The QT interval as it relates to the safety of non-cardiac drugs

Peter R. Kowey1* and Marek Malik2,3

1 Main Line Health Heart Center, Lankenau Hospital, 558 Medical Office Building East, 100 Lancaster Avenue, Wynnewood, PA 19096, USA
2 University of London, London, UK
3 St Paul’s Cardiac Electrophysiology, London, UK

The ability of some non-cardiac drugs to alter cardiac repolarization and thereby increase the likelihood of cardiac arrhythmias, in particular life-threatening torsades de pointes, has led regulatory agencies to request that modifications of the QT interval, manifesting repolarization changes, should be intensively investigated in every drug developed. However, although prolongation of the QT interval is a relatively easily measured marker of repolarization changes, it is widely viewed as a poor surrogate of the arrhythmogenic potential of a drug. Despite intensive and costly investigation, the prediction of pro-arrhythmic risk based on pre-clinical and clinical data therefore remains imperfect. How QT interval relates to the safety of non-cardiac drugs, and how physicians can best integrate pre-clinical and clinical information in assessment of the risk profile of a drug, remain somewhat open questions.

Introduction

Many commonly prescribed non-cardiac drugs have the potential for pro-arrhythmic effects associated with QT interval prolongation on the ECG. This is a safety concern in that prolongation of the QT interval is a simple (but not entirely precise) sign of repolarization changes that can lead to the polymorphic ventricular tachyarrhythmia known as torsades de pointes (TdP). Although TdP occurs rarely, it is life-threatening, and consequently, the use of agents causing changes in cardiac repolarization can increase the risk of sudden death.

During recent years, much emphasis has been placed on the pro-arrhythmic effects of pharmaceuticals that are associated with QT interval prolongation, and regulatory bodies have ruled that the QT interval-prolonging properties of every new chemical entity should be intensively investigated.1-3 Substantial prolongation of the QT interval, with or without documented arrhythmias, could constitute a reason for not approving a drug or discontinuing its clinical development. Greater than expected rates of TdP, whether fatal or non-fatal, have resulted in the withdrawal of several drugs from the market or at least restriction of their use to second-line therapy.

The use of drugs with the potential for prolongation of the QT interval and pro-arrhythmic effects is a growing challenge facing both physicians, as prediction of the risk of TdP in an individual patient remains difficult, and the pharmaceutical industry, which spends hundreds of millions of dollars every year on assessing the pro-arrhythmic potential of its new compounds. How this assessment can be best achieved and how physicians can best integrate pre-clinical and clinical information about drug-induced QT prolongation to construct a pro-arrhythmic risk profile is still not fully resolved.

Determination and normal limits of the QT interval

The QT interval, measured from the beginning of the Q-wave to the end of the T-wave, is an indirect
measure of the total duration of ventricular repolarization. The most appropriate lead(s) and methodology to measure the QT interval are still debated, although experience shows that the most accurate assessment requires all 12 leads of the standard ECG to be measured. Uncertainties persist in ECG interpretation, as the QT interval can vary considerably between leads within the same ECG due to the possibility of differing projection of the three-dimensional T-wave loop into the various leads. Although conventional two- or three-lead Holter monitoring has the advantage of measuring QT interval over a longer period and over a wide range of heart rates, the measurements may and frequently do differ from those obtained on 12-lead ECGs. The interpretation of data obtained from such Holter monitoring should therefore be limited to comparisons with similarly derived Holter recordings and not be compared with standard 12-lead ECGs. In contrast, ECGs derived from digital 12-lead Holter recordings are considered to be equivalent to bedside 12-lead ECGs.

In view of its inverse relation with heart rate, the measured QT interval is corrected by means of various formulae to a heart rate-independent value known as the QTc. In the past, numerous universal methods were proposed for the correction of QT interval but none of these methods proved to be sufficiently accurate. Although in clinical practice, the errors caused by the simplest methods, such as Bazett’s (QTc = QT/RR1/2) and Fridericia’s corrections (QTc = QT/RR1/3), are unlikely to lead an informed physician to erroneous conclusions, the errors of these methods may easily invalidate investigations of drug effects. This is because the relationship of QT interval with heart rate shows considerable inter-individual differences while, for the same individual, exhibiting great stability over time. Moreover, for a given individual, QTc is affected by a wide range of influences, both internal (genetic, physiological, and pathophysiological) and external (foods, drugs). In general, women have a longer QTc than men, and there is a positive correlation between QTc and age.

