Evolution of the Thorough QT/QTc study

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Abstract

Following the discovery that certain medications were associated with sudden death due to the potentially fatal arrhythmia, Torsade de Pointes (TdP), regulators and drug developers sought how best to identify the culprit compounds. This article outlines the stumbling blocks on the regulatory journey towards current legislation, and the insights gained through a proactive regulatory approach.

TdP was merely an exoteric diagnosis until the 1980s and 1990s when it was recognised as a major cause of drug-induced sudden cardiac death. Its recognition prompted the withdrawal of several popular medications from the market.[1,2]

TdP results, in part, from a prolongation in the cardiac action potential's return to baseline manifested by QT prolongation on the ECG.[3] (The QT interval is a measure of the time between the start of the Q-wave and the end of the T-wave in the heart's electrical cycle. 'QTc' is the QT interval corrected for heart rate.)

TdP has a highly variable clinical presentation. The arrhythmia can be asymptomatic, associated with mild symptoms like palpitations, or present more serious symptoms such as syncope, or result in cardiac arrest. The implications of mild symptoms may not be apparent until someone suffers sudden death. Since it usually does not occur with the first administration of a drug and often only occurs after concomitant medications or comorbid conditions intervene, the association with the culprit compound is blurred. These factors, combined with a very low incidence, made it difficult to detect a safety signal in post-marketing surveillance.[4] Often hundreds of thousands of patients were exposed to risk before a relationship to a specific compound became apparent. A nearly decade-long regulatory journey ensued to develop a mechanism to detect the QT problem prior to extensive patient exposures. After the implementation of ICH E14 and S7B guidances in 2005, the approach to QT assessment has continued to evolve. This discussion will centre on the US FDA's approach to ICH E14 and the regulatory evolution of the TQT study (see Figure 1).

Cisapride

Cisapride, a GI prokinetic agent previously marketed as Propulsid in the US, was one such drug that caused TdP[5] and exemplifies the difficulty in tying QT prolongation to unexpected sudden deaths and the need for a proactive regulatory approach.

Cisapride was indicated in the US only for "symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease" unresponsive to other therapy.[6] However, it was widely used off-label for other indications. Despite the lack of demonstrated efficacy, cisapride was often used to treat conditions such as diabetic gastric atony or peptic ulcer disease. There was also a heated debate over cisapride's use in premature neonates to improve gastric motility in an effort to allow earlier institution of enteral nutrition.[7] Kohl subsequently showed that the benefit to neonates was small; ECGs revealed a significant prolongation of the QTc interval and two of 59 infants developed cardiac rhythm disturbances.[8]

Cisapride underwent several labelling changes meant to educate physicians on which conditions and medications cisapride was contraindicated. However, these labeling changes had no impact on the prescription of the compound when contraindicated.[9,10] As of 31 December 1999, there had been 341 reports of heart abnormalities and 80 deaths associated with cisapride use, mostly in patients taking medications that inhibited the metabolism of cisapride.[5]

The regulatory odyssey

Because TdP is so rare, in the range of 1/10,000 to 1/100,000 of patients on the medication, the typical regulatory submission has little chance of documenting such an event.[4]

The European regulator's former Committee for Proprietary Medicinal Products (CPMP) convened an *ad-hoc* group of experts to address the preclinical and clinical testing of compounds to identify drug-induced QT prolongations. In December 1997, the EMEA reported the outcome of that work as a "Points to Consider" document.[1]

The European Society of Cardiology assembled a Policy Conference in 1999 and published the results in the *European Heart Journal* in 2000. This document outlined the knowledge to that date and explored the regulatory implications.[2]

Subsequently Health Canada released a Concept Document.[11] A collaboration between Health Canada and the FDA resulted in the release of a Joint Concept Document in 2002.[12] This document was then submitted to ICH and formed the basis for the ICH E14. The finalisation of ICH E14 in 2005 changed the expectations for evaluating cardiac safety in pharmaceutical development.[13] ICH issued a companion document for the preclinical assessment, S7B, at the same time.[14] The EMEA and FDA implemented E14 in 2005, Health Canada in 2006 and Japan's PMDA in 2010.

