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Drug-induced Proarrhythmia and Torsade de Pointes: A Primer for Students and Practitioners of Medicine and Pharmacy

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Abstract

Multiple marketing withdrawals due to proarrhythmic concerns occurred in the United States, Canada, and the United Kingdom in the late 1980s to early 2000s. This primer reviews the clinical implications of a drug's identified proarrhythmic liability, the issues associated with these safety-related withdrawals, and the actions taken by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and by regulatory agencies in terms of changing drug development practices and introducing new nonclinical and clinical tests to asses proarrhythmic liability. ICH Guidelines S7B and E14 were released in 2005. Since then, they have been adopted by many regional regulatory authorities and have guided nonclinical and clinical proarrhythmic cardiac safety assessments during drug development. While this regulatory paradigm has been successful in preventing drugs with unanticipated potential for inducing the rare but potentially fatal polymorphic ventricular arrhythmia torsade de pointes from entering the market, it has led to the termination of drug development programs for other potentially useful medicines because of isolated results from studies with limited predictive value. Research efforts are now exploring alternative approaches to better predict potential proarrhythmic liabilities. For example, in the domain of human electrocardiographic assessments, concentration-response modeling conducted during phase 1 clinical development has recently become an accepted alternate primary methodology to the ICH E14 "thorough QT/QTc" study for defining a drug's corrected QT interval prolongation liability under certain conditions. When a drug's therapeutic benefit is considered important at a public health level but there is also an identified proarrhythmic liability that may result from administration of the single drug in certain individuals and/or drug-drug interactions, marketing approval will be accompanied by appropriate directions in the drug's prescribing information. Health-care professionals in the fields of medicine and pharmacy need to consider the prescribing information in conjunction with individual patients' clinical characteristics and concomitant medications when prescribing and dispensing such drugs.

Keywords

Proarrhythmic cardiac safety, thorough QT/QTc study, comprehensive in vitro proarrhythmia assay, concentration-response modeling, therapeutic use of QTc-prolonging drugs

As Link and colleagues[1] observed in 2010, "One of the most feared complications in medicine is sudden death caused by drug-induced proarrhythmia. Accordingly, concerted efforts have been made to define a drug's proarrhythmic potential before regulatory approval." Their quote succinctly captures two aspects of proarrhythmic cardiac safety, the topic of this primer. The first is the need to determine to the greatest extent

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possible in premarketing nonclinical and clinical investigations whether a new drug has a proarrhythmic propensity. Reports of these investigations, which are governed by a regulatory landscape, must be provided when submitting a marketing application. If a drug is considered to have an overall favorable benefit-risk balance at the public health level but also has an identified proarrhythmic liability, appropriate risk management strategies (including directions provided in the prescribing information) will need to be considered. The second aspect is the actual implementation of risk management strategies and, hence, the optimally safe therapeutic use of drugs known to have a certain degree of proarrhythmic liability.

Multiple marketing withdrawals due to proarrhythmic concerns occurred in the United States, Canada, and the United Kingdom in the late 1980s to early 2000s. Scientific, clinical, and regulatory interest concerning these marketing withdrawals led to the release in 2005 of 2 guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH S7B, which focuses on nonclinical assessments,[2] and ICH E14, which addresses preapproval clinical assessments.[3] Subsequent updates on ICH E14 in the form of 4 "Question & Answers" documents have been released, with the most recent, ICH E14 Q&As (R3), released in December 2015.[4] Since the adoption of ICH S7B and ICH E14 by participating regulatory authorities, they have guided nonclinical and clinical proarrhythmic cardiac safety assessments. Both sets of investigations are discussed in the first part of this primer, while the second part focuses on clinical considerations influencing the appropriate therapeutic use of drugs with a proarrhythmic liability.

Drug Withdrawals due to Proarrhythmia and Torsade de Pointes

Torsade de Pointes (TdP)[5] is a rare polymorphic ventricular arrhythmia that typically occurs in self-limiting bursts that can lead to symptoms of dizziness, palpitations, syncope, and seizures, and can occasionally progress to ventricular fibrillation and sudden cardiac death. The electrocardiographic waveform of TdP is characterized by rapid, irregular QRS complexes that appear to twist around the isoelectric baseline. Torsade de pointes can result from inherited factors and/or be drug-induced.

Table 1[6] provides examples of drug withdrawals in the United Kingdom and United States in the late 1980s to the early 2000s due to proarrhythmic concerns. Consider terfenadine, an antihistamine indicated for allergic symptoms.[7] This drug received marketing approval from the US Food and Drug Administration (FDA) in 1985. Following initial identifications of TdP in patients who had overdosed, the first identification of TdP with therapeutic doses (resulting in elevated plasma exposures due to drug-drug interactions with inhibitors of CYP-metabolizing enzymes) occurred in 1990. In 1992 the drug received a black box label warning, at which point 83 cases of TdP and 15 deaths had been reported. In January 1997, the FDA proposed removing the drug from the market.[8] The drug was removed from the US market in February 1998, by which time safer alternatives (eg, fexofenadine) were available.

Table 1. Examples of Drug Marketing Withdrawals in the United Kingdom and United States due to Proarrhythmic Concerns

Drug	Indication	Year Withdrawn
Prenylamine	Antianginal	1989 (UK)
Terodiline	Urinary incontinence	1991 (UK, US)
Sparfloxacin	Antibiotic	1996 (US)
Sertindole	Antipsychotic	1998 (UK)
Terfenadine	Antihistamine	1998 (US)
Astemizole	Antihistamine	1999 (US)
Grepafloxicin	Antibiotic	1999 (UK, US)
Cisapride	Gastroesophageal reflux	2000 (UK, US)
Levacetylmethadol	Opiate addiction	2003 (UK)

Adapted from Talbot and Waller.[6]

As noted previously, concerns regarding these marketing withdrawals led to the release in 2005 of the ICH S7B and ICH E14 guidelines. Most drugs associated with TdP have been associated with repolarization delays, represented in electrocardiogram (ECG) tracings as prominent QT prolongation. The QT interval is the time, expressed in milliseconds (msec), between the onset of the QRS complex and the offset of the T wave: it is shown schematically in Figure 1. Drug-induced proarrhythmia is a highly prominent cardiac safety issue because the consequences of drug-induced TdP can be catastrophic and, while certainly not a perfect surrogate, the QT interval is relatively easily measured and has functioned for more than a decade as a primary surrogate. The key nonclinical biomarkers of interest in ICH S7B are reduction of I_{Kr}, the rapid component of the cardiac delayed rectifier potassium ionic current responsible for the transition from plateau to terminal (phase 3) repolarization, and prolongation of the QT interval as seen on the ECG in non-rodent laboratory animals. The ICH E14 addresses evaluation of drug effects on the QT interval in humans in clinical trials.