Despite long-standing recognition of this variability of the QTc among healthy individuals, attempts have been made to define an upper limit of normal. The European regulatory body, the Committee for Proprietary Medicinal Products, has suggested upper limits of normal (Bazett’s QTc correction) of 450 ms for adult men and 470 ms for adult women. Although the precise relationship between the extent of QTc prolongation and the risk of sudden death is unknown, and it is recognized that an absolute threshold of risk for TdP cannot be proved, it is evident that almost all reported cases of TdP have occurred in individuals with a measured uncorrected QT exceeding 500 ms. Consequently, values of QT greater than 500 ms should cause concern.

It is not clear whether the development of arrhythmias is more closely related to an increase in the absolute QT interval or in QTc, but most drugs that have caused TdP clearly increase both the absolute QT and the QTc. The risk of arrhythmia appears to increase with the extent of QT prolongation. Consideration should be given to whether the test substance belongs to a chemical/pharmacological class including some members that have already been shown to induce QT interval prolongation in humans. Many drugs have been shown to produce TdP, including antihistamines, antibiotics (such as macrolides and fluoroquinolones), antimalarial, anti-depressants, neuroleptics, antipsychotics, and antifungal agents.

The pre-clinical characterization of potential for pro-arrhythmic effects

It is recognized that the assessment of drug-induced QT interval prolongation is not equivalent to assessment of the potential for drug-induced TdP. Nevertheless, an adequate pre-clinical investigation of the safety of a new pharmaceutical agent must include rigorous characterization of its effects on repolarization. The results of these investigations can help to design subsequent clinical trials.

Ventricular repolarization, determined by the duration of the cardiac action potential, is a complex physiological process. It is the net result of the activities of many ion channels and receptors, highly interdependent, the activity of which can be affected by multiple factors such as intracellular and extracellular ion concentrations, membrane potential, heart rate, and the autonomic nervous system. Many in vitro and in vivo pre-clinical tests have been developed to assess the potential of new drugs to induce TdP. Although no single test can predict with absolute accuracy which drugs will produce TdP in humans, evaluation of the occurrence of electrophysiological events underlying TdP, including prolongation of the ventricular action potential duration, generation of early after-depolarization-induced extrasystoles, and increased transmural dispersion of repolarization, is useful for identifying drugs that have the potential to cause TdP.

Topic 57B of the International Conference of Harmonization (ICH) is dedicated to the non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. The objectives of pre-clinical studies are to identify the potential of the test substance and its metabolites to delay ventricular repolarization and to relate the extent of delayed ventricular repolarization to the concentrations of the test substance and its metabolites.

According to Topic 57B, four functional levels can be investigated by in vitro and in vivo methods:

- ionic current measured in isolated animal or human cardiac myocytes or cultured cardiac cell lines;
- action potential parameters in isolated cardiac preparations or specific electrophysiology parameters indicative of action potential duration in anaesthetized animals;
- ECG parameters measured in conscious or anaesthetized animals;
- pro-arrhythmic effects measured in isolated cardiac preparations.
In vitro electrophysiology studies can explore potential cellular mechanisms that might not be evident from in vivo data and provide valuable information concerning the effect of a test substance on action potential duration and/or cardiac ionic currents.

