LEADING ARTICLE

Drug Safety 2005; 28 (2): 115-125
0114-5916/05/0002-0115/$34.95/0



# Drugs, QT Interval Prolongation and ICH E14

## The Need to Get it Right

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## Abstract

Regulatory concerns on the ability of an ever-increasing number of non-cardiovascular drugs to prolong the corrected QT (QTc) interval and induce potentially fatal ventricular tachyarrhythmias have culminated in initiatives to harmonise internationally the regulatory guidance on strategies by which to evaluate new drugs for this liability. The International Conference on Harmonisation (ICH) has released consensus texts for clinical (ICH topic E14) and non-clinical (ICH topic S7B) strategies as regulatory drafts for wider consultation.

Draft ICH E14 calls for a clinical 'thorough QT/QTc study' (typically in healthy volunteers) for new drugs with systemic bioavailability, regardless of the non-clinical data. This indifference to non-clinical data has sparked off a major debate, even among the regulators. The 'thorough QT/QTc study' is intended to determine whether a drug has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc prolongation, and proposes the use of a positive control to validate the study. The guideline recommends exploration of the effect of concentrations that are higher than those achieved following the anticipated therapeutic doses and, consequently, a negative 'thorough QT/QTc study', even in the presence of non-clinical data of concern, will almost always allow standard collection of on-therapy ECGs. The proposed threshold of a 5ms increase in mean placebo-corrected QTc interval for designating a study as positive for an effect, with all its implications for subsequent development of the drug and its regulatory assessment and labelling, has also generated a controversy.

This paper provides an overview commentary on some contentious or ambiguous aspects of draft ICH E14 with a view to stimulating a debate and inviting scientifically supported comments from stakeholders in order to ensure that the application of the ICH E14 strategy, when finalised and adopted, does not result in either restriction in the use (or even rejection) of a potentially beneficial drug or approval of an otherwise hazardous drug without the restrictions required to promote its safe use.

Prolongation of the corrected QT (QTc) interval on the surface ECG is inevitable with class III antiarrhythmic drugs, such as sotalol, amiodarone, dofetilide and ibutilide. This class of drugs is intended, by design, to produce the desired therapeutic benefit by delaying ventricular repolarisation, which is reflected as prolongation of the QTc interval. In fact, this is the criterion of Vaughan-Williams' clas-

sification of drugs as class III antiarrhythmic agents. These drugs act by blocking the rapid component of the delayed rectifier potassium current ($I_{Kr}$), which is the major repolarising current in the ventricles. However, drug-induced prolongation of the QTc interval, when excessive in the right setting, can be proarrhythmic and degenerate into torsade de pointes, which is a unique form of polymorphic ventricular tachycardia. Furthermore, many non-antiarrhythmic drugs also carry what has been termed as the 'QT liability' and their number continues to increase almost daily.[1,2] Given the potentially fatal consequences of this mechanism-based, concentration-dependent adverse drug reaction, it is not surprising that, more than any other drug-induced adverse reaction, it has been responsible in recent times for the withdrawal of a wide range of non-antiarrhythmic drugs from the market (table I).

Regulatory authorities have reacted to this apparently new 'pharmaco-epidemic' by denying or delaying the approval of a number of new drugs and placing severe restrictions on the use of many old and some new drugs because of concerns arising from their potential to prolong the QTc interval. Regulatory and clinical expectations of a better preapproval characterisation of new chemical entities (NCEs) for this potential risk have had a very profound influence on their development, assessment and approval. For sponsors of new drugs, there is an urgent need for an internationally harmonised guidance on what the regulatory authorities, especially in the US, EU and Japan, expect in terms of preapproval characterisation of a new drug for this potential risk.

**Table I.** Non-antiarrhythmic drugs withdrawn from the market because of their torsadogenic potential

| Drug | Therapeutic class | Year withdrawn |
|---|---|---|
| Prenylamine | Antianginal | 1988 |
| Terodiline | Originally antianginal. Re-developed for use in urinary incontinence | 1991 |
| Terfenadine | Histamine $H_1$-receptor antagonist | 1998 |
| Sertindole[a] | Atypical antipsychotic | 1998 |
| Astemizole | Histamine $H_1$-receptor antagonist | 1999 |
| Grepafloxacin | Fluoroquinolone antibacterial | 1999 |
| Cisapride | Gastric prokinetic | 2000 |
| Droperidol | Antiemetic and antipsychotic | 2001 |
| Levacetylmethadol | Opioid analgesic | 2001 |

a Now recommended for re-introduction to the market.

