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Review Article

Thorough QT/QTc (TQT) study

Lakshmi Balasundaram[1]*, Bharatraj Kidambi[2], Surya Singaravelu[1]

[1]Department of Pharmacology, JIPMER, Puducherry, India
[2]Department of Cardiology, AIIMS, Delhi, India

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***Correspondence:**
Dr. Lakshmi Balasundaram,
Email: shivani.arangan@gmail.com

ABSTRACT

With a number of drugs entering the market, cardiac safety remains a cause of major concern for the regulatory authorities, before approval. The incidence of drug induced arrhythmia with non-cardiovascular drugs is low, however the result is fatal, hence much focus is being given to assess the pro-arrhythmic potential of a drug. The arrhythmogenic risk of the drug is higher if the patient is on polypharmacy or has other risk factors such as an electrolyte imbalance or an underlying structural heart disease. QT prolongation can be either due to congenital causes such as Long QT syndromes (LQTS) which include Romano-Ward syndrome, Jervell and Lange-Nielson syndrome or can be acquired, which is mainly due to drugs. Several drugs such as terfenadine, astemizole, cisapride and grepafloxacin have been withdrawn from the market due to QT prolongation and development of a fatal ventricular arrythmia - torsades de pointes (TdP). This has led to implementation of guidelines to assess cardiac safety. The pro-arrhythmic risk can be assessed using thorough QT/QTc studies or exposure response modelling of intensive ECGs. This article will give an overall view of the use of QT/QTc interval as a biomarker for cardiac safety and the current guidelines for thorough QT/QTc studies which are mainly done to assess the pro-arrhythmic potential of a non-anti-arrhythmic drug.

Keywords: TQT study, Torsades de pointes

INTRODUCTION

A drug which is intended to benefit a patient, ideally, should have undergone rigorous safety testing. Unfortunately, drugs are tested under controlled environment during clinical trials, which contrasts the real-life situation. In the 80's the release of terfenadine, the first non-sedating antihistamine was found to be associated with QT prolongation and development of torsades de pointes (TdP) especially in patients who took ketoconazole or erythromycin concomitantly.[1] TdP can result in seizures, syncope or sudden death. This led to the US Food Drug Administration (FDA) compelling the manufacturers to issue letters to physicians warning them about the potential risks with this drug, and finally ended up with the withdrawal of the drug from the market.[1] Experiences as such, led to the formulation of guidelines to ensure that a new drug undergoes rigorous cardiac safety testing. QT interval is considered a biomarker for cardiac safety testing. However, its measurement shows variation – with respect to age, gender, heart rate, postural changes, food ingestion, autonomic tone and exhibits diurnal variation also. In addition to these difficulties, it is also noted that not all patients with QT prolongation will develop TdP.[2] With due consideration, the International Council of Harmonization (ICH) S7B specified regulatory guidelines for non- clinical evaluation for potential QT prolongation and ICH E14 in the year 2005, laid guidelines for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. A 'thorough QT/QTc study' is thus, a dedicated study to

evaluate the effect of the new molecular entity on the QT interval.[3]

PHYSIOLOGY OF CARDIAC CONDUCTION

The conduction system of the heart consists of the SA node, internodal atrial fibres, atrioventricular node, the Bundle of His along with its branches and the purkinje system. Impulses pass along these structures in the same order to reach the muscles of the ventricles. The SA node due to its maximum discharging rate, is called the pacemaker cells. The resting membrane potential of a cardiac myocyte is -90 mV.[4,5] There are 5 phases in a ventricular action potential which are as following:

Phase 0: Characterised by a rapid influx of Na+ (I^{Na}), this causes initial upstroke in the action potential.

Phase 1: Upstroke is terminated by the inactivation of Na+ channels and transient efflux of K+ (I^{to}) channels.

Phase 2: Plateau phase due to balance between an influx of Ca2+ channels and outward repolarising K+ channels.