ICH E14

ICH E14 codified the need for a dedicated study, the Thorough QT/QTc (TQT), to assess QT liability for nearly all compounds. ICH E14 also mentions exceptions such as the potential use of definitive preclinical data, lack of bioavailability or toxicity precluding the administration of the drug to healthy volunteers. The assumption is that a small QT prolongation in a TQT could predict larger prolongations in patients. A positive study is defined as a drug-induced QT interval prolongation of approximately 5 milliseconds (ms), the threshold of regulatory concern, and is defined as a single-sided upper 95% confidence interval of less than 10 ms.[13] Drugs that cause such a prolongation will be required to do extensive ECG collection and analyses in later stage studies. These later stage requirements would be expensive and most drug developers have abandoned compounds with positive TQT studies

Figure 1: The regulatory evolution of the TQT study.
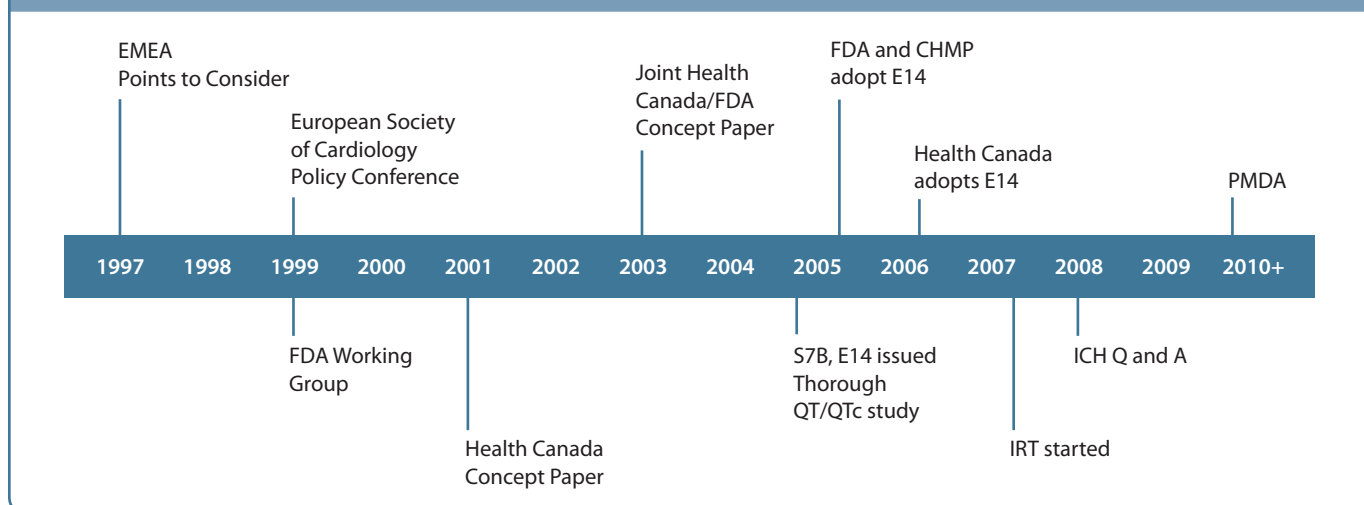
unless the benefit clearly outweighs the risk from QT prolongation.[15]

The "classic" TQT is a randomised, double-blind study to minimise bias and a crossover study is preferred. The four treatments recommended are placebo, active control and two doses of study drug. The positive control arm (usually moxifloxacin) is used to show that the study is sensitive enough to pick up QT prolongation around the threshold of regulatory concern. The study must show appropriate peak and time course of QT changes in the active control arm. Finally, both a therapeutic and supratherapeutic exposure to the drug is tested. E14 does not provide a statement of what constitutes a supratherapeutic dose, but the FDA has stated that such an exposure should mimic the exposures likely seen in patients on concomitant medications or with impaired metabolism.[16] The TQT should not be done too early in development because a significant amount of information about a compound is required to design a TQT properly.

The ICH E14 Implementation Working Group issued a Questions and Answers document on 4 June 2008, to address some of the issues not resolved in ICH E14 and to reflect insights gained from TQT studies. It addressed in general terms what constitutes an adequate positive control, ECG reading technology, ECG reader training, gender differences in QTc, baseline adjustments, and placebo comparison in parallel studies.[17]

The Implementation Working Group met in 2009 and decided not to reopen the ICH E14 document for review.

The FDA

The FDA has implemented certain processes and procedures specific to its interpretation of ICH E14. The agency has communicated changes in its general thinking about TQT study design and analyses in publications and at meetings, such as the Cardiac Safety In Drug Development meeting co-sponsored by the FDA and DIA and the Cardiac Safety Research Consortium (CSRC).