## 1. Regulatory Guidance on Investigating Drug-Induced Prolongation of the Corrected QT (QTc) Interval

The EU Committee for Proprietary Medicinal Products (CPMP), now known as the Committee for Medicinal Products for Human Use (CHMP), was the first scientific advisory body of a regulatory authority (European Medicines Agency) to issue, in December 1997, a formal guidance note on a strategy by which all NCEs should be investigated for their effect on the QTc interval.[3] This guidance includes recommendations on a set of non-clinical as well as clinical investigations. All strategies devised subsequently are an elaboration of, or minor variations on, the broad pattern set by the CPMP.

In November 2002, the US FDA and Health Canada issued a joint document that focused exclusively on clinical strategies for evaluating the effects of NCEs on QT/QTc interval prolongation (a preliminary concept paper for discussion).[4] Following a number of amendments, it was entered into the International Conference on Harmonisation (ICH) process in February 2003 for adoption as a topic that merited global harmonisation (ICH topic E14). ICH is composed of representatives from regulatory authorities and industry associations in the US, EU and Japan. Representatives from the WHO, European Free Trade Area and Canada also attend as observers. For a detailed description of the ICH process, the reader is referred to the ICH website at http://www.ich.org.

At present, there are two guidance notes under discussion at ICH: one dealing with non-clinical strategy (ICH topic S7B) and the other dealing with clinical strategy (ICH topic E14) by which to evaluate an NCE for these effects during drug development. Although the focus of S7B is detecting delayed ventricular repolarisation and QT interval

prolongation, E14 focuses on detecting QT/QTc interval prolongation. In June 2004, the Expert Working Groups of S7B and E14 and the ICH Steering Committee agreed to, and accepted draft consensus texts of, the two corresponding ICH guidance notes (step 2 of the ICH process). These have been released as regulatory drafts for consultation (step 3) and can be accessed for comments at the following web addresses:

- ICH S7B guidance (Nonclinical testing for effect on ventricular repolarisation) http://www.emea.eu.int/htms/human/ich/safety/ichdraft.htm
- ICH E14 guidance (Clinical testing for effect on QT interval) http://www.emea.eu.int/htms/human/ich/efficacy/ichdraft.htm

Both ICH S7B and E14 recognise in their preamble that the subject of drug-induced changes in cardiac repolarisation is one of active research and as further data (non-clinical and clinical) are accumulated in the future, their contents may be re-evaluated and revised. The Expert Working Group of ICH E14 took a conscious decision to promote wide and detailed discussions on contentious or ambiguous aspects of the guidance in whatever way was feasible, especially through open scientific meetings. As a member of the ICH E14 Expert Working Group, the author has already made presentations at a number of such meetings in Europe. Given the implication of prolongation of the QT interval by a drug for its development and ultimate regulatory appraisal and labelling, it is important that any contentious or ambiguous aspects of ICH step 3 proposals are discussed and examined carefully so that the draft consensus text can be amended if necessary before the guidance is finally adopted and implemented. These issues are identified in section 3, with a view to promoting an informed scientific debate, together with a commentary by the author.

QT interval prolongation has been regarded as a liability since it is the measure that has been used most frequently as a marker of delayed ventricular repolarisation. Regulatory actions against a wide range of drugs,[1] the discovery of the human ether-a-go-go gene (hERG) α-subunit of the $I_{Kr}$ channel,[5] the role of the mutant hERG α-subunit in the aetiology of congenital long QT syndrome[6] and the adoption by the CPMP in December 1997 of their seminal document on drug-induced QT interval prolongation[3] have jointly stimulated research. Although there are still major gaps in our knowledge, there has been a considerable progress in our understanding of cardiac electrophysiology, delayed ventricular repolarisation and potential proarrhythmic mechanisms. Therefore, it is worth questioning the performance of QTc interval prolongation as a surrogate of torsade de pointes and whether it is prudent for any one single parameter of delayed ventricular repolarisation, QT interval in the context of CPMP and ICH E14 guidance notes, to be allowed to so dominate the risk assessment process.