Although delay of repolarization can occur through modulation of several types of ion, it has been observed that most drugs that prolong the QT interval have the potential to block the HERG (human ether-a-go-go-related gene) ion channel which is responsible for the repolarizing outward current $I_{\text{kr}}$, a process that may lead to prolongation of the QT interval and arrhythmias, and in particular may cause TdP.\(^{11,17,18}\) It is worth pointing out that in pre-clinical studies, the choice of the species is important. The ionic mechanisms of repolarization in adult rats and mice, for example, differ from those seen in larger species including humans.\(^{1}\)

As cardiac cells and tissue have a limited capacity for drug metabolism, in vitro studies using the parent substance do not provide information on the effects of metabolites, and testing metabolites in the relevant in vitro systems should be considered. Moreover, an appropriate positive control substance should be used to establish the sensitivity of the in vitro assay system, and the dose range tested should exceed the anticipated human exposure. However, the action of a drug in blocking HERG channels may be poorly correlated with its likelihood to increase the duration of the ventricular action potential.\(^{19}\) Furthermore, studies have indicated that drugs that do not increase transmural dispersion of repolarization have little or no potential to induce TdP despite causing prolongation of the QT interval.\(^{16}\) QT prolongation, which is not mechanistically linked to pro-arrhythmia, can therefore be considered as a poor predictor of TdP.

**Clinical development**

The potential of a drug to significantly increase the QTc interval and to be proarrhythmic has been consistently assessed on the basis of electrophysiological and clinical studies, and all drugs are expected to undergo clinical electrocardiographic evaluation early in clinical development. The design and conduct of human studies to detect and quantify QT interval prolongation induced by a new chemical entity have been specified in the ICH document E14 developed by several regulatory agencies.\(^{2,3}\)

The pivotal so-called thorough QT/QTc study, conducted if possible in healthy volunteers, is intended to determine whether the drug has a threshold pharmacological effect on cardiac repolarization, as detected by QT prolongation. Healthy volunteers constitute the ideal population for this study, as they are not on medication, have no electrolyte abnormalities, and present normal T-waves. The thorough QT/QTc study, which must be capable of detecting a QTc change as small as 5 ms, has a critical role in determining the intensity of ECG gathering during later stages of development.

A control group receiving placebo, or preferably, a placebo study period, is useful to interpret spontaneous variability and to increase confidence in the ability of the study to detect QT/QTc prolongation. The use of a concurrent positive control group is mandatory to validate assay sensitivity. As drugs that prolong the mean QT/QTc interval by around ≤5 ms do not appear to cause TdP, the positive control should have an effect on the mean QT interval slightly over this limit. Previous experience with regulatory attitudes concerning drugs such as terfenadine, cisapride, or moxifloxacin suggests that the present threshold of regulatory concern is approximately one case of pro-arrhythmia per $10^5$–$10^6$ patients exposed.\(^{10}\) Providing the power to detect a QTc prolongation of 5 ms is challenging, even when using advanced technologies for ECG reading, and necessitates obtaining a large number of ECGs. Enhanced precision in handling the ECG data might help to reduce the size and therefore the cost of the thorough QT/QTc study.\(^{21}\) Substantial savings in the cost of the thorough studies can be achieved in this way. Moreover, enhanced precision of semi-automatic approaches to ECG processing allows the performance of pilot QT/QTc studies very early in the clinical development programme, perhaps as early as in the first-in-man investigations.

Detailed description of practical requirements for the conduct of thorough QT/QTc studies or of the corresponding pilot studies is beyond the scope of this text. Among other factors, stability of the ECG recordings (in terms of both underlying heart rate and noise content) needs to be carefully monitored, the relationship of the ECG samples to the pharmacodynamics of the drug and its metabolites needs to be confirmed, and distinctive drug-free electrocardiographic profiles of individual study participants must be characterized. Standard thorough QT/QTc studies require the collection and measurement of no less than several tens of thousands of separate ECG samples.

A negative thorough QT/QTc study is defined as one in which the upper limit of the 95% one-sided confidence interval for the largest time-matched mean effect of the study drug excludes 10 ms. A negative study will almost always permit simplification of ECG safety monitoring during the subsequent stages of drug development. Conversely, a positive thorough QT/QTc study will almost always call for expanded ECG and safety evaluations during further development, increasing the cost and complexity of phase III studies. For example, ECGs may need to be gathered from a large number of subjects in a phase III trial, a more difficult population, likely to have concurrent pathological conditions and to be taking concomitant medication.

