). However, other attempts to use this methodology have not all been successful. For example, in a study of 36 743 patients prescribed cisapride in the United Kingdom and Canada, a prescription database and post-marketing surveillance was utilized and found an odds ratio of cisapride use and adverse cardiac outcomes of 1.0 (after correcting for clinical variables) (Walker, 1999). However, it has been calculated (Malik and Camm, 2001; Barbey *et al.*, 2002) that the incidence of TdP with cisapride is only 0.4–0.7 per 100 000 patient-months of exposure, suggesting that the above study was underpowered. This may also have been an issue with other similar analyses (Hanrahan *et al.*, 1995). Thus, it is important that the studies be adequately powered and that the methodological considerations when using this technique be carefully examined. When performed across a number of drugs, it would be preferable that the analysis be done in a uniform manner.

Implications

If such a preclinical testing approach was validated and widely accepted, it is possible that there might be three general outcomes of these tests: (1) no QT signal and no TdP risk; (2) QT signal and no TdP risk and (3) TdP risk (with or without QT signal). The goal in the first instance is that no special QT testing would be required during the clinical development programme, whereas for the last scenario human testing, possibly including outcome studies for some agents to show the absence of a mortality risk, would be expected to permit clinical development to advance. In the case of a finding of a QT signal but no TdP risk, the approach is likely to be individualized and hopefully the results of the preclinical test would meaningfully impact the development strategy.

Summary

Drug-induced QT prolongation currently plays a critical role in drug development as a surrogate biomarker for TdP risk. Although currently the best available clinical surrogate, its imperfect characteristics for this purpose and the challenges posed by finding a mild-modest QT signal for clinical development, regulatory approval and commercial success along with accurately assessing the actual risk of TdP development prior to the years it takes to accrue sufficient post-marketing data, speak to the need for newer methodologies that can be employed during the discovery process to assess TdP risk. If a battery of preclinical assays could be rigorously validated and accepted by the scientific community, drug developers and regulatory authorities, this is likely to favourably impact the discovery pipeline and speed clinical development. This is, however, a challenging task from a scientific and regulatory perspective.

Acknowledgements

We thank Dr Borje Darpo for his critical review of the paper and Ms Norma Carre-Grebe for her excellent editorial assistance.

Conflict of interest

Dr Sager is employed as the Chief Medical Officer of CardioDx, a company involved in research on arrhythmias and the development of cardiac diagnostic platforms. The opinions expressed in this paper are those of the author and do not necessarily reflect the views of CardioDx Inc.

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