Cardiac Ion Channels and Ionic Currents

Ion channels are structured transmembrane molecular complexes comprising multiple protein subunits that are embedded in cell plasma membranes.[9] Multiple α-helix subunits organize to form a transmembrane pore,

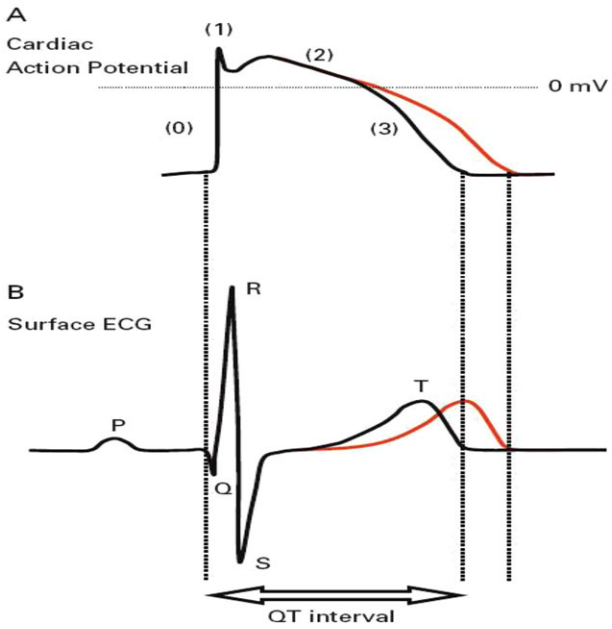

Figure 1. Action potentials, ECG recordings, and QT interval prolongation A. A typical ventricular action potential, representing changes in the transmembrane potential over time that occurs with each heartbeat. The phases of the action potential (phase 0 for initial depolarization, phase 1 as early repolarization, phase 2 representing the action potential plateau, and phase 3 representing terminal repolarization) are also labeled. Drugs that delay ventricular repolarization (illustrated by the red line) typically prolong the later plateau (phase 2) and terminal repolarization (phase 3) phases of the action potential. B. A typical surface ECG recording. Ventricular depolarization is noted by the QRS waveform, while ventricular repolarization is reflected in the T wave. Delayed ventricular repolarization is manifest as prolongation of the QT interval, defined as the time between the Q-wave onset and T-wave offset that results from the summation of delayed repolarization manifest on a cellular level. (Figure reproduced with permission from Satin et al.[34])

or channel, through which ions can flow across the cell membrane according to their electrochemical gradients. In the heart, these ionic currents affect signaling and allow for propagation and modulation of the electrical impulse. While not contributing to the structure of the central pore, ancillary subunits provide stabilizing and modulatory influences that allow the channel to adapt to changes in metabolic and hormonal status.

Ion channels, including I_{Kr}, have various defining characteristics. Of immediate relevance are these: most are highly selective for one ion; abnormal variants of genes encoding them can cause specific arrhythmias; and their activities can be affected by drugs.[10]

An ECG recording represents the sum of the cardiac electrical activity recorded on the body surface, which reflects the characteristic action potentials of atrial and ventricular cardiomyocytes. The action potential of a typical ventricular myocyte, shown in part A of Figure 1, maps onto the Q, R, and S waves (representing ventricular depolarization) and T waves (representing ventricular repolarization) of the ECG, shown in part B. The figure also highlights the phenomenon of QT interval prolongation (shown in red in part B) and indicates the linking mechanism of delayed repolarization (a more gradual slope of phase 3 of the action potential, shown in red in part A) with this prolongation. As noted earlier, the QT interval is the time between the onset of the QRS complex and the offset of the T wave. This time encapsulates both ventricular depolarization and repolarization, measured for any given cardiac cycle. Corrected values for the duration of the QT interval (QTc) are typically reported based on formulas used to correct for changes in heart rate, which affects QT duration.

Origins of Interest in Drug-induced Reduction in I_{Kr} and QT Interval Prolongation

In clinical medicine, QT interval prolongation is of concern because it is the defining phenotypic characteristic of a group of inherited long QT syndromes that have been associated with TdP and sudden death.[11–17] One long QT syndrome, LQT2, is seen when an individual's genetic inheritance includes an abnormal variant of the human ether-a-go-go–related gene (*hERG*, or *KCNH2*) that encodes the α-helix subunit of the cardiac potassium ion channel through which I_{Kr} flows.[18] Abnormal *hERG* variants lead to a cascade of consequences, including loss of function of the expressed hERG channel (ie, decreased I_{Kr} flow), a less gradual slope in phase 3 of the action potential (ie, delayed repolarization), and manifest QT prolongation on the ECG.

Recall now that one of the defining characteristics of ion channels is that their activities can be affected by drugs. For reasons related to the hERG channel structure (its relatively large size and the nature of the amino acid residues lining the internal walls of the pore[19,20]), some drug molecules can readily become trapped inside the central pore of hERG channels, resulting in a cascade of biological consequences (reduced I_{Kr}, reduced net repolarizing influence, QT prolongation, and sometimes proarrhythmia) that are in many ways similar to those resulting from genetically altered channels. Thus, while the mechanisms underlying reduced I_{Kr} and consequent QT prolongation in LQT2 vs drug-induced hERG channel blockade differ, the generally similar phenotypic characteristics make drug-induced I_{Kr} reduction (ICH S7B) and QT prolongation (ICH E14) of scientific, clinical, and regulatory concern. It is also appropriate to note here that a given drug with a proarrhythmic liability may more readily lead to proarrhythmia when administered to an individual with LQTS.