It is worth noting, however, that a positive thorough QT/QTc study does not necessarily indicate a risk of TdP in the absence of effects on other electrophysiologically markers associated with this, in particular induction of early afterdepolarizations, leading to ectopic beats, and increased spatial dispersion of ventricular repolarization, creating conditions favourable to re-entry.

Since intrinsic variability resulting from many factors is a major problem in measurement of the QT/QTc interval, the collection of multiple ECGs at baseline and during the course of the thorough QT/QTc study is required.
The number and timing of ECG recordings are critical in the design of such studies and recording time points should be clustered more densely around the $T_{\text{max}}$ of the drug. The duration of dosing and the dosing regimen should be sufficient to characterize the effects of the drug and its active metabolites at relevant concentrations. An adequate drug development programme should ensure that the dose–response and generally the concentration–response relationship for QT prolongation have been characterized, including exploration of concentrations that are much higher than those achieved following the anticipated therapeutic dose.

Regulatory authorities have encouraged the use of doses resulting in plasma concentrations substantially larger (e.g. three to five times) than those determined after administration of the highest recommended therapeutic doses. Assuming a direct relationship between the plasma concentration of a drug and the likelihood of QT prolongation (which is far from guaranteed), the administration of high doses is important to assess the likely effect of metabolic inhibition. The risk of TdP may also be amplified by drug–drug interactions, e.g. when an inhibitor of a CYP450 metabolic enzyme is co-administered with a QT-prolonging drug that is a substrate of this enzyme, or in the presence of other factors affecting drug pharmacokinetics such as liver or renal disease. In essence, response to an overdose administered to healthy volunteers is used as a model of a possible response to a standard clinical dose administered to the target population of patients, who might have increased susceptibility to any repolarization changes.

From the results of the thorough QT study, i.e. the extent of the QTc prolongation, three clinical situations may be distinguished: drugs that prolong the mean QTc interval by around $\leq 5\text{ ms}$ do not appear to cause TdP (or the increased risk is too small to be detected); drugs that prolong the mean QTc interval by $>10\text{ ms}$ and $<20\text{ ms}$ have an uncertain risk of inducing TdP, although some of these compounds have been associated with a risk of pro-arrhythmia (especially when the QTc interval was measured after administration of doses close to the therapeutic dose range). This is a situation where gathering more pre-clinical data may be particularly helpful in determining TdP risk. Drugs that prolong the mean QTc interval by $>20\text{ ms}$ have a substantially increased likelihood of being pro-arrhythmic and would be expected to cause clinical arrhythmic events apparent during drug development.

Although increases in QTc interval to $>500$ or $>600\text{ ms}$ over baseline are commonly used as threshold values for potential regulatory concern, the exact criteria chosen for a given trial will depend on the risk–tolerance level considered appropriate for the indication or patient group. In other words, the greater the benefit of the drug and the more unique the treatment advantage, the greater the tolerance of some effect on QT interval. Complementary analyses may be necessary in the event of outliers showing greater QTc prolongations.

The probability that QT-prolonging drugs will induce TdP may be amplified by a variety of factors increasing the likelihood of a drug-induced exacerbation of myocardial heterogeneity, e.g. hypokalaemia, bradycardia, activity of the autonomous system, heart disease, or pharmacokinetic interactions. The influence of such differences on susceptibility, which may clearly vary from one drug to another, is best investigated in studies in the patient populations likely to be treated with the particular drug, e.g. if the drug is to be used in patients with heart failure, its potential QT-prolonging effect should be tested in these patients. However, such studies in target populations require careful design and expert electrocardiographic input, since the ECG stability in clinical populations is frequently much lower and the conduct of exact ECG studies much more problematic compared with studies in healthy volunteers.

Previously, arrhythmias induced by non-antiarrhythmic drugs have been observed with compounds that prolong QTc interval. Much less experience exists with pro-arrhythmic properties of drugs that shorten total cardiac repolarization. However, it might be inappropriate to conclude that QT/QTc shortening is fully benign or perhaps beneficial. On the contrary, there are several reasons to be concerned about drug-related QTc shortening. First, it is widely recognized that QT/QTc prolongation is not the core of the problem with drugs acting in that way. Rather, some of these drugs are pro-arrhythmic because they increase the heterogeneity and irregularity of repolarization within ventricular tissue.