Phase 3: Sustained downstroke due to efflux of K+ (I^{Kr} and IKs) through delayed rectifier channels.

Phase 4: Resting membrane potential maintained by inward rectifier potassium current (I^{Kr}).

The delayed rectifier potassium currents play a determining role in the action potential and hence on the QT interval.[4,5]

QT/QTC MEASUREMENT

Ideally, the QT interval is recorded using a 12-lead electrocardiography (ECG) strip with a running speed of 50 mm/s and an amplitude of 0.5 mV/cm. Lead II is preferred for measurement of the same. QT interval is measured from the beginning to the QRS complex to the end of the T wave (Figure 1) .[6-8] It is the time taken for the ventricular depolarisation and repolarisation, in other words, it measures the ventricular action potential.

As the QT interval depends on the heart rate (faster heart rate = shorter QT interval), corrections should be made in the QT interval measurement to account for the effects of heart rate which can be done using several formulas such as Bazett's square root formula ($QTc = QT/\sqrt{RR}$), Fridericia's cube root formula ($QTc = QT/\sqrt[3]{RR}$), Framingham method (QTc= QT+0.154 [1-RR]), a new linear model which is relatively unaffected by heart rate is the Hodge's formula (QTc = QT+1.75 [HR-60]).[9]

For all the formulas, the preceding RR interval should be measured. Normal QT interval ranges from 350 ms to 440 ms. The upper limit of normal QTc interval is 450 ms in males and 460 ms in females. Precaution must be taken while measuring the QT interval in case of atypical T waves. The end of the T wave is considered the point of intersection of the steepest last slope of the T wave with the baseline.[10] U waves can be found in ECGs of adolescents and inclusion of a U wave may lead to a false positive QT prolongation by 80-200 ms, hence care must be taken not to include the U waves.[10]

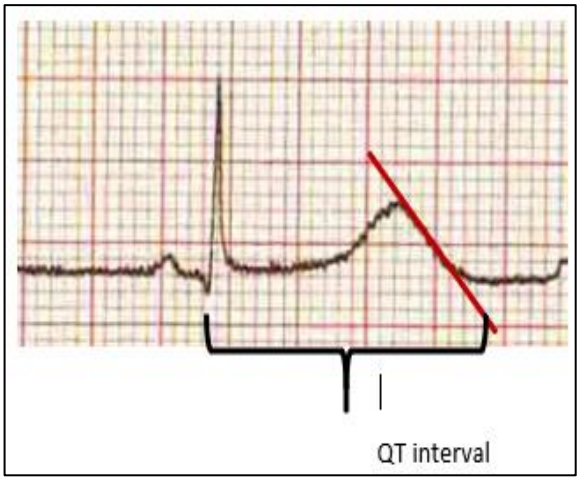

Figure 1: Measurement of QT interval.

CONDITIONS ASSOCIATED WITH QT PROLONGATION

Congenital long QT syndromes are due to loss of function mutations of KCNH2, KCNJ2 and KCNQ1 and gain of mutation of SCN5A genes. Long QT syndromes include Romano-Ward syndrome and Jervell and Lange-Nielson syndrome.[2] Acquired QT prolongation are mainly due to pharmacological agents through their action on IKr channels. Some of the drugs commonly known to affect QT interval include moxifloxacin, levofloxacin (quinolones), erythromycin, azithromycin (macrolides), hydroxyzine (antihistamine)fluconazole, ketoconazole (antifungals) and electrolyte imbalance such as hypokalemia, hypomagnesemia and hypocalcemia.[2] Some drugs that caused QT prolongation and were withdrawn from market are given in Table 1.