Additional references are provided.[21–23]

Table 2. Summary of Events in the Formalization of Proarrhythmic Cardiac Safety Assessments

Date	Event
1997	EMEA Committee of Proprietary Medicinal Products released a "Points to Consider" document on the assessment of the potential for QT interval prolongation by noncardiovascular medicinal products.
1999	FDA set up a working group and generated internal documents on QT assessment
2001	Health Canada issued a draft guidance document entitled "Assessment of the QT Prolongation Potential of Non-Antiarrhythmic Drugs." The ICH S7B guideline process was also initiated
2003	A joint Health Canada/FDA Concept Paper was issued and the ICH E14 guideline process was initiated
2005	ICH issued guidelines S7B and E14, which were adopted in Europe and the United States in 2005, in Canada in 2006, and in Japan in 2010.
2006	FDA established its QT IRT, which reviews protocols and study reports for thorough QT/QTc studies and advises review divisions accordingly
2006	Health Canada released regional guidance documents to support the interpretation and implementation of ICH E14
2008/2012/ 2014/2015	The ICH E14 Working Group released a "Questions & Answers" document in 2008, which was expanded with additional questions and answers in revised documents issued in April 2012, March 2014, and December 2015. The last of these is referred to in this paper as ICH E14 Q&As (R3)

Modified from Turner et al.[24]
EMEA, European Medicines Evaluation Agency (now known as EMA, European Medicines Agency); FDA, US Food and Drug Administration; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; IRT, interdisciplinary review team.

The ICH S7B-E14 Cardiac Safety Regulatory Landscape

ICH S7B and ICH E14 (and the 4 ICH E14 Q&A documents) have governed the regulatory landscape for preapproval cardiac safety investigations since their adoption by regulatory agencies following their release. Recall that Table 1 provided examples of drug withdrawals in the United Kingdom and United States in the late 1980s to the early 2000s due to proarrhythmic concerns. During that time there was increasing scientific, clinical, and regulatory concern over this issue, and Table 2[24] provides a summary of events in the creation of this formalized proarrhythmic cardiac safety regulatory landscape.

Nonclinical Assessments

The ICH S7B describes a nonclinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. Its central components are the in vitro hERG current assay and the evaluation of QT interval prolongation in non-rodent laboratory animal models. Human cardiac ion channel proteins (such as the hERG channel) can be expressed in heterologous expression systems to assess a drug's effect on specific individual ionic currents in isolation from others using a voltage clamp assay. Additional electrophysiology studies (representing more complex, integrated systems) can also be conducted using native myocytes from animals, induced pluripotent stem cell–derived human cardiomyocytes, and isolated cardiac tissue to study a drug's effect on repolarization (eg, evaluation of action potentials in isolated, perfused rabbit hearts).

In vivo testing employing telemetry, a powerful tool for real-time monitoring of electrocardiographic parameters,[25] provides additional (if still imperfect) understanding of electrophysiological effects of parent drugs and metabolites prior to screening human participants for drug-induced effects on ventricular repolarization in clinical trials.[26] Two years after the release of ICH S7B, Greaves[27] commented, "The beagle dog probably represents the best [nonhuman] model for drug-induced electrocardiographic effects in humans, particularly if electrocardiographic investigation is conducted carefully with consideration of peak plasma drug concentration."

The guinea pig model is also useful in this domain. Ruppert et al[28] discussed how improvements in animal housing, ECG electrode placement, and data evaluation have facilitated an established model for obtaining ECG recordings via telemetry in conscious, freely moving guinea pigs. The model is sensitive to drug-induced block of I_{Kr}, as well as other ionic currents. In contrast, rats are not an appropriate nonclinical model, as repolarization is minimally influenced by I_{Kr} current in that species.

Finally, while the hERG voltage clamp assay and the in vivo cardiovascular safety pharmacology studies are required prior to first-in-human clinical trials, they do not serve as exemption from an adequately powered investigation of ECG effects in human participants.

Clinical Assessments I: The Thorough QT/QTc Study

The ICH E14 recommends an evaluation of the effects on the QT/QTc interval of all new small-molecule drugs having systemic bioavailability. This guidance introduced the concept of the thorough QT/QTc (TQT) study, a randomized, placebo- and positive-controlled clinical trial assessing the extent, if any, of drug-induced QT prolongation. Because concurrent heart rate affects the QT interval independently of any drug-induced influence, the measured QT interval is "corrected" for heart rate via correction formulas, leading to the term "QTc."

Well-known correction formulae include Bazett square-root formula, $QTc = QT/RR^{1/2}$ (QTcB) and Fridericia cube-root formula, $QTc = QT/RR^{1/3}$ (QTcF).

Section 1.5 of ICH E14 Q&As (R3) notes that Bazett correction "has clearly been shown to be an inferior method of correcting for differences in heart rate among and within subjects,"[4] and it is not currently used for regulatory decision making. ICH E14 Q&As (R3) also notes that Fridericia correction is likely to be appropriate in most situations: where appropriate, guidance is provided for alternate correction methods, such as individualized correction factors.

Bloomfield[29] noted that "The explicit objective of the [TQT] study is to provide an accurate and precise estimate of a drug's effect on the QTc" and, based on this assessment, to guide the extent of ECG monitoring needed in subsequent therapeutic confirmatory (phase 3) clinical trials. The TQT study typically employs 4 treatment arms:

- A positive control arm, comprising a drug that is known to increase the mean QTc by approximately 10 to 14 msec. This is employed to establish assay sensitivity (ie, that the methodology employed can indeed detect an increase near the threshold of regulatory concern when one is truly present)
- A placebo arm, against which the drug is compared
- The proposed maximum recommended therapeutic dose of the drug
- A supratherapeutic dose of the drug that, unless the proposed dose is close to the maximum tolerated dose, is typically likely to be several multiples of the proposed therapeutic dose. The purpose of including a supratherapeutic dose is to evaluate drug-induced changes in ECG parameters under "worst case scenarios," ie, the highest exposures that could be attained due to effect modifiers, including pharmacokinetic variability, drug-drug interactions, alterations in metabolism or elimination, or underlying heart disease

Historically, TQT studies have typically been conducted relatively late in phase 2 development, when a drug's sponsor has sufficient evidence of therapeutic benefit to wish to proceed to phase 3 development. By that time, additional studies such as single-ascending and multiple-ascending dose studies, renal impairment and hepatic impairment studies, and drug-drug interaction studies may have been completed and will inform the choice of the supratherapeutic dose, which, as just described, comprises one treatment arm employed.