## 2. Reliability of QT Interval Prolongation as a Surrogate of Torsade de Pointes

One review in 1993 concluded, "At present, our knowledge base about the relation of the QT interval and torsades de pointes is grossly incomplete".[7] Unfortunately, despite extensive research for more than a decade since, this still remains the case today. Prolongation of the QTc interval is only one parameter that reflects a delay in ventricular repolarisation and when drug-induced it is almost always because of inhibition of the $I_{Kr}$.

To a large measure, the (near) theological reliance on QT interval prolongation as a surrogate of torsade de pointes originates from the very definition of this unique polymorphic ventricular tachyarrhythmia.[8] Ventricular tachyarrhythmias, even when meeting the morphological criteria of torsade de pointes, are not labelled by many clinicians as torsade de pointes unless preceded by QTc interval prolongation.[9-11] When interpreting data from a study designed to evaluate the effect of a drug on the QTc interval, it is important to appreciate that QTc interval prolongation *per se* does not constitute a direct risk. Although QTc interval prolongation is one of the major precursors of drug-induced torsade de pointes, this arrhythmia does not develop invariably in all individuals with equivalent prolongation of the QTc interval. Neither do all drugs that prolong the QT interval to an equivalent duration carry the

same risk of inducing torsade de pointes.[12,13] The $I_{Kr}$ channel is composed of an α-subunit and β-subunit named miRP1. The α-subunit is encoded by hERG or KCNH2 and when expressed in heterologous systems, this subunit is considered to recapitulate the function of the $I_{Kr}$ channel. However, hERG studies show that not all drugs causing torsade de pointes are potent $I_{Kr}$ blockers and $I_{Kr}$ block is not necessarily associated with torsade de pointes.[13] The risk of torsadogenesis following prolongation of the QTc interval is significantly modulated by other ancillary pharmacological properties of a drug.[14-18] These include its effects on α- and β-adrenergic receptors and calcium channels. Modulation of α-adrenoceptor activity seems to have greater effect than that of β-adrenoceptor activity.[19]

QTc interval duration is only a partial indicator of drug-induced delay in ventricular repolarisation. Clearly, the question arises as to whether other indices of delayed ventricular repolarisation, either singly or in combination with increases in the QTc interval, may be more helpful in assessing the potential clinical risk. Transmural dispersion in repolarisation is now thought to be a better marker of the risk of torsade de pointes.[18,20-25] QTc interval prolongation in the presence of normal or reduced transmural dispersion in repolarisation is associated with antiarrhythmic properties.[21-23] Indeed, proarrhythmic QTc interval prolongation might even be regarded as an epiphenomenon of an increase in transmural dispersion in repolarisation. In further support of the role of transmural dispersion of repolarisation in torsadogenesis, Di Diego et al.[26] have demonstrated, in the same isolated arterially perfused canine left ventricular preparation, the development of torsade de pointes by cisapride at a concentration that maximally increases transmural dispersion of repolarisation and the failure of torsade de pointes to develop after an increase in the concentration of cisapride that reduces transmural dispersion of repolarisation despite increasing QT interval. In one study, 50 patients receiving long-term oral amiodarone therapy included 20 patients who developed arrhythmic events during a mean follow-up period of 15 months. Excessive QT prolongation associated with increased transmural dispersion of repolarisation was predictive of recurrence of ventricular tachycardia/ventricular fibrillation in these patients.[27] For a thorough non-clinical evaluation of the effect of a drug on ventricular repolarisation, consideration should be given to including not only the *in vitro* ion channel and *in vivo* QT assays but also repolarisation assays, modern proarrhythmia models and evaluation of transmural dispersion in repolarisation. Since QTc interval prolongation is an inadequate surrogate of the risk of torsade de pointes, a conclusion based solely on the potential of a drug to prolong the QTc interval may result in either restriction in the use (or even rejection) of a potentially beneficial drug or approval of an otherwise hazardous drug without the restrictions required to promote its safe use. Thus, although evaluating the effect of an NCE on the QTc interval is important, conclusions on the potential clinical risk of torsade de pointes associated with its use, based solely on the ability of the drug to prolong the QTc interval, might turn out to be highly flawed. The assessment of clinical risk following drug-induced delay in ventricular repolarisation by an NCE should be an integrated evaluation of its full pharmacological profile and all parameters indicative of changes in repolarisation and not just the QT interval.[28]