Torsades de pointes (TdP)

TdP is also described as a polymorphic ventricular tachycardia, commonly associated with QT prolongation. Ventricular tachycardia is said to be monomorphic when the QRS complexes are uniform and said to be polymorphic when the QRS complex varies from beat to beat. The ventricular polymorphic tachycardia has a tendency to oscillate around the baseline in the ECG mimicking "turning of the points" or "torsades de pointes" as described by Francois Dessertenne in 1966, where "torsades" means twisting of hair or threads and "pointes" refers to peaks or points.[11]

Clinically, sustained TdP leads to haemodynamic collapse and treatment is with emergency asynchronous

defibrillation and pharmacological measures include lidocaine or amiodarone.

GUIDELINES

ICH S7B

This guideline provides methods to test the ventricular repolarization delaying potential of drugs in the preclinical phase.

Objectives are to identify the ventricular repolarisation delaying potential of the new chemical entity and to identify the association between the concentration of the drug or its metabolite and the risk of causing ventricular repolarization delay.[4]

Study designs

In vitro – Human cardiac myocytes or cultured cardiac cell lines can be used to measure ionic currents, action potential parameters can likewise be measured. IKr assay is done to evaluate the effect on native ion channels, as encoded by human ether a go-go related gene (hERG) which has homology with the Drosophila melanogaster gene – ether a go-go. The hERG is now called KCNH2 and the protein encoded is hERG channel or Kv11.1 which is a voltage-gated potassium channel.[12]

In vivo – ECG recordings in anaesthetised animals and QT assays. Laboratory animals that are commonly used include dogs, guinea pigs, ferrets, monkeys and pigs.

Other clinical and non-clinical information required for integrated risk assessment include pharmacokinetic and pharmacodynamic studies, drug-drug interactions, safety and toxicology studies and tissue distribution and accumulation studies.

ICH E14 guidelines[7]

Study design and subjects

The scope of the ICH E14 guidelines extends to drugs other than antiarrhythmic drugs, drugs with systemic bioavailability, approved drug but for a new dose or route of administration, new indication or for a different target population and for drugs found to cause QT/QTc prolongation or sudden cardiac death in post-marketing surveillance.

The study aims to determine if the drug possesses a threshold pharmacological effect on cardiac repolarization time as measured by QT/QTc prolongation. The threshold level of regulatory concern, is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms. The TQT study helps to confidently exclude that a drug prolongs the QT interval by more than 10 ms or more at one-sided 95% confidence interval.

Design of a QT/QTc study is a double-blind, randomised, controlled trial. ICH E14 does not specify any particular timing for the conduct of the TQT study, but states that it is best done in the early phases of clinical trials so that if the QT interval is found to be prolonged, further evaluation can be carried out. Most studies are now done well before the pivotal trial.[3]

Study subjects: The study is done on healthy volunteers both males and females, except in usage of drugs such as neuroleptics and cytotoxic agents. People with baseline QT >450 ms, additional risk factors for TdP such as hypokalaemia, family history of long LQTS and concomitant medications that can prolong QT interval are excluded from the study.[3]

The study is discontinued in case the QT/QTc is >500 ms or more than 60 ms from baseline.[3]

The study is usually a well-controlled (both placebo and active) cross-over or parallel arm design where bias and blinding have been adjusted for. A cross-over design is an efficient design as it can assess intra-subject variability and the sample size is small. It allows better heart rate correction.[13] Parallel design is beneficial when the drug has a long half- life. A positive control in the study should have an effect size of 5ms on the mean QT/QTc interval.[13] In conditions where the drug is from a class of agents previously found to be associated with QT/QTc prolongation, positive control should be an agent from this class. The drug should be tested both at therapeutic and at supratherapeutic doses, unless there is a safety or tolerability issue.