The choice of study design to be employed for a TQT study, crossover or parallel-group design, is an important one. In the crossover design, which is usually preferable when possible, each participant sequentially receives all 4 treatments in a randomized order. Each participant therefore serves as his or her own control, thus reducing interparticipant variability for estimates of the drug's effects on the QTc. A direct corollary of this reduction in variability is that, compared with a parallel-group design, a smaller sample size is required for an appropriately statistically powered study. A meaningful estimate of the sample size in these studies is 35 to 60 participants.

Consider now the parallel-group design. In this case, each participant receives only one treatment and, hence, to achieve the same statistical power as the crossover design provides, the parallel-group design usually necessitates 4 times as many participants. That said, the parallel-group design does offer an advantage for test drugs that have a long elimination half-life, requiring long washout periods.

Participants in TQT studies are typically healthy adults. However, it is acknowledged that for some drugs and some diseases, this may be impractical or even unethical: cytotoxic oncologic drugs under development, for example, cannot be administered to healthy individuals. In such cases, QTc prolongation liability must still be evaluated. Alternative approaches to QTc risk assessment may be employed, such as the participation of patients and adjustments to study design, with the goal of being "as thorough as possible."[30]

The regulatory threshold of concern for drug-induced QTc prolongation discussed in ICH E14 is described as a mean value of "around 5 msec" for the placebo-adjusted change from baseline at a supratherapeutic exposure that adequately reflects high-exposure scenarios. The primary (inferential) statistical analysis employed operationalizes this value by placing a 2-sided 90% confidence interval (CI) around the mean difference point estimate of QTc prolongation (mean change from baseline value for the test drug minus mean change from baseline value for the placebo) for each time point in the study for both the therapeutic and supratherapeutic doses. Typically 10 to 14 time points are chosen, with some falling shortly before, at, and shortly after the expected time to maximal serum concentration of the parent drug and major metabolites, and others ranging from the time of administration to approximately 24 hours after administration (possibly longer if the drug has delayed active metabolites). The analysis is therefore a by–time point analysis, and the statistical test employed is called the intersection-union test.[31] If no upper bound of a (CI) breaches 10 msec at supratherapeutic exposures of the drug, ECG assessments in the subsequent phase 3 trials will be typical for any drug in its class. If any upper bound of the CI breaches 10 msec, more extensive and intensive ECG/QTc evaluations may

occur during subsequent phase 3 trials. Effects on heart rate, QRS duration, and PR interval will also be considerations in determining the intensity of the ECG assessment strategy in phase 3 trials.

It should be noted here that the 10 msec upper limit of the 90%CI for the QTc interval is not the only consideration in regulatory decision making for the purposes of drug approval. Regulatory decision making is based on the totality of evidence assessment, involving multiple considerations that include, but are not limited to, the point estimate of the effect size, the slope of the concentration-response relationship, the time course of the pharmacodynamic effect, categorical analyses of outliers, the potential for drug-drug and drug-disease interactions that increase exposure, effects on serum electrolytes, and adverse events suggestive of proarrhythmia.

The ICH E14 guideline also recommends categorical analyses of outliers. The number and percentage of participants having 1 or more observations falling in each of the following categories for absolute QTc and change from QTc baseline are reported:

Absolute QTc interval:

- QTc >450 msec
- QTc >480 msec
- QTc >500 msec

Change from baseline QTc interval:

- Change from baseline QTc >30 msec
- Change from baseline QTc >60 msec

Analyses of the number and percentage of observations falling into each of these categories is sometimes provided as a follow-up analysis.

Taken in conjunction with the primary analysis, these analyses address 2 main concepts in this field. First, drugs that produce mean changes of less than 5 msec at high supratherapeutic exposures in healthy participants have rarely been associated with significant cardiac risk in the clinical use setting and, hence, this criterion can reasonably be utilized to exclude risk. Second, proarrhythmic events have usually been associated with individuals having QTc values greater than 480 msec or with changes from baseline in QTc of more than 60 msec.

Technical Challenges in Conducting a TQT Study

The TQT study is a dedicated clinical pharmacology study, typically performed in healthy adult subjects, that assesses the potential for drug-induced QT interval prolongation. However, complexity arises from the fact that the extent of QTc prolongation of interest, around 5 msec, is a very small percentage of the typical QT interval. Therefore, acquisition and robust evaluation of high-fidelity digital ECGs is of paramount importance.

These ECGs are transmitted to the laboratory (core ECG lab) where they will be analyzed. Extremely rigorous methodology is employed to maximize the accuracy and precision of ECG interval measurements. Each core ECG lab has a small number of highly trained readers: these are individuals (often, but not necessarily, cardiologists) who "read" the ECGs to determine QT interval values. All ECGs from the same participant in a TQT study should be read by the same reader (blinded to treatment arm) to maintain consistency in QT measurement. A specific assessment of reader variability is also required, with a subset of the ECGs being reread to quantify inter- and intrareader variability. Each core lab should have a well-defined approach to quantifying reader variability.[32]

Reviews published in 2005 by Strnadova[33] and 2011 by Satin and colleagues[34] capture respective "snapshots in time" in this field. References to examples of individual TQT studies and related considerations are provided.[35–42]

An Example of an Alternative Approaches to QTc Risk Assessment When Necessary

As noted in the previous section, while cytotoxic oncologic drugs under development cannot be administered to healthy individuals, QTc prolongation liability must still be evaluated. Consider the example of alectinib, a kinase inhibitor indicated for the treatment of patients with anaplastic, lymphoma kinase–positive, metastatic non-small cell lung cancer as detected by an FDA-approved test. Two alectinib single-arm trials were conducted, with 221 patients participating in total.[43] As is the case for TQT studies, intensive ECG collection was employed, with the ECGs being read centrally: matched pharmacokinetic data were also collected. Alectinib did not cause a clinically relevant change in QTcF. The drug's prescribing information (Section 12.2, Pharmacodynamics, Clinical Electrophysiology) reads as follows:[44] "The ability of alectinib to prolong the QT interval was assessed in 221 patients administered ALECENSA [Genentech Inc; South San Francisco, CA] 600 mg twice daily in clinical studies. ALECENSA did not prolong the QTc (QT corrected for heart rate) interval to any clinically relevant extent. One patient had a maximum post-baseline QTcF value of greater than 500 msec, and one patient had a maximum QTcF change from baseline of greater than 60 msec."

