Journal of Pharmacokinetics and Pharmacodynamics (2021) 48:183–186
https://doi.org/10.1007/s10928-021-09754-z

EDITORIAL

QTc interval analysis—an ever-evolving endeavor

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Accepted: 31 March 2021 / Published online: 7 April 2021

The first company I worked for after completing my PhD was Hoechst Marion Roussel (HMR) in Kansas City, MO. One of our biggest selling products was Seldane® (terfenadine), approved in 1985, which was the first nonsedating antihistamine for seasonal allergies. Sales were huge, making it one of the first billion-dollar-a-year drugs. But around 1992, a series of case reports of sudden cardiac death in patients taking Seldane caught the attention of the Food and Drug Administration (FDA) through its MedWatch program. Eventually it was discovered that this adverse event tended to occur in patients with liver impairment or when used in combination with erythromycin or other CYP3A inhibitors. Terfenadine is a prodrug and metabolism to an active metabolite is needed for its antihistamine therapeutic effect. However, terfenadine itself does block a particular cardiac ion K + channel called the human-ether-a-go-go, now commonly referred to as the HERG channel, and inhibition of its metabolism results in terfenadine concentrations many fold higher than normal. It was soon identified that blockade of HERG channels resulted in prolongation of the QT interval on an ECG and could lead to a rare arrhythmia known as Torsades de Pointes. Eventually, in agreement with the FDA, HMR removed Seldane from the market in 1998 [1]. This was the first drug removed from the market for QT liability issues.

Prior to its removal, HMR realized that since terfenadine was a prodrug, and it was the primary metabolite that was the active moiety, they could develop the metabolite as a drug to replace Seldane when it was removed from the market. The metabolite was named fexofenadine. One hurdle the company needed to overcome was demonstrating that fexofenadine did not prolong QTc intervals. The company conducted two double-blind, placebo-controlled clinical trials using a range of doses administered for 2 weeks. Statistical analysis using analysis of variance of mean QTcB intervals (Bazett's correction was the standard at that time and remained so for many years until replaced by QTcF intervals) showed no difference between fexofenadine-treated patients and placebo-treated patients, nor was any dose–effect detected [2]. The company also conducted three long-term safety studies which came to similar conclusions. In 1996, fexofenadine was approved for seasonal allergy use by the FDA and today is marketed as the over-the-counter medicine Allegra®. At the time of the fexofenadine analysis, there was no ECH E14 guideline; that would not come for a decade later until 2005. HMR conducted the most scientifically rigorous cardiac studies ever done at the time and analyzed the data using standard statistical methods. But Seldane was not alone in its ability to prolong QT intervals and induce cardiac rhythm abnormalities. The FDA soon started to review of other drugs that might prolong QT intervals and quickly identified some others, like Propulsid® (cisapride), which was removed from the market in 2000. Internally, however, HMR realized that the chemical backbone used for terfenadine was also currently in use with some other drugs in development and therefore might have the same QT interval liability.

In the late 1970s and 1980s, Lewis Sheiner and Stuart Beal proposed the analysis of pharmacokinetic data using a new methodology, called nonlinear mixed effects modeling, and with it developed a software program called NONMEM that could be used to develop these models [3–5]. NONMEM was not easy to use and, despite its potential, did not start to be used by companies until the 1990s with the release on NONMEM IV, the first version that could be installed from floppy disks. When I joined HMR in 1996, my manager, Vijay Bhargava, asked me to learn this new tool and see what we would do with it. My colleague, Sam Hutcheson, trained me and a few others, like Danny Howard and Gene Williams, on how to use NONMEM and we soon centered on whether we could use NONMEM to analyze QTc interval data collected in our clinical trials. Sam Hutcheson, the year prior, was the first to use a mixed effects model to analyze QT interval data

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collected in clinical trials for a new antinausea drug we were developing called Anzemet® (dolasetron).

HMR had a unique way to train new employees, one you don't often see in use today. Everyone in the Clinical Pharmacokinetics department (there was no clinical pharmacology department; that wasn't a thing then because only physicians were clinical pharmacologists) learned every function, from study design, to protocol writing, to study start-up and site initiation, study monitoring, analysis, both pharmacokinetic and statistical, and report writing. When I look back now, I am kind of shocked they did this, but they assigned me, the most junior person in the department, the cardiac trial for one the most important new investigational products we had in our pipeline. Working with Doris Robbins-Weilert, who was the lead clinical pharmacokineticist on the project, and Tanya Russell, who was the lead pharmacokineticist for fexofenadine, we designed a 4-period, crossover, placebo-controlled (with overencapsulation for blinding), multiple dose study that controlled for food effects, with ECG overreads, and was appropriately statistically powered. This, in my opinion, was the first modern thorough QT study (sans positive control) because an integral part of the analysis was a concentration-QT interval analysis using mixed effect methods. The model at that time was simply a random coefficients model with concentration as the sole predictor in the model. A secondary analysis modeled QT intervals over time controlling for factors like food effect, overencapsulation, chest lead, and sex (but this was not included in the study report) [6]. At the time, we were the only company doing these analyses and we never envisioned the behemoth it would become. By 2001, I left to join a startup biotechnology company in Texas and put QT analysis behind me. I feel like the culmination of all those analyses, on so many different drugs, and some early papers I wrote on the topic [7, 8] was when the FDA asked me to speak at a Clinical Pharmacology Advisory Committee on the topic [9] (and if you've read my book on model communication, you know that this presentation was a disaster in my mind).