The FDA developed an electronic ECG Warehouse in a public private-partnership with Mortara Instruments to allow the FDA to review the ECG recordings from TQT studies submitted to the agency.[18] Instrumental to this was the development of an ECG XML file format specifically for these studies.[19] The Warehouse not only allows the agency to view the recordings, but the system provides proprietary metrics to the FDA reviewer allowing assessment of such things as recording quality and whether the measurements were all obtained as defined in the protocol.[18]

Some drugs with multiple potential indications are submitted to different divisions within the FDA. There was initially little uniformity between divisions in their approach as to whether a TQT was needed or how it would be designed. The FDA assembled an Interdisciplinary Review Team (IRT) with members from project management, medical, statistics, and pharmacology from across several divisions in 2006.[20] The IRT has been successful in providing more uniformity in QT evaluation across these divisions. The IRT should review all TQT study designs to make sure they are complying with E14, especially if the study is not the "classic" design outlined above. In order to evaluate the study design, the IRT requests a significant amount of data about the compound. They developed a document, the Clinical Highlights of Pharmacology,[21] to collect all that information in one place. Inadequate characterisation of a compound's pharmacology has resulted in delayed IRT reviews in the past. The IRT is advisory to the review divisions and those divisions still make the ultimate decision about TQT assessment, though they do tend to follow the IRT recommendations closely.

The IRT has reviewed more than 170 TQT study reports. As mentioned above, it has intermittently shared information gathered from those exercises at meetings and in the literature. For example, the FDA recently revealed that eight TQT studies had an inadequate moxifloxacin response, making the studies uninterpretable. Seven of these studies were parallel design. The FDA has advocated that parallel studies have a combined placebo/moxifloxacin arm (nested) rather than two separate arms. This allows a closer temporal assessment of moxifloxacin and study drug QT effects, which may decrease the moxifloxacin failures in parallel studies.[22]

Blinding of moxifloxacin has been an issue from the beginning with concern that because there is not a readily available moxifloxacin placebo and over-encapsulation will affect the pharmacokinetics and QT changes associated with moxifloxacin administration. The FDA has alternately suggested blinding and not blinding moxifloxacin. The most recent recommendation is that in crossover studies there is the potential to unblind the study drug with a single Williams Square design and a double Williams Square may be necessary.[23] Our recommendation has been to perform a double blind moxifloxacin because we have a placebo moxifloxacin tablet available and the agency can never criticise blinding moxifloxacin.

Heart rate correction is another example where the agency has

reversed itself based on information it has garnered analysing TQT studies. Clinicians have used Bazette's correction (QTcB) since the 1920s because it is based on the square root of the interval between heart rates and makes manual calculation much easier. QTcB has the known limitation of overestimating QT duration when the heart rate is above 60. Fridericia's correction (QTcF) was developed around the same time, but is less widely used because it utilises the cube root of the interval between heart beats. Early on, the FDA recommended using an individual heart rate correction factor (QTcl) because of limitations associated with population-generated correction factors applied to individuals. However, an adequate QTcl is very difficult and expensive to obtain due to large number of heart beats being required over a broad range of heart rates. QTcF has similar accuracy to most limited QTcl assessments and is much cheaper.[23]

TQT study trends

ICH E14 states that, "While ambulatory ECG monitoring has historically not been considered sufficiently validated to be used as the primary assessment of QT/QTc interval, newer systems that allow for the collection of multiple leads that more closely approximate a surface ECG have potential value to collect interval data". Even when implemented in 2005, this approach was antiquated. Data have demonstrated that 12 lead Holter and standard 12 ECG machines provide similar data.[24] The rationale for adoption of Holter monitoring technology for TQT has been driven by simplifying study conduct and minimising data lost to poor acquisition with standard ECG machines where only a 10 second strip is recorded.[3,4] Currently, Holter monitors are the standard for ECG data collection in TQT trials and the majority of TQT submitted to the FDA have utilised Holter monitors.[25]

ECG data review methods have also changed over time, progressing from manual reading of paper recordings to review of digital tracings on a computer monitor. Typically, a computer algorithm does the initial measurement and a cardiologist changes or confirms the interval measurements, the so-called semi-automated or manual adjudication method. This requires a cardiologist to review every ECG. However, as computer algorithms have improved, cardiologists have questioned the need for review of every ECG by a cardiologist in normal subjects. At this time, more highly automated methods are used in which most ECGs are automatically measured, and only those exhibiting characteristics that impair automated measurements are reviewed by a cardiologist. Highly automated and fully automated methods actually decrease measurement variability, a major component of study sample size.[25] At the current time, fully automated methods may have a lower variability than semi-automated methods, but still produce measurement outliers. The highly automated approach addresses those outliers produced by fully automated methods to potentially further reduce variability.[26]

Conclusion

TdP risk assessment has evolved significantly since the 1990s. Knowledge gained by regulators and drug developers, combined with new technologies, will surely result in further refinements in the assessment TdP risk and make medications safer.

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