Similar considerations may easily apply to QTc shortening—both lengthening and shortening of the interval might be indirect indicators that a drug is affecting cardiac repolarization, thus possibly increasing intramyocardial heterogeneity which directly translates into pro-arrhythmic risk. Second, analogous to congenital long QT syndromes, representing genetically determined equivalents of channelopathies caused by QTc-prolonging drugs, genetically determined abnormalities of myocyte function manifested by shortened ventricular repolarization have been demonstrated; these abnormalities induce pro-arrhythmic effects similar to those characteristic of congenital long QT syndromes. Third and finally, there might be a good clinical reason for our limited experience with pro-arrhythmia induced by QT/QTc-shortening drugs. The tachycardia related to QTc prolongation is a distinct morphological form of TdP. This particular morphological form seems to be related to the prolonged repolarization, since prolonged repolarization limits the possibilities of re-entrant pathways, thereby leading to a single particular form of intra-ventricular propagation. In contrast, shortened repolarization, together with increased intra-myocardial heterogeneity, is likely to increase the possibilities of re-entrant pathways. It is thus more likely to lead to disorganized patterns of fast ventricular fibrillation, without any distinct morphological form that would be easily recognizable as a side effect of drug therapy. In a standard clinical situation, ventricular fibrillation might rather be linked to the underlying pathology, ischaemic episode, etc. Thus, it seems not unreasonable to speculate that existing drugs that shorten cardiac...
repolarization might also induce infrequent fatal arrhythmias (perhaps with a similar incidence to that of the rather rare TdP) but that the true cause of these arrhythmias is not clinically recognized. However, as yet, there is no evidence for such an association.

Discussion

Clearly, there is concern about drug-induced TdP, but its occurrence is rare, so it is usually not seen during clinical development. Relying on a surrogate marker for pro-arrhythmic risk, it is nevertheless a very accessible, relatively easily used indicator. Despite scepticism regarding the methodologies used for its measurement, there is generally a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause substantial prolongation of the QT interval. To date, no other clinical test appears to be more accurate in distinguishing drugs with the potential to induce this potentially lethal arrhythmia. Although a more accurate clinical surrogate would be most helpful (perhaps combining both delayed and accelerated repolarization), research in this field is presently only ongoing.

In order to reduce the risk of TdP, regulatory bodies insist on intensive non-clinical and clinical evaluation of a new drug’s potential for delayed ventricular repolarization and may decline to approve a drug with a potential to prolong the QTc interval that is poorly characterized. It remains questionable if induction of a QTc change as small as 5 ms has any meaning in terms of assessing a drug’s potential to induce TdP. Nevertheless, since clear delineation of risk is difficult, it is understandable that regulatory decisions are based on arbitrary definitions. Since regulators consider any QTc change below the threshold of 5 ms as equivalent to no change at all, it seems reasonable to set the threshold this low.

It may be noted that the main study, the so-called thorough QT study, is usually performed in healthy volunteers, whereas the occurrence of TdP for the most part depends on a combination of the drug’s liability to prolong the QT interval and the patient’s susceptibility. However, to explore the full range of doses under all relevant conditions is frequently unrealistic or highly impractical, and it seems unlikely that a drug that has been shown to have absolutely no QTc effect in healthy volunteers will have an appreciable effect in more susceptible patient populations.

An important point to consider is the economic implications of drug-induced repolarization changes in drug development. Although current pre-clinical tests are acknowledged to be imperfect predictors of cardiac drug safety, and the exact relationship between electrophysiological events and the development of TdP is not perfectly clear, the results of early pre-clinical studies may lead to the premature discontinuation of drug development and the possible abandonment of highly useful drugs.