Clinical Assessments II: QT Concentration-response Modeling

The TQT study typically analyzes the change in QTc duration as a function of time and as a function of concentration. Concentration-response modeling facilitates analysis of data across multiple dose cohorts in a single model.[29] Using all data collected, this approach permits estimation of the relationship between drug exposure and its effect (if any) on a parameter of interest over a wide range of concentrations.[45]

Following an orchestrated assessment of its viability, concentration-response modeling has recently become an accepted alternate primary methodology to the ICH E14 TQT study for defining a drug's QTc prolongation liability under certain conditions.[4] A 2014 publication from the Cardiac Safety Research Consortium (CSRC) discussed whether the TQT study could be replaced by rigorous early QTc assessment in routine early-phase clinical pharmacology studies and concentration-response modeling.[46] A collaboration between the CSRC and the International Consortium for Innovation and Quality in Pharmaceutical Development facilitated the conduct of a study designed to address this question.[47] Six marketed drugs with well-characterized QTc effects, five of which have been shown to be "positive" (ie, prolong the QT interval to a degree of concern to regulatory agencies), were evaluated in healthy study participants by concentration-response modeling. Drugs and doses were identified in collaboration with the FDA "based on a shared understanding that if the study successfully detects the QT effect of the positive drugs, a similar approach (i.e., QT assessment in early-phase clinical studies) could potentially serve as an alternative to the [TQT] study." The 5 QTc-prolonging drugs were ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide. Levocetirizine was the non–QTc-prolonging (control) drug. The supratherapeutic dose for this drug was 6 times the therapeutic oral dose of 5 mg, ie, 30 mg orally.

The first set of results comprised the means and 2-sided 90%CIs for the predicted placebo-corrected QTc change from baseline in geometric maximum observed concentration. These were as follows: 9.5 msec (CI, 7.2-13.5) for ondansetron; 9.8 msec (6.7-17.3) for quinine; 6.8 msec (3.4-11.6) for dolasetron; 11.7 msec (10.6-17.9) for moxifloxacin; 11.3 msec (6.1-14.6) for dofetilide; and 2.0 msec (−2.6 to 6.0) for levocetirizine. These results showed that the upper bound of the 90%CI for all 5 QTc-prolonging drugs exceeded 10 msec. In contrast, the upper bound for levocetirizine was less than 10 msec, even when a single dose 6 times the therapeutic dose was administered.[47]

The second set of results focused on the slope of the concentration-response model for each drug. Such models plot predicted QTc prolongation on the y-axis and drug concentration on the x-axis. If the slope of the resulting concentration-response relationship is flat, there is no relationship between drug concentration and QTc prolongation. If the slope is positive, QTc prolongation increases as concentration increases. In this study, the slope of the concentration-response model was positive for all 5 QT-prolonging drugs. In contrast, the slope of the concentration-response model for levocetirizine was shallow and not statistically significant.[47]

Given that all 6 drugs were correctly identified, scientists and regulators involved in the study[48] argued for the revision of ICH E14, which was implemented in December 2015 via the release of ICH E14 Q&A (R3).[4] The relevant question asked is "How can assessment of the concentration-response relationship guide the interpretation of QTc data?" The opening paragraph of the detailed answer provided starts as follows: "Concentration-response analysis, in which all available data across all doses are used to characterize the potential for a drug to influence QTc, can serve as an alternative to the by-timepoint analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug."[4]

Several new and important considerations were then outlined, 2 of which are noted here. If single-ascending and multiple-ascending dose studies are utilized in phase 1 clinical development to answer questions related to drug-induced QTc prolongation, ECG recording strategies require as much quality control as is needed for a dedicated ECG study. Second, if data from multiple studies are to be pooled, it is important to test for heterogeneity: if the individual datasets differ in important ways, it may not be appropriate to conduct a combined analysis.

An example of testing for heterogeneity was provided by Murphy et al[49] when investigating the proarrhythmic liability of lemborexant, a novel dual orexin receptor antagonist being developed to treat insomnia, using concentration-response modeling. Corrected QT intervals were evaluated using a linear mixed-effects concentration-response model for each study separately and for the pooled data set. Shallow and statistically nonsignificant slopes of the concentration-response relationship were obtained when each study was analyzed separately and when data were pooled.

A recent publication by Garnett and colleagues[50] provided additional discussion. Co-authors from the FDA, industry, and academia provided recommendations on how to plan and conduct a definitive QTc assessment of a drug using concentration-response (concentration-QTc) modeling. Topics discussed included modeling objectives and approach, prespecifying the linear mixed-effects model chosen, general principles for model development and evaluation, and expectations for modeling analysis plans and reports.