## 3. ICH E14 and the 'Thorough QT/QTc Study'

Draft ICH E14 calls for a clinical 'thorough QT/QTc study' (typically in healthy volunteers) for new drugs with systemic bioavailability, regardless of the non-clinical data. The study is intended to determine whether a drug has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc prolongation, and proposes the use of a positive control to validate the study. The threshold that is currently proposed is a 5ms increase in the mean placebo-corrected QTc interval for designating a study as positive for an effect, with all its implications for subsequent development of the drug and its regulatory assessment and labelling. It recommends exploration of the effect of concentrations that are higher than those achieved following

the anticipated therapeutic doses. The guidance also provides recommendations concerning presentation and analyses of data on the QT/QTc interval (in terms of analyses of central tendency as well as categorical responses). However, a number of issues require clarification or scientific support. There are also areas where the guideline could be improved for greater clarity. ICH E14 is the first ICH guideline that deals with a specific drug-induced adverse reaction. Therefore, it is important that it is logically structured and informed by current scientific evidence if it is to serve as a model for future guidance notes on the characterisation of drugs for other serious adverse effects.

First, the guidance should recognise that the risk is related to heart rate-corrected QTc interval and not to (measured) QT interval[28] and, therefore, the study is better referred to simply as a 'thorough QTc study'. This is especially the case given that elsewhere, the document recommends applying the most accurate correction formula available (e.g. methods using individually-derived relationships between RR and QT intervals).

Depending on how narrow the definitions of a 'new drug' and 'systemic bioavailability' are, the guidance should be clearer in its scope. Topical products applied to raw surfaces and respiratory products administered by inhalation may well have a systemic bioavailability, albeit very low. Apart from rare protein toxins such as sea anemone or scorpion toxin, which has an effect on cardiac ion channels in experimental settings, there is no evidence that blood or plasma products, hormones, infusions of amino acid or ion solutions or vaccines have an effect on cardiac repolarisation. Another important area for clarification is the applicability of these recommendations to orphan medicinal products such as biotechnology products and enzyme replacement therapy. The sponsors should be reassured that in these circumstances, the requirement for a 'thorough QT/QTc study' would be made on a case-by-case basis depending on the pharmacology of the product concerned.

The ICH E14 document acknowledges that "the ability of a drug to prolong the QT/QTc interval is linked to pharmacological effects that can be investigated in non-clinical models as well as clinically" but expresses doubts as to whether non-clinical testing can exclude a clinical risk of QTc interval prolongation. Studies performed over the 18 months (since the preliminary concept paper was formulated) strongly support the conclusion, which is shared by a vast majority of experts in this field, that an ICH S7B-compliant package of non-clinical studies, when interpreted with a careful attention to safety margins and problems related to hERG trafficking, appears capable of excluding a clinical risk[29-33] and, therefore, informing the clinical development programme. Currently available data would require any claims to the contrary to be substantiated by robust scientific evidence. There is at present no drug found to be negative in non-clinical studies that has proved to be torsadogenic in man. Neither is there a drug known to be torsadogenic in man but found to be negative in non-clinical studies. Clearly, when clinical studies investigating a drug are designated as positive and the corresponding non-clinical studies are designated as negative for an effect on ventricular repolarisation, there should be a careful scrutiny of the criteria used for these designations and one must inquire whether the human metabolites of the drug were adequately tested in non-clinical studies. No doubt, a rare drug with discordant non-clinical and clinical data may well emerge in future, but it seems rather imprudent to formulate a major policy with significant impact on drug development on the basis of a potential rarity.

It has been argued that non-clinical data may be necessary to the extent that when positive, they are helpful in guiding safety monitoring during early human tolerance studies. This argument sidesteps the core issue on the value of negative non-clinical studies and the extent to which they can exclude a clinical risk. An inconsistent aspect of the draft consensus text, even on the value of positive non-clinical studies in guiding subsequent drug development, is the statement that a negative 'thorough QT/QTc study', even in the presence of non-clinical data of concern, will almost always allow the collection of on-therapy ECGs in accordance with the current

practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development. Such an exemption from the safety monitoring of ECGs in patients places excessive reliance on the results of a 'thorough QT/QTc study' in healthy volunteers, especially when the non-clinical data are indicative of risk, and it may not always be possible to investigate the effects of high systemic exposure in such a study (see later in this section).