The timing of the ECGs during the study is based according to the pharmacokinetic profile of the drug, a single recording is sufficient in the case of a single dose study when there is no active metabolite. Ideally, ECG recordings should be timed around the Cmax. As the QT interval is subject to variations due to activity, circadian rhythm etc Multiple ECGs should be taken at baseline and during the study.[13]

Standard 12-lead ECG collection and analysis methods

ECG recording machine should be well-calibrated and standardised. Either fully manual or manual adjudicated methods are acceptable. In case of multicentric studies, a training session for the technicians must be organised prior to the study in order to achieve consistency in recording technique. The standard norm nowadays is to take replicates of ECG recordings at any time point and average is calculated. ECG reading and interval measurement should be done by only skilled readers. Data including uncorrected QT, RR intervals, corrections using both Bazett's and Fridericia's formulas and any other formulas that were used, should be submitted. Bazett's method tends to over correct when the heart is high and under corrects at heart rates lower than 60 bpm and is ideal only when the

heart rate is between 60-100 bpm. Fridericia's method is the preferred method of correction.[7]

Although there is no defined upper-limit value for QT interval, a value of more than 500ms is a threshold of concern in clinical trials.[7]

Interpreting the results and further course of action

The primary analysis is done using Analysis of variance (ANOVA) where the change in the QTc from baseline is the dependent variable and the drug or placebo are the independent variables. The upper confidence limit at 95% for one-sided confidence limit is calculated at various time points as the difference in the QTc between the drug and placebo (ddQTc) as least square means.

Negative test results: If the upper confidence limit is less than 10 ms at all time points, then the result is said to be negative for QT prolongation and on-therapy ECGs must be collected according to the area policies

Positive results: drug goes for expanded ECG safety evaluation.

Negative test results but positive preclinical results: Expanded ECG safety evaluation.

In addition, information on T and U wave morphologies should also be provided.

Labelling considerations for drugs that increase the QT interval

Both the ICH E14 and FDA recommend the following be considered for drug labelling a warning regarding the risk of arrhythmia, results of trials that evaluated the effects of the drug on the QT interval, conditions that can increase the risk of arrhythmia such as family history of LQTS, a warning statement regarding use of other drugs concomitantly that can precipitate arrhythmia and an advisory to patients regarding monitoring with ECG.

Positive control

A positive control is used to ensure that the study is able to pick up changes in the QT interval. Most of the studies use the fluoroquinolone-moxifloxacin as the positive control, as it produces a mean increase in the ventricular repolarisation greater than 5 ms (range between 8ms to 15ms).[3] The peak effect of moxifloxacin can be recorded 1-3 h after administration. Other positive controls that can be used are low-dose ibutilide infusion and sparfloxacin.[3]

An assay sensitivity analysis is performed by taking the lower confidence limits, 95% of the one-sided confidence limits for the difference in the QTc between moxifloxacin and placebo. The test is considered to be positive if the largest ddQTc ranges from 8-15 ms and occurs between 1-3 hours post-dose, the lower 95% one sided confidence interval in the ddQTc between moxifloxacin and placebo is greater than 5ms at least one time point, ddQTc versus time-curve follows the one typical of moxifloxacin.[3]

SOME OF THE FDA RECOMMENDATIONS BASED ON E14—GUIDANCE FOR INDUSTRY[14]

ECG reading is to be done by a skilled technician with a cardiologist over-reading the ECGs. Bazett's correction is considered to be inferior and needs to be submitted only when there is a comparison required with historic reports where Bazett's correction was used.

Clarifications regarding enrolment of both genders for TQT study: post pubertal males have lower QTc duration compared to pre pubertal males and women. Women being smaller than men will be expected to have a greater exposure to a fixed amount of drug when compared to males and hence are expected to have a greater QT prolongation. Hence, it is encouraged to recruit both men and women for TQT studies and analyse the concentration-response by gender. However, this is not mandatory. For a parallel arm study design, it is recommended to follow a time-matched baseline measurement, so that the effect of diurnal variation is alike in every arm. In case of combination drug products, if the individual drugs are not known to prolong QT interval, there is no requirement for a TQT study for the combination product. For monoclonal antibodies, there is again no requirement for TQT study as they have little impact on ion channels, TQT should be done only if preclinical tests are positive.