The acceptability of concentration–QTc response modeling from first-in-human studies for regulatory decision-making purposes can be determined only retrospectively, after the therapeutic dose has been determined, the metabolite profile characterized, and effects of intrinsic and extrinsic factors explored. Use of the exposure-response approach is expected to be challenging and/or erroneous in many situations, including, but not limited to, the following:

- When testing of a broad concentration range is not possible because of dose-limiting tolerability or saturating absorption
- When the concentration range is narrow because of an extended-release formulation or a long elimination half-life
- When 2 or more analytes are contributing to the cardiodynamic effect (eg, combination drug products or regimens or parent drug–metabolite interactions)
- When the drug causes QTc prolongation through delayed effects on cardiac ion channel synthesis, trafficking, or depletion of serum electrolytes
- When testing drugs with prominent effects on heart rate
- When testing drugs that are also endogenous compounds
- When testing immunogenic drugs with antidrug antibodies that affect pharmacodynamic activity or clearance

Additional references are provided.[51–58]

Potential Future Modifications to the Regulatory Landscape

The regulatory landscape to date has unquestionably been successful in one important regard: no drug with unanticipated liability for TdP has entered the market since its implementation. However, de Ponti[59] estimated that "as many as 60% of new molecular entities developed as potential therapeutic agents, when assayed for I_{Kr} blocking liability, test positive and are thus abandoned early in development." This is unfortunate because, in some cases, a sufficient margin exists between therapeutic plasma concentrations and the concentrations that cause I_{Kr} blockade and blockade of different channels may lead to lack of proarrhythmic risk, even to antiarrhythmic properties (eg, amiodarone, ranolazine). Verapamil, a potent I_{Kr} blocker, does not cause QTc prolongation (except possibly at very high intravenous exposures), likely because it blocks calcium current as well.

The Comprehensive In Vitro Proarrhythmia Assay

The central goal of the Comprehensive in Vitro Proarrhythmia Assay (CIPA) initiative focuses on the assessment of potential ventricular proarrhythmia risk via mechanistically robust input data rather than employment of just one ionic current (I_{Kr}) and one ECG interval (QT/QTc) to direct evaluation of proarrhythmic risk. An important characteristic of this initiative is therefore to broaden the array of ionic currents of interest, including sodium and calcium currents. Additionally, the paradigm moves away from dichotomous categorizations of prolongation vs no prolongation of QTc: a graduated nonbinary risk scale is envisioned in which novel compounds are given a proarrhythmic risk score predicated on a continuous scale that has been calibrated against a test set of clinical drugs spanning the range of proarrhythmic risk.

The CIPA Initiative,[60–63] which is driven by an international consortium comprising multiple collaborators, is administered by the Health and Environmental Sciences Institute. It brings together an integrated set of nonclinical investigations and a final clinical component to evaluate any electrophysiological effects unanticipated from the nonclinical components: see Figure 2.[62] As Gintant et al[62] observed, "These new strategies have the potential to improve sensitivity and specificity in the early detection of genuine cardiotoxicity risks, thereby reducing the likelihood of mistakenly discarding viable drug candidates and speeding the progression of worthy drugs into clinical trials."

The first component of CIPA investigates drug-induced effects on multiple isolated human depolarizing and repolarizing currents of interest via heterologous expression systems assessed electrically using voltage/patch clamp techniques. The second component involves the employment of in silico models of cellular human ventricular activity to integrate drug effects on multiple cardiac currents mathematically, providing reconstructions of cellular electrical activity. Third, drug-induced effects on the electrical activity of human induced pluripotent stem cell–derived cardiomyocytes are evaluated. This approach provides a cell-based integrated electrophysiological drug response.

Following these nonclinical assessments, drug-induced effects on ECGs from early, well-controlled, first-in-human studies will be evaluated. QTc concentration-response modeling will be a primary assessment methodology with specific reference to QTc prolongation, and a wider range of ECG components, discussed in the following section, may likely be of interest.

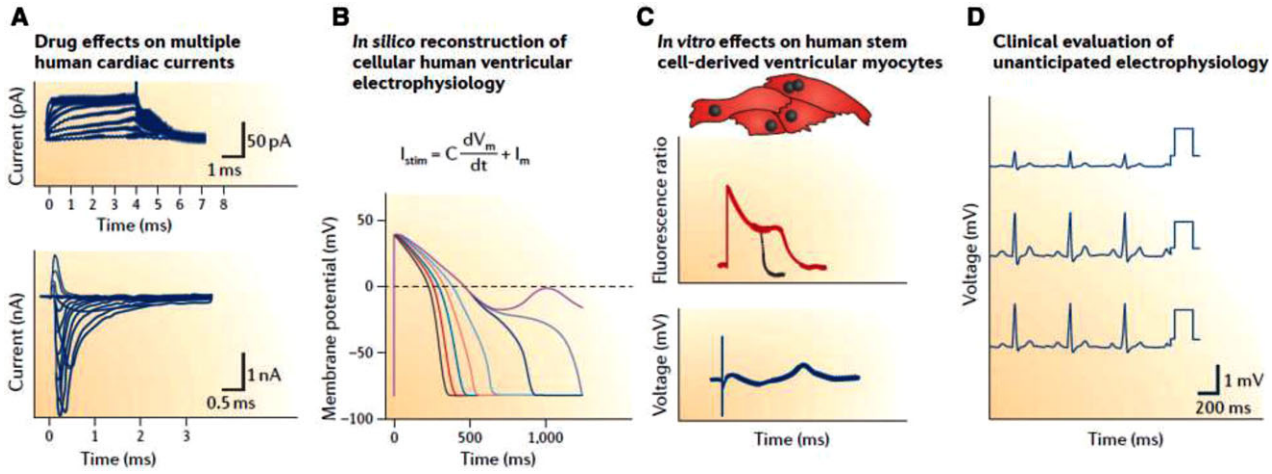

Figure 2. The four central pillars of the comprehensive in vitro proarrhythmia assay. (Figure reproduced with permission from Gintant et al.[62])

The CIPA initiative continues work to define, standardize, and validate the human ionic current assays, define the metrics of an in silico model to define proarrhythmic risk, test and validate human cardiac stem cell–derived cardiomyocyte-based approaches, and define and test phase 1 ECG biomarkers. Results of this research are expected to emerge over the coming years to influence best practices in drug discovery, as well as in regulatory reviews.

Additional references are provided.[64–82]

Additional ECG Parameters Currently Under Evaluation

Various additional ECG parameters that may eventually be found to be useful in drug development for identifying proarrhythmic potential are currently being investigated, although at this time they should be regarded as ancillary or supportive. These include additional time intervals (eg, the time interval between the peak and the end of the T wave) and morphology measures. Vicente et al[83] reported drug-induced T-wave morphological patterns of change associated with dofetilide, quinidine, ranolazine, and verapamil, concluding that a combined approach of assessing multiple ion channels along with ECG intervals and T-wave morphology may provide the greatest insight into interactions between drugs and ion channels and the resultant risk of TdP.

