AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

As stated by Dr. Norman Stockbridge in the last issue of AMPS-QT: "You might think that after about a decade of Thorough QT studies, there wouldn't be all that much going on, but in fact this is a very dynamic period."
ERT is one of the companies that helped shaping the cardiac safety industry during the last decade both by being proactively in the lead for the search of new methods and by being an early adopter of confirmed technology. In this issue we publish an essay collectively produced by the people behind the ERT success, which will give you an excellent perspective on the past and a glimpse to what lays ahead.

A Noteworthy Contribution:

Drug Induced Torsade de Pointes and the Growth of Cardiac Safety in Drug Development
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It is the purview of the various national regulatory agencies, such as the FDA or EMA, to evaluate data on the efficacy and safety of new drugs prior to their approval for marketing. However, during the 1980s and 1990s, there was a dramatic increase in the number of cases of drug induced Torsade de Pointes (TdP) leading to the withdrawal from the market of a number of drugs which produced QT prolongation and TdP. These events highlighted the inability of the drug development and regulatory approval processes, as they existed at that time, to predict this extremely infrequent but often life threatening side effect of drugs that prolonged cardiac repolarization. Standard pre-approval clinical trials simply were not powered or designed to detect such an infrequent event.

With this realization, members of academia, pharmaceutical companies and regulatory groups independently worked to respond to the challenge of better protecting the public from the release of drugs which may produce TdP. No single governmental agency or private group had the mandate, authority or resources to detect, investigate and mitigate this issue on its own. However, through a combination of efforts by many individuals and groups, progress was made in a reasonably short time, and the changes subsequently made to the drug development and approval processes have largely succeeded in preventing the release in recent years of new agents with unacceptable risk/benefit profiles for QT prolongation and TdP.

The first part of the puzzle was the identification of TdP as the mechanism for drug induced syncope and sudden arrhythmic death, and the subsequent realization that drug induced TdP was invariably preceded by QT prolongation. Not all drugs which lengthen the QT produce TdP – but every drug that produces TdP produces QT prolongation. Despite several decades of attempts to find preclinical indicators of a drug's liability to produce TdP, the detection of QT prolongation in clinical trials remains the most reliable method of assessing a drug's proclivity for inducing TdP.

However, the QT interval is difficult to measure on the surface ECG, and the detection of drug induced QT prolongation is not a trivial matter. First of all, the QT interval duration changes significantly with changes in heart rate (HR), and in order to allow comparison of QT data collected at varying times, the QT must be corrected for HR (QTc). There is, unfortunately, little consensus on the ideal method for QT correction for heart rate, and it remains unclear how best to assess QT for drugs which produce substantial changes in HR. Methods commonly used include derivation of individual based QT correction formula for each individual subject (QTcI) or use of HR independent methods based on Holter binning. The time

course of QT changes in response to HR changes (QT hysteresis) is also variable, further complicating matters.

In addition, the QT interval can be difficult to measure when the T wave is of low amplitude or has multiple components, or when ECGs contain artifact. The QT interval may also vary from lead to lead. There is little consensus on whether the QT should be measured on a single lead, or using a superimposed global median beat. Each method has its advantages and disadvantages.

Finally, QT and QTc are highly variable, and in a normal individual, may vary up to 75 msec over the course of a day. In contrast, the threshold for regulatory concern for drug induced QT prolongation is only 5-10 msec, making the detection of drug induced QT prolongation very difficult in a single individual or in underpowered poorly designed trials assessing ECG changes.

Despite these difficulties, over the past 10 years we have seen the development of standardized methods for detecting drug induced QT prolongation. The principles described in the ICH E14 document "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs", ratified by the FDA, EMA and Health Canada in 2005, outline the design and conduct of a "Thorough ECG Trial" (TET), to be performed in healthy volunteers, which is adequately powered and designed to detect drug induced QT prolongation of only 5-10 ms. As stated in this guidance, a TET is required for all new agents, as well as for approved agents for which a new formulation, dosage, or indication is proposed for which there may be increased drug exposure. A major exception would be for drugs which cannot be given to healthy volunteers such as geno or cyto-toxic chemotherapeutics. The design of a TET must include a supratherapeutic dose of the agent (to test the worst case scenario in healthy volunteers compared to the target population), an active comparator to demonstrate assay sensitivity at the 5-10 ms threshold, and a placebo control. The guidance and follow-up commentary detail the statistical requirements to demonstrate assay sensitivity, and defines what the regulatory agencies consider to be a negative TET, i.e. that the new drug has no clinically relevant liability on cardiac repolarization and other ECG effects (HR, PR and QRS durations). Depending on the pharmacokinetics of the agent, a parallel or crossover design may be used.

Since the approval of ICH E14 in 2005, the principles for the design and conduct of TETs have been further refined. Most TETs currently have an additional therapeutic dose arm, and the active comparator is almost invariably Moxifloxacin, which has very predictable absorption, PK and a 5-10 ms QT effect. ECGs are now collected in replicate to enhance the point estimate of QT duration at the time point, and usually are recorded on continuous digital 12 lead ECG recorders rather than on cart based 12 lead ECG machines. ECG measurement techniques have improved, and modern core labs generally have a QTc within subject variability in the 6-9 ms range. We have also made progress in understanding how to collect good QT data using intense ECG and PK designs for drugs which cannot be given to healthy volunteers (such as cytotoxic oncologic agents) and for which the standard E14 3 or 4 arm trial is not feasible.