CHALLENGES WITH QT/QTC STUDIES

QT interval is generally prolonged in females compared to males hence there remains a possibility of QT variation with respect to menstrual cycles. Secondly, there can be situations where drug cannot be tested in healthy volunteers such as while evaluating cytotoxic cancer drugs. Another challenge is the QT/RR hysteresis which means the speed at which the QT interval changes with change in the heart rate.[15]

EXPOSURE-RESPONSE (ER) MODELLING OF ECGS

ER analysis establishes the association between the drug or its metabolites with the clinical data by statistical means. In the first ER modelling, concentrations of procainamide were plotted against QTc changes and hysteresis was observed. This model easily accounts for time dependent effects, covariates such as age, gender, ethnicity and hence is flexible.[16]

ER analysis is useful in scenarios such as when there is QTc prolongation when drug is used at lower dose than in a TQT study, QTc prolongation in an underpowered study and during evaluation of the assay sensitivity of a positive control.[16]

To demonstrate the advantage of ER modelling, let us take the example of the analysis of TQT studies done on a drug - losmapimod (product of GlaxoSmithKline), the drug was shown to cause a larger QT prolongation than the supratherapeutic dose, besides not showing any efficacy. When ER analysis was done using concentration of the drug and QTc, it showed that the false positive results was due to multiple dosing of the drug which had resulted in shift of the baseline.[16]

Table 1: Drugs causing QT prolongation and withdrawn from the market.[19-21]

Drug	Therapeutic class	Year of withdrawal
Prenylamine	Antianginal	1988
Terodiline	Antianginal	1991
Terfenadine	Antihistamine	1998
Sertindole	Antipsychotic	1998
Grepafloxacin	Antibiotic	1999
Astemizole	Antihistamine	1999
Cisapride	Prokinetic	2000
Sparfloxacin	Antibiotic	2001
Droperidol	Tranquiliser/analgesic	2001
Levacetylmethadol	Methadone substitute	2003
Thioridazine	Antipsychotic	2005
Propoxyphene	Opioid analgesic	2010

DRUGS CAUSING QT SHORTENING

Although arrhythmias due to QT shortening are extremely rare, physicians have reported cases of Short QT syndrome (SQTS) and this is gaining interest. So far, five variants of SQTS have been identified (SQTS1-SQTS5). Gain of function mutations of KCNH2, KCNJ2, KCNQ1 are some of the genetic causes of SQTS. Risk of arrhythmia increases when the QT interval is less than 300 ms.[17,18]

Primidone was found to shorten QT interval in patients with LQTS. Rufinamide, an anticonvulsant was also found to shorten QT interval during cardiac safety studies and is probably the first QT shortening drug to be approved after the release of ICH E14. As it holds an orphan drug status for the management of Lennox-Gastaut syndrome, the drug's adverse effect is not of a serious concern. Drugs activating ATP-potassium channels such as nicorandil, pinacidil and levcromakalim have been found to reduce QT interval in preclinical studies.[17,18]

CONCLUSION

QT prolongation has been a concern after reports of fatal arrhythmias with non-cardiac drugs like cisapride, halofantrine, pimozide, astemizole and terfenadine. Regulatory authorities consider the risk: benefit ratio of a drug before its approval, a drug with a very mild risk of arrhythmia but with good efficacy in cancer would still be approved however the same for a minor medical condition would be rejected. ICH guidelines have ensured that the drugs undergo vigorous cardiac safety evaluation before they enter the market. As a result, there has been no QT prolonging drug that has been released after 2005. Attempts are being made to improvise the TQT study, in terms of cost reduction and by developing better models with good predictability so that drugs affecting QT interval may be filtered out in the earlier stages of trials. Last but importantly, it is the awareness amongst physicians, pharmacists and the patients that will help avoiding fatal cardiac adverse reactions from occurring.

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