Although positive controls are a norm in studies aimed at comparing efficacy, their use for investigating safety will likely prove to be contentious ethically and/or legally in some ICH regions, especially Japan. However, on balance the use of positive controls seems worthwhile in establishing assay sensitivity as well as permitting a comparison of effect sizes. With regard to the positive control and the choice of an appropriate threshold value, there are frequent calls for 'E14-calibre' data on mean QTc effects of drugs known to be torsadogenic and non-torsadogenic in man. The author believes that we already have these data. An appreciation of inter-study consistency of the effect size(s) produced by a widely used positive control may also be helpful in resolving the debate on what is an appropriate threshold.

Moxifloxacin, a widely used positive control, is one of the few drugs for which there are available 'E14-calibre' QTc interval data from multiple clinical pharmacology studies of reasonable rigour. Single oral doses of moxifloxacin 400mg, tested during the last 24 months in well over 20 specially designed studies in healthy volunteers that used standardised approaches and methods, have consistently produced mean increases in the QTc interval ranging from 5ms to 10ms (Morganroth J, personal communication). Despite this, there have been no reports of torsade de pointes or other ECG markers of proarrhythmic risk among these healthy volunteers. Even in patients, moxifloxacin has not been reported to induce torsade de pointes in the absence of other risk factors. Therefore, regardless of whether this type of inter-study variability is typical of other drugs, the 5ms threshold proposed in ICH E14 appears to require reconsideration. This is especially the case since the threshold value selected will inevitably be used to designate the investigational drug for its QT liability. Additionally, the purpose of this positive control should be clarified; is it intended indirectly to guide only the ECG monitoring in phase III clinical studies or also to have an effect on the regulatory appraisal and labelling of the drug concerned? Furthermore, given the inter-study variability in effect size already observed with moxifloxacin, it might be prudent to provide an acceptable range of effect by the positive control. Otherwise, there is a risk that an occasional well executed study may fall short of meeting the criterion of assay sensitivity.

In addition, it seems highly inappropriate to categorise drugs clinically as simply having an effect or no effect on QTc interval, even if the 5ms threshold is well founded. Rather, there are three possible outcomes from the analysis of clinical QTc-related data. These are: no effect, a clinically insignificant effect or a clinically significant effect. Otherwise, a low threshold will result in a large number of new drugs attracting unwarranted restrictive labelling. This ultra-cautious labelling may, in turn, prove counter-productive if a 'warning fatigue' develops among prescribing physicians. Clearly, the threshold must be a realistic one – not so low that there is a high false positive rate with consequences for labelling and not so high that there is high false negative rate with consequences for public safety. With regard to drugs inducing torsade de pointes in man, it also seems rather inappropriate to categorise together a drug with a torsade de pointes incidence of 1 per 500 000 patients with another that has an incidence of 1 per 3000 patients. The objective of ICH E14 should be to identify drugs that may have a potential to induce torsade de pointes at an unacceptable frequency, for example ≥1 per 100 000 patients. Since benefit-risk analysis is critical in drug development and the regulatory approval process, the seriousness of the condition under treatment and alternatives already available are additional important considerations.

Whereas there is little doubt that drugs that prolong the mean QTc interval by >20ms have a substantially increased likelihood of being proarrhythmic, and might even have clinical arrhythmic events captured during drug development, the currently proposed threshold of 5ms seriously requires a scientific support. If it is intended to 'catch' all drugs with clinically relevant QT liability, this ultracautious threshold is rendered nebulous by the fact that torsade de pointes may occur, on very rare occasions, even without QT interval prolongation. Therefore, it would appear that a risk of torsade de pointes might exist even for drugs that pass the test set by the 'thorough QT/QTc study' with its current threshold of 5ms. Of course, the risk in clinical practice in this instance is far too small to be intolerable, but this observation does underscore the fact that it may not be possible to identify all the drugs with a very low torsadogenic potential even following a 'thorough QT/QTc study'.