Additional references are provided.[84–90]

Optimizing Therapeutic Use of QTc-prolonging Drugs

Proarrhythmic cardiac safety considerations are important in therapeutic use, as well as in drug development, and discussions now turn to this domain. The intent is to help clinical practitioners distinguish to the greatest degree possible, on a patient-by-patient basis, between appropriate[91] and inappropriate therapeutic use of drugs with a certain degree of proarrhythmic liability that have received marketing approval at the public health level (see also refs. 92–94).

A question that arises here is, "What magnitude of QTc interval is of concern?" It must be admitted that there is no certainty, but expert opinion suggests that a QTcF greater than 450 msec for men and greater than 460 msec for women should be viewed with concern, depending on the clinical context.

Marketed Drugs With Acknowledged Proarrhythmic Liability

There are many marketed drugs with acknowledged proarrhythmic liability. As an example of data from one regulatory agency (similar outcomes are available from other regulatory agencies as well), Park et al[95] evaluated the regulatory outcome of drugs whose TQT study reports revealed QTc prolongation exceeding the threshold presented in ICH E14. They identified 205 drugs from a database of TQT study reviews performed by the FDA from May 2006 to March 2013.[96] Forty-six drugs were identified as prolonging the QT interval and 41 (89%) of them were approved. Twelve different therapeutic areas were represented, with oncologic and psychiatric indications being the most common. Twenty-five labels had QT-related warnings and precautions, 5 had QT-related contraindications, and 3 had QT-related boxed warnings. The mean effect size of QT prolongation for these 3 categories were 15.6 msec, 18.1 msec, and 40 msec, respectively. All 3 agents with boxed warnings—nilotinib, vandetanib, and toremifene—are oncologic agents. These data emphasize that, in therapeutic areas with significant threat to life and an overall unmet medical need, greater magnitudes of QT

Table 3. CredibleMeds Drug Risk Categories for QT Interval Prolongation and Occurrence of TdP and Examples of Drugs (and Therapeutic Use) in Each Category

TdP Risk Category	Definition and Examples
Known risk	Drugs that prolong the QT interval **AND** are clearly associated with a known risk of TdP, even when taken as recommended: • Arsenic trioxide (leukemia) • Azithromycin (bacterial infection) • Chloroquine (malaria) • Chlorpromazine (schizophrenia, nausea, many others) • Ciprofloxacin (bacterial infection) • Citalopram (depression) • Donepezil (Alzheimer disease) • Droperidol (anesthesia [adjunct], nausea) • Fluconazole (fungal infection) • Methadone (narcotic dependence, pain) • Ondansetron (nausea, vomiting) • Propofol (anesthesia) • Sevoflurane (anesthesia) • Thioridazine (schizophrenia) • Vandetanib (cancer, thyroid)
Possible risk	Drugs that can cause QT prolongation **BUT** currently lack evidence for a risk of TdP when taken as recommended: • Alfuzosin (benign prostatic hyperplasia) • Apomorphine (Parkinson disease) • Asenapine (schizophrenia) • Atomoxetine (ADHD) • Bedaquiline (multidrug-resistant tuberculosis) • Crizotinib (metastatic non-small cell lung cancer) • Dexmedetomidine (sedation) • Efavirenz (HIV) • Felbamate (epilepsy) • Lithium (bipolar disorder) • Nicardipine (hypertension) • Vardenafil (erectile dysfunction) • Vemurafenib (melanoma) • Venlafaxine (depression) • Vorinostat (lymphoma)
Conditional risk	Drugs that are associated with TdP **BUT** only under certain conditions of their use (eg, excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP): • Amantadine (influenza, Parkinson disease) • Atazanavir (HIV/AIDS) • Chloral hydrate (sedation, insomnia) • Diphenhydramine (allergic rhinitis, insomnia) • Esomeprazole (gastric hyperacidity, GERD) • Fluvoxamine (depression, obsessive-compulsive disorder) • Indapamide (hypertension, diuresis) • Loperamide (diarrhea) • Metoclopramide (nausea, vomiting) • Metronidazole (trichomoniasis, amebiasis, bacterial infection) • Quinine sulphate (malaria, leg cramps) • Telaprevir (hepatitis C) • Trazodone (depression, insomnia) • Voriconazole (fungal infection) • Ziprasidone (schizophrenia)

Source: Summarized from information publicly available at www.CredibleMeds.org.[92]

ADHD, attention deficit hyperactivity disorder; GERD, gastroesophageal reflux disease; LQTS, inherited long QT syndrome; TdP, torsade de pointes.

prolongation are deemed acceptable when balanced with therapeutic benefit.

As an example, consider nilotinib, a kinase inhibitor indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase, and the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia in adult patients resistant to or intolerant to prior therapy that included imatinib. The prescribing information contains a boxed warning for "QT prolongation and sudden deaths."[97] Consequently, various procedures should be conducted when using the drug. These include monitoring for hypokalemia and hypomagnesemia prior to nilotinib administration and correcting identified deficiencies and monitoring QTc at baseline, 7 days after initiation of treatment, and periodically thereafter, especially following any dose adjustments. There are also instructions regarding not administering nilotinib to patients with long QT syndrome; avoiding the use of concomitant drugs known to prolong the QT interval and strong CYP3A inhibitors; and avoiding food 2 hours before and 1 hour after taking a dose.

For one QTc-prolonging drug in the oncology therapeutic area, vandetanib, indicated for the treatment of medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease, a restricted distribution plan is in place as a component of the risk management strategy.

A list of drugs known to prolong the QTc is maintained by CredibleMeds[98] (AZCERT; Oro Valley, Arizona; see also Schwartz and Woosley[99] and Woosley et al[100]). To assess risk of harm from medicines scientifically, CredibleMeds has developed a risk-stratification process, the Adverse Drug Event Causality Analysis (ADECA),[101] that includes monitoring and analysis of scientific articles in the published medical literature; information in drugs' official drug label; reports

submitted to its website; and data in the FDA's Adverse Event Reporting System (AERS) using the Oracle Health Sciences Empirica Signal software (Oracle; Redwood City, California). The list of several hundred drugs is divided into categories based on a drug's likelihood to cause QTc prolongation or TdP. List 3 contains those with a conditional risk; List 2 contains those with a possible risk; and List 1 contains drugs with a known risk of TdP: examples are provided in Table 3.