In the late 1990s and earlier 2000s, many other drugs were identified to prolong QT intervals: antibiotics like moxifloxacin, erythromycin, and ketoconazole, antidepressants like imipramine, fluoxetine, and sertraline, antipsychotics like haloperidol, and, of course, antiarrhythmics like sotalol. Soon, the FDA was asking drug sponsors to determine whether every new drug in development prolonged QT intervals. Suddenly, the analyses of QT interval prolongation became important and in 2005, the ICH E14 guidance on the evaluation of QT/QTc interval data was released detailing study design, analysis, and interpretation of results [10]. The trial necessary to address whether a drug prolonged the QT interval had a special name, the thorough QT trial (TQT), and companies would soon find that these studies were expensive and difficult to conduct. What the guidance said about analysis of the relationship between drug exposure and QT/QTc interval changes was simply the following:

> "Establishing the relationship of drug concentrations to changes in QT/QTc interval may provide additional information to assist the planning and interpretation of studies assessing cardiac repolarization. This area is under active investigation."

After that, analysis of QT intervals became the Wild West. Christine Garnett and colleagues at the FDA issued a white paper advocating a random coefficients model [11]. Brian Smith, Alex Dmitrienko, and colleagues at Eli Lilly and Co. published a series of papers advocating individual correction, use of repeated measure models, and log–log transform of corrected QT intervals [12, 13]. Piotrovsky published a circadian rhythm model for QT intervals over time, incorporating drug effect into the model [14]. And there were many others with no standardization. Every new method advocating "this method" is how analyses should be conducted.

Over time it was realized that the primary analysis method for QT intervals proposed by the ICH, the Intersection Union Test (IUT), was prone to a high false positive rate, and could range from negligible to 60%, depending on the study characteristics [15]. In 2010, the Journal of Biopharmaceutical Statistics published a themed issue on the design and analysis of TQT trials, which had 3 separate papers on sample size issues and four separate papers on how to analyze QT intervals [16]! In 2012, the largest TQT trial ever conducted was published, a four-arm, parallel, 2-way crossover, multiple dose study with mirabegron having more than 350 patients with an estimated cost of more than $30 million dollars [17]. The FDA soon started asking companies to perform QT assessments for monoclonal antibodies and in special populations like cancer populations (internal communication). Entire companies formed around these studies and TQT studies became big business for contract research organizations. Many felt that this was getting out of hand.

In the early 2010s, the Clinical Pharmacology Leadership Group of the Consortium for Innovation and Quality in Pharmaceutical Development (IQ) and the Cardiac Safety Research Consortium (CSRC) joined in a collaborative research initiative to determine whether ECG data obtained from early Phase 1 studies could be used in lieu of a TQT study to address the prolongation question for new chemical entities [18]. Six drugs with QT liability, and one without (negative control), were studied in 20 healthy volunteers in an incomplete block crossover study design. ECG data were overread using the same rigor as a TQT

study. Change from baseline QTcF intervals were analyzed using linear mixed effect exposure–response models and the upper bound on the 1-sided 95% confidence interval (CI) of the peak QTcF interval effect at the drug's projected maximal concentration was calculated. If the 1-sided CI exceeded 10 ms, prolongation was declared. The slope of the concentration-effect relationship was significant for all five pro-QT liability drugs and negative for the negative control. Further, at the lowest doses studied, all five had an upper 1-sided CI exceeding 10 ms, whereas the negative control did not exceed 10 ms at sixfold the therapeutic dose [19].

Recognizing that the IQ/CSRC results demonstrated that exposure–response modeling could be used to assess QT prolongation in lieu of a TQT study under certain conditions, and the statistical issues related to the IUT, the ICH issued a question and answer (Q&A) document to clarify issues surrounding the E14 guidance [20]. One of these had this game-changing statement:

> 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-time-point analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug.

But again, what model to use for these analyses was left vague in the guidance.

Knowing that the ICH was going to amend their E14 guidance to allow exposure–response analysis in lieu of the IUT, Christine Garnett at the FDA organized in 2015 a group of industry and FDA experts in the analysis of QTcF interval data to write a white paper (which is now referred to as "the white paper" in industry) in support of the ICH E14 Q&A document. After many, many meetings and much discussion the white paper was published in 2018 [21]. The model was soon adopted and has already been used by drug companies used to obtain TQT waivers from regulatory agencies. One might think that would be the end of the story, but alas, in order to complete the white paper in a timely manner (it already took almost 3 years to get to a publishable manuscript), certain elements had to be ignored. For example, the model does not apply to studies in special populations like cancer where a placebo arm might be lacking. Another being recommending examination of hysteresis by visual inspection, which leaves its conclusions open to interpretation.

In this issue of the journal, three more QT analysis papers are being published, which address some of the limitations of the white paper. Ferber et al. [22] demonstrate that hysteresis can reduce the power to detect a positive QT prolongation signal and then present a novel metric to assess QT interval hysteresis that may be used in lieu of visual inspection. Heinrich et al. [23] take a different approach to assess hysteresis through use of an indirect response model between drug concentrations and drug effect. Orihashi, Ohwada, and Kumagai [24] present alternative models to the white paper model for single arm studies where placebo data might not be available. Do these papers address all the limitations of the white paper? No. Can we expect these to be the last word on the subject? Certainly not. If anything, what the QT story has taught us, is that this is an evolving science. A white paper is the final word only until the next paper is published. For now, the story continues.

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