The analysis of data (including those generated recently on sildenafil, vardenafil, alfuzosin, moxifloxacin, ziprasidone and a few other antipsychotic drugs) on mean changes in the QTc interval and associated clinical risk suggests that a threshold of 10ms may be more realistic for designating a study as positive for a clinically relevant effect. Although ziprasidone prolongs the mean QTc interval (uncorrected for placebo) by 16ms,[1] there are no reports of associated torsade de pointes following its extensive clinical use or overdoses. The study did not include a placebo arm but even if a nominal placebo effect of 6ms is subtracted, the effect of ziprasidone is still 10ms. When a positive control is selected from the same class as the investigational drug, it is helpful in establishing relative safety and benefit-risk ratio of the two drugs, which are two important considerations in the drug approval process.

Another area that appears to require clarification is the computation of changes in central tendency. Sponsors, as well as many regulators, seem to vary in their understanding of what is meant by the 'largest time-matched mean difference between the drug and placebo (baseline-subtracted) over the collection period', 'time-averaged QT/QTc intervals' and 'analysis of changes occurring at the $C_{max}$ for each individual'. Under the ICH recommendations, if and when adopted, the US, EU and Japan will all assess the data both on the basis of changes in central tendency (understood by the author to be mean placebo-corrected increases in peak QTc intervals) as well as outlier analysis of categorical responses. The central tendency analysis involves correction for placebo effect on QTc interval. Thus, a high placebo effect might 'protect' the new compound from being declared positive and *vice versa*. The relative merits of the two approaches mentioned to analyses of the effect of the drug on the QTc interval require urgent systematic investigation. Available clinical data support the notion that outlier analysis may be more predictive of the risk than mean changes in the QTc interval.

One simulation study assessed the type I error rate and rank order of power for six different QTc-derived metrics using linear mixed-effect models.[34] These included maximal change in QTc interval from baseline, maximal QTc interval, area under the QTc interval-time curve (QTc–AUC), time-averaged QTc interval, maximal QTc interval with baseline QTc interval as covariate and QTc–AUC with baseline QTc interval as covariate. It was concluded that when the $IC_{50}$ (the concentration required to produce 50% inhibition of the drug target) was lower than or equal to the maximal plasma concentration of the drug, the maximal change from baseline had a fairly good statistical power. The power of maximal QTc interval was not as good. However, better than either of these was maximal QTc interval with baseline QTc interval as covariate. Nevertheless, there appears to be different emphasis between the three ICH regions on these indices. Whereas the CPMP document is silent on the predictive utility of mean changes and recommends analysis only in terms of categorical responses, the emphasis in North America appears to be on changes in central tendency. However, it is acknowledged that there is a clear need for more comparative, simultaneously gathered data on these three variables ($\Delta$QTc $\geq$60ms, a new absolute QTc interval $\geq$500ms and/or a mean increase in placebo-corrected maximum or

peak QTc interval) in order to reach a more informed consensus on which of them is the best predictor of torsade de pointes in the population at large as opposed to predicting the risk in a given individual. Unless the drug has a potent effect on the QTc interval, this information may have to be gathered retrospectively since it is almost impossible (and impractical) to power the 'thorough QT/QTc study' on outlier analysis. The study that compared ziprasidone to five other antipsychotic drugs (including the torsadogenic drug thioridazine) is a good example of the difficulties involved.[1] An integrated analysis of all three variables, each appropriately weighted, might well prove to be necessary for an optimal assessment of the risk.

With regard to measuring ECG intervals in clinical trials, the guidance acknowledges that the method chosen will depend on the level of precision needed for a given trial. For the 'thorough QT/QTc study', this would usually involve measurement by a few skilled readers operating from a centralised ECG laboratory, although other methods (e.g. semi-automated ECG reading) can be acceptable when appropriately supported. The E14 document also states that in the absence of a concern in the early clinical trial(s), automated ECG readings no doubt have a role in the rapid assessment of ECGs for safety. However, it would be helpful to elaborate on when semi-automated readings can be acceptable for the 'thorough QT/QTc study'. The document should emphasise the lack of experience with even semi-automated readings and clarify the circumstances when these might be acceptable. For example, when focusing on outlier analysis is it acceptable for sponsors to substitute manual analysis with semi-automated ECG interval analysis, with skilled readers being asked to over-read only those measurements that are close to categorical responses?