Conducting the thorough QT study early during the development programme, i.e. before the proof of concept has been established in phase II trials, is problematic as the development programme could be stopped later for other reasons. Furthermore, in the early stages of development, the final therapeutic dose may not be known and QT is measured in first-in-man studies essentially for safety reasons. Conversely, performing the thorough QT study later leads to the risk of discontinuing drug development when a substantial part of the cost of the programme has already been committed. The difficulties and cost of conducting detailed ECG monitoring in large phase III clinical studies, when the results of the thorough QT study indicate a QT/QTc interval prolongation exceeding 10 ms, may lead to discontinuation of the study before the therapeutic potential of the drug has been properly evaluated. The solution to this dilemma seems to lie in pilot QT/QTc studies that could be conducted at a reduced cost and could therefore be envisaged before proof of concept has been obtained. Such pilot studies seem to be capable of detecting large QT/QTc-related signals, making it more acceptable to delay the true thorough QT/QTc study until after proof of concept has been established.

Conclusion

Although the assessment of pro-arrhythmic toxicity and the likelihood of induction of TdP appears to be a justified requirement in the development of any pharmaceutical agent, the most important point to be evaluated by a regulatory agency when deciding whether or not to approve a drug must be the benefit/risk ratio.

Although TdP is a catastrophic event, the overall benefit of the drug may outweigh the risk. This applies particularly when a drug is effective in an otherwise fatal disease, such as cancer, or in patients who are intolerant to available therapeutic agents or for whom these agents are contraindicated. Until an alternative therapy becomes available, the development of such a drug should not be delayed or stopped solely because of its potential to cause arrhythmia. On the other hand, even a low risk of arrhythmia would be unacceptable if there are safer alternatives, or if the indication does not concern a serious illness.

Conflict of interest: none declared.

References

3. European Agency for the Evaluation of Medicinal Products (EMEA). ICH Topic E14: note for guidance on the clinical evaluation of
QT/QTc interval prolongation and proarrhythmic potential for non-
4. Malik M. Errors and misconceptions in ECG measurement used for the
detection of drug induced QT interval prolongation. J Electrocardiol
2004;37(Suppl.):25–33.
6. Camm AJ. Clinical trial design to evaluate the effects of drugs on
cardiac repolarization: current state of the art. Heart Rhythm
7. Malik M. The imprecision in heart rate correction may lead to artifi-
cial observations of drug induced QT interval changes. Pacing Clin
between QT and RR intervals is highly individual among healthy sub-
jects: implications for heart rate correction of the QT interval. Heart
2002;87:220–228.
Dilaveris P, Camm AJ, Malik M. QT-RR relationship in healthy subjects
exhibits substantial intersubject variability and high intrasubject
10. Committee for Proprietary Medicinal Products (CPMP). Points to con-
sider: the assessment of the potential for QT interval prolongation by
non-cardiovascular medicinal products. European Agency for the
11. Heist EK, Ruskin JN. Drug-induced proarrhythmia and use of
QTC-prolonging agents: clues for clinicians. Heart Rhythm 2005;2:
S1–S8.
13. Joshi A, Dimino T, Vohra Y, Cui C, Yan GX. Preclinical strategies to
assess QT liability and torsadogenic potential of new drugs: the
14. Carlsson L. In vitro and in vivo models for testing arrhythmogenesis in
validation of the isolated arterially perfused rabbit ventricular
wedge in preclinical assessment of drug-induced proarrhythmias.
16. Antzelevitch C. Role of transmural dispersion of repolarization in the
genesis of drug-induced torsades de pointes. Heart Rhythm 2005;2:
S9–S15.
17. Fenichel RR, Malik M, Antzelevitch C, Sanguinetti M, Roden DM,
Priori SG, Ruskin JN, Lipicky RJ, Cantilena LR, Independent Academic
Task Force. Drug-induced torsades de pointes and implications for
18. Fitzgerald PT, Ackerman MJ. Drug-induced torsades de pointes: the
19. Belardinelli L, Shryock JC, Wu L, Song Y. Use of preclinical assays to
predict risk of drug-induced torsades de pointes. Heart Rhythm 2005;
20. Malik M. Detection of drug-induced proarrhythmia: balancing precli-
Sample size, power calculations and their implications for the cost
of thorough studies of drug induced QT interval prolongation.