Several important issues remain to be resolved. Foremost, it seems are concerns about the specificity of drug induced QT prolongation for predicting that a drug produces TdP. It is clear that there are drugs which prolong the QT interval, but which do not produce TdP, perhaps due to modulation of inward ionic currents. In addition, many drugs which produce modest QT prolongation are still valuable agents with a good risk/benefit profile, and many such drugs have been approved in the past 8 years. Nevertheless, those of us involved in drug development are aware of many potentially valuable new compounds whose development has been halted prematurely due to almost paranoid concerns about possible QT prolongation. Regulators have repeatedly explained that the TET is designed to allow decisions about the level of cardiac monitoring to be required in Phase III trials and to provide data for drug labeling, and that a "positive" TET will not necessarily prevent a drug from being approved if their risk: benefit analysis is favorable. Still, there is a sense in the industry that many good drugs are being shelved unnecessarily because of QT concerns which may be unnecessary.

Another concern voiced by the pharmaceutical industry has been the added cost which a TET imparts to a drug development program. In this age of resource constraints, the TET, which is a study purely dedicated to collecting cardiac safety data, is an obvious target of scrutiny. There are currently a number of strategies being investigated to reduce the cost of a TET, or even better, to replace the TET with intense Phase I QT ECG and PK assessments. Despite a decade of frustrations in the attempts to supplant clinical QT assessments with newer preclinical assessments, efforts continue in this vein as well.

In response to balancing the concern of costs related to the conduct of a TET, core ECG laboratories have devised centralization strategies, workflows and utilized algorithms, such as AMPS's CalECG, to effect an economic and scientifically based-approach to conduct these trials. These advances provide for a consistent high quality cardiac safety assessment by enabling a standards-based approach achieving strict consistency in the measurement of ECG parameters.

A larger issue relates to the generally piecemeal, unorganized response of the various parties to the entire issue of drug induced QT prolongation and TdP during the 1980s and 1990s. Many individuals, government agencies and nongovernmental groups worked very diligently to advance the field to where it is today – but without any central coordination, and often with significant duplication of efforts. When the next cardiac safety issue arises, can we do better? Will we be able to mobilize the various stakeholders in pharma, academia and the regulatory bodies to work in unison, and not as independent agents?

There still is no single organization which has the mandate, authority and resources to single handedly tackle the next drug-induced safety crisis. There has been substantial progress, however. With the advent of modern computer technology and large databases, there are now several initiatives to attempt to improve our ability to detect new signals of concern for drugs which have already been marketed. A number of groups with varied constituents have formed which are well suited to address concerns about new issues in drug development, such as the Cardiac Safety Research Consortium (CSRC), the WHO Collaborating Centre for International Drug Monitoring, the Council for International Organizations of Medical Sciences (CIOMS), the International Conference on Harmonization (ICH), and the Drug Information Association (DIA). We can only hope that these and other organizations will provide a coordinated rapid response to the next safety crisis.

Products News

Latest Releases

In Q2 2013 we have released:

- Fat-QT v. 1.3.0, with the very latest version of BRAVO algorithm (v 4.2.6);
- CalECG v. 3.5.0, with the latest BRAVO algorithm (v. 4.2.6);

AMPS Recommends

In this issue we recommend an interesting paper recently published on the Journal of Electrocardiology (1). In this article, Meyer and colleagues report about a novel pattern-recognition based method for QT measurements that provides encouraging results. The new approach is based on the pre-determination of subject-specific libraries of representative template waveforms which are used in a conformational match fashion to characterize the markers of each cardiac beat. Apart for the manual adjudication of measurements on the library templates, the new method is fully automated.
The pattern-recognition approach was tested on continuous Holter data from a Thorough QT study and its performance was assessed comparing the result analysis with that from a core laboratory which applied (on the same data) a semi-automated method. Frequency of T-end measurement errors and intra-individual QT variability evidences a significant reduction, thus eliciting better accuracy and precision using the pattern-recognition approach.

This promising work raises one point of discussion which is the appropriateness of the Thorough QT study as a valid paradigm to assess the precision and accuracy of new computerized measurement techniques. This specific issue has been addressed in an invited editorial from our Chief Scientist Fabio Badilini (2), published back-to-back to Meyer's article. The editorial underlined potential confounding factors related primarily on the lack of a gold standard for the QT interval (and thus the risk to use a potentially biased benchmark) and secondly on the specific type of ECG data from Thorough QT studies which, enrolling young and healthy subjects, will rarely present challenging ECGs. This limitation is mitigated, at least for the data from the active drug arm, in studies based on compounds that induce T-wave morphology changes, such as that from Meyer.

[1] Meyer O, Ferber G, Greig G, Holzgrefe HH. Pattern recognition analysis of digital ECGs: Decreased QT measurement error and improved precision compared to semi-automated methods. J Electrocardiol 2013;46:118-125.

[2] Badilini F. The "Thorough QT study": A valid paradigm to test new algorithms for QT interval measurements? J Electrocardiol 2013;46:126-127.
This paper is available on our website in the Documents-> Publications page.