It must also be a matter of concern that one can obtain very different summary statistics from the same dataset simply by using alternative heart rate corrections or baseline computations. One wonders whether the issue of heart rate correction formula needs to be better discussed in the guideline. Given the significance of the 'thorough QT/QTc study', it may be worth specifying one, or at the most two, correction formula such as the Fridericia correction and the one derived for each subject in the study. Nevertheless, the designation of a study as either positive or negative requires criteria in terms of not only an increase in mean QTc interval but also in terms of outlier analysis. This is important not only for the labelling of the drug but also for the implication the results of a 'thorough QT/QTc study' have on subsequent drug development.

As stated previously, one of the more contentious aspects of the step 3 ICH E14 guidance note is the proposed implication of a negative 'thorough QT/QTc study'. It proposes that a negative 'thorough QT/QTc study', even in the presence of non-clinical data of concern, will almost always allow the collection of on-therapy ECGs in accordance with the current practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development. Given that some patients have increased pharmacodynamic susceptibility to the QT-prolonging effects of a drug (those with 'low repolarisation reserve'), it is difficult to see how data from healthy volunteers, however reassuring they may be, can be confidently extrapolated to this population if the non-clinical data indicate a concern. A 'negative' dedicated clinical trial in healthy volunteers may well impart a false sense of clinical security when using the drug concerned in patient populations that are at a higher risk. It has been presumed, seemingly without much evidence, that exploration of the effects of supratherapeutic concentrations in the healthy volunteers will simulate the potential for risk in these susceptible patient populations. It seems more likely that for a vast majority of drug classes (e.g. cardiovascular, antineoplastic and psychoactive drugs), considerations of safety or tolerability because of adverse effects will preclude their testing at substantial multiples of the anticipated maximum therapeutic exposure. It is this inability to test supratherapeutic concentrations that may limit the predictive value of the 'thorough QT/QTc study'. If on-therapy ECGs, in accordance with the current practices in each therapeutic area, or even more rigorous ECG monitoring is adequate to

identify any potential problem in these circumstances, then it is necessary to challenge the very basis of a 'thorough QT/QTc study' for other drugs. Furthermore, producing high concentrations of a drug by maximal inhibition of its metabolism (as recommended in ICH E14) in healthy volunteers will provide no information on the QT-prolonging potential of its metabolites. Therefore, the circumstances when this may be a judicious approach to achieving high concentrations need to be spelt out.

The draft guidance note acknowledges in passing the role of ancillary pharmacology of a QT interval-prolonging drug in modulating the clinical risk of proarrhythmia. This aspect needs a greater emphasis when it comes to assessing the clinical risk, approval and labelling of a QT-prolonging drug. The effect of this ancillary pharmacology in modulating the clinical risk of torsade de pointes following prolongation of QTc interval further challenges the choice of a fixed arbitrary threshold value. Two drugs may have an equivalent effect on the central tendency of QTc interval but the one with powerful α-blocking activity is far less likely to be torsadogenic. Unless this property is given the importance it deserves in assessment of clinical risk, both drugs may attract similar restrictive labelling.

ICH E14 guidance, like its precursor the CPMP guidance note, cautiously approaches the subject of QT/QTc interval dispersion as a supplement to more standard analyses of QTc interval data. Although this parameter, defined as the maximum inter-leads QTc interval range (maximum minus the minimum QTc intervals), may have a utility in prediction of proarrhythmic risks in disease states, its utility in predicting drug-induced proarrhythmias has proved to be inconsistent and disappointing.[35] Since it adds little to the risk assessment process, it is worth considering whether there is any value in retaining this parameter in the ICH E14 document.

## 4. 'Thorough QT/QTc Study' in Perspective

ICH E14 aims to provide a sound and effective framework for preapproval clinical characterisation of a potentially fatal drug-induced toxicity. Doubtless, a single dedicated clinical trial has much to recommend it. Apart from the use of a placebo and a positive control to facilitate evaluation of a drug effect, a single dedicated clinical trial allows study designs, sample sizes and drug administration protocols to be optimised to suit the pharmacokinetics of the NCE. Techniques for recording ECGs and measuring the QT interval can be robust and standardised while correction of the measured QT interval for changes in heart rate can be made more reliable by employing additional correction formula, derived during placebo administration, for each individual or for the study population as a whole. A single dedicated clinical trial is also ideal for prospectively gathering all the data needed in a format that allows comparison across different drugs.