Furthermore, when drugs with QTc prolongation liability are being considered, health-care providers need to be aware of the potential for drug-drug interactions with metabolic inhibitors that can elevate the plasma concentration of the QTc-prolonging drugs, thus increasing the magnitude of the QTc prolongation effect. The Indiana University School of Medicine, Department of Medicine, Clinical Pharmacology, maintains a P450 Drug Interaction Table.[102]

Online Resources for Managing Potential Drug-Drug Interactions

The CredibleMeds[98] website offers a mobile application to make its online QT drugs database instantly available to health-care providers and patients. Healthcare providers are encouraged to become familiar with the website's content.

Risk Factors for TdP

As Ikram and colleagues[103] noted, "It is clear that the association between QTc and sudden cardiac death is not one-to-one and that other risk factors are important." The occurrence of drug-induced TdP itself (rather than just QT/QTc prolongation) typically requires multiple factors to be present at the same time. As Beach and colleagues[104] observed in the context of psychiatric medicine, "The most important risk-reducing intervention clinicians can make is undertaking a careful analysis of other QT risk factors when prescribing psychiatric medications." The same is true in other therapeutic areas as well.

The specific example of nilotinib's prescribing information discussed earlier provided a glimpse at other risk factors for one drug. Information from 3 recent publications pertinent to multiple drugs is summarized here. While there is not 100% concordance among these publications (perhaps not surprisingly because we do not yet fully understand everything related to drug-induced QTc prolongation and TdP), major themes relate to demographic characteristics (age and female sex), electrolyte imbalances, and concomitant medications.

Vlachos et al[106] commented as follows: "Clinical risk factors, such as female gender, structural heart disease, metabolic and electrolyte abnormalities, bradycardia and conduction disease, increased drug bioavailability, and silent channelopathies act as effect amplifiers which can make an otherwise relatively safe drug dangerous with regard to risk for polymorphic ventricular tachycardia in the setting of QT interval prolongation."

Vandael et al[107] performed a systematic review of 10 observational studies containing a total of nearly 90,000 individuals to summarize and assess the evidence for different risk factors associated with QTc prolongation. They allocated 1 of 5 evidence levels—very strong, strong, moderate, low, and no evidence—to each factor within different groups: demographic factors, comorbidities, electrolytes, and QTc-prolonging medications. They reported that "Very high evidence was found for hypokalemia, diuretics, antiarrhythmic drugs and QTc-prolonging drugs of list 1 of CredibleMeds."

Heemskerk et al[108] analyzed all ECGs that were taken during routine practice between January 2013 and October 2016 in a general teaching hospital in the Netherlands. In total, 133,000 ECGs from 40,000 patients were included (multilevel linear regression analysis was employed to correct for multiple ECG recordings per patient). They identified several independent risk factors for prolongation of QTc by at least 10 msec: age, female sex, hypokalemia, hypocalcemia, the use of QT-prolonging drugs, and the use of loop diuretics. With regard to 2 of these factors, while QTc increased with age, the difference in prolongation between men and women decreased.

Patients receiving QTc-prolonging drugs should be counselled regarding signs and symptoms suggestive of TdP (eg, dizziness, palpitations, presyncope, syncope, and seizures) and instructed to seek immediate medical attention if these occur. Patients should also be advised to inform their health-care provider of any changes to, or new use of other, medications, including over-the-counter drugs and natural health products.

Additional references are provided.[109–117]

Important Consideration Beyond the Scope of This Paper: Strengths of the Consortium Model for Future Action

The creation and employment of clinical decision support systems in the context of QTc prolongation and proarrhythmic liability has been advocated by various authors, and this approach certainly has potential.[118–121] Pragmatically speaking, however, many clinicians experience "warning fatigue" from the myriad warnings that can be showered on them every time a prescription decision is being considered.

The CSRC, on behalf of which this manuscript has been written, is a public-private partnership coordinated under a Memorandum of Understanding

between the FDA and Duke University that was signed in 2006. Its mission is to advance the regulatory science of cardiac and vascular safety assessment by bringing together stakeholders from industry, academia, and government in a neutral, precompetitive paradigm to share data and expertise and to support research into issues related to medical product cardiac and vascular safety.[122] Accordingly, CSRC may be a productive venue not only for exploring the science of cardiac and vascular safety (see Turner et al[123] for a review of our activities and publications during our first decade) but also for arriving at practical and highly applicable solutions for the practice community to optimize the therapeutic use of QTc-prolonging drugs.

Concluding Comments

Proarrhythmic cardiac safety considerations in drug development and therapeutic use have become central components of contemporary pharmaceutical medicine. Since regulatory agencies' adoption of ICH guidelines S7B and E14, released in 2005, concerted efforts have been undertaken to define a new drug's proarrhythmic liability before submitting a marketing application. The ICH S7B-E14 regulatory landscape has focused on 2 biomarkers: drug-induced reduction in the cardiac repolarizing ionic current I_{Kr} and drug-induced QTc prolongation. Ongoing research projects, such as the CIPA, may eventually bring additional dimensions to this assessment.

Identification of a proarrhythmic liability does not automatically lead to a marketing application being unsuccessful. Indeed, the examples of some oncologic agents show that drugs associated with a considerable degree of QT prolongation can be approved, with appropriate risk mitigation measures. When a drug's therapeutic benefit is considered important at a public health level but there is also an identified proarrhythmic liability, appropriate language will be placed in the drug's label. It is then the responsibility of physicians to heed this language and make judicious decisions regarding the drug's incorporation into treatment regimens on a patient-by-patient basis, taking into account an assessment of multiple clinical risk factors. Given their expert knowledge of clinical pharmacology, pharmacists are well placed to work closely with physicians as influential arbiters of sound prescribing decisions.[124]

Disclaimer

While representatives from regulatory agencies are co-authors, this paper does not represent new regulatory guidance.

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