Morganroth[36] has recently discussed the features of a 'thorough QT/QTc study' and it is evident that execution of such a study is a major undertaking, especially when non-clinical data are negative. The benefits of a single dedicated clinical trial must be seen in the context of its impact on the safety evaluation of the NCE, availability of future new drugs[1,37] and the cost of developing new drugs.[38] Another important issue is whether such a study provides information that cannot be gathered otherwise. A typical phase I study for a single compound with non-clinical QT signal is estimated to cost $US1 million and if the drug proceeds to phase II, the cost is estimated to increase 6-fold.[37] These costs are of no relevance when there are real safety concerns from non-clinical studies. Of course, this cost is only a fraction of the average overall cost of $US802 million for developing an NCE and some might consider the investment worthwhile even when non-clinical studies are negative. However, when there are no non-clinical signals of what is a mechanism-based toxicity, one needs to ask whether the cost of a 'thorough QT/QTc study' is better invested in improved postmarketing surveillance of the safety of the drug shown in non-clinical studies to have no proarrhythmic potential.

One issue that is certain to emerge in the future is whether a short QTc interval is proarrhythmic. Early evidence suggests that just as prolongation of the

QT interval can be proarrhythmic, shortening of the QT interval can also be proarrhythmic.[39-41] Mutant hERG or KvLQT1 channels have been reported, which hasten the repolarising current, shorten the QTc interval and predispose the affected individuals to potentially fatal ventricular tachyarrhythmias.[42,43] Increased transmural dispersion in repolarisation, resulting from heterogeneous abbreviation of the action potential duration among different cell types spanning the ventricular wall, also creates the substrate for the genesis of ventricular tachycardia even under conditions associated with short QT intervals.[44] Whether or not, following a normal QT interval at baseline, a proarrhythmic shortening of the QT interval can be induced by a drug remains to be seen. Nevertheless, these clinical observations have important implications for the use of only the prolongation of QTc interval as a surrogate of torsade de pointes and other associated proarrhythmias.

## 5. Conclusions

No battery of non-clinical studies or clinical trials, however robust, will always identify all the drugs with extremely low risk of torsade de pointes. The complete elimination of the risk of torsade de pointes is an unrealistic expectation since the proarrhythmia can occur simply as a result of electrolyte imbalance or following an interaction between the drug and a variety of host factors, including the presence of genetic mutations. Torsade de pointes is said to be a 'moving target'.[2] In the final analysis, as with other potentially fatal adverse drug reactions such as myelotoxicity, gastrointestinal haemorrhage, hepatotoxicity or rhabdomyolysis, a level of risk may have to be tolerated. Depending on the benefits offered by the new drug, an incidence of a potentially fatal event at the rate of 1 per 3000 patients may be unacceptable whereas an incidence of 1 per 500 000 patients may be considered acceptable, with a whole range of benefit-risk in between. As stated earlier, benefit-risk assessment in drug development and the regulatory approval process includes the seriousness of the condition under treatment and alternatives already available.

Both ICH S7B and ICH E14 are expected to have a significant impact on drug development and public safety. Depending on the data that may become available for review following the consultation process, a 'thorough QT/QTc study' may be recognised as the only way forward in evaluating a clinical risk. However, if these guidance notes are to evolve into worthy documents, it is important that academia and industry, as well as other stakeholders, offer constructive comments not only on their limitations, supported by robust scientific evidence, but also on their strengths to make sure that we get them right.

## Acknowledgements

The views expressed in this article are those of the author and do not necessarily reflect the views or opinions of the International Conference on Harmonisation (ICH) Expert Working Groups or Steering Committee, Medicines and Healthcare products Regulatory Agency, other regulatory authorities or any of their advisory bodies. The author is a member of the ICH E14 Expert Working Group, which is aware of the preparation of this manuscript and that it is intended to promote debate. The author has not received any funding from any source for this purpose. There are no conflicts of interest directly relevant to the contents of this review.

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