New Technologies Offer Solutions for Cardiac Safety

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The challenges posed by stringent regulation, high research and development costs, and drug safety issues have become a familiar refrain in the drug development industry. Despite these hurdles, however, recent trends provide reason for optimism. According to a 2007 industry outlook report from the Tufts Center for the Study of Drug Development, one positive trend is the increasing willingness of drug-developers to embrace new technologies that reduce late-stage failures and curtail rising development costs. Cardiac safety testing represents an area where emerging technologies can significantly improve the productivity and pace of drug development while substantially reducing cost in clinical trials.

The importance of cardiac safety testing increased in the last 15 years with the discovery that many drugs—whether in development or on the market—have the potential to cause a life-threatening arrhythmia, a condition known as torsades de pointes (TdP). These drugs affect the potassium ion channel (I_{kr}) and prolong the heart's ventricular repolarization process—the brief period between two heart beats and a vulnerable point for arrhythmia induction. This prolongation can trigger TdP, which can lead to sudden cardiac death.[1] Currently, the classes of drugs associated with a prolongation of the QT interval include opioid, anti-migraine, anti-malarial, anti-asthmatic, antihistamine, anti-infective, anti-neoplastic, anti-lipidemic, diuretic, gastrointestinal, hormone, antidepressant, anti-emetic and antipsychotic medications[2].

Drug-induced arrhythmia is a leading cause for withdrawal of drugs from the market. Since 1985, 24 drugs have been withdrawn from the US market because of safety concerns. Of these 24 drugs, nine were withdrawn for cardiac safety issues, of which five were dangerous drug-induced arrhythmias. Many more drugs received "black-box" warnings on their labels that, understandably, discourage physicians from writing prescriptions even though an incidence of arrhythmia may not be known.
The use of pre-computing era tools to assess subtle changes in the highly-complex, physiologic process—repolarization of the heart—too often leads to beneficial new medicines being prohibited from development. Even worse, in some cases, the inadequacy of these tools can lead to underestimation of the cardiac risk posed by drugs.

New electrocardiogram (ECG)-based biomarkers provide more precise and objective methods for evaluation of cardiac risk of pharmaceuticals. With more precise tools, drug-developers can substantially decrease false-positives and false-negatives of the current safety tests while at the same time decreasing the number of patients needed for a cardiac safety study.

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[1] Shah RR. Drug-induced QT interval prolongation--regulatory guidance and perspectives on hERG channel studies. Novartis Found Symp. 2005; 266:251-80; discussion 280-5.
[2] Arizona Center for Education and Research on Therapeutics (www.torsades.org).

Cardiac Safety Testing Today

Currently, FDA requires a clinical cardiac safety measure that tests for possible drug-induced prolongation of a segment called the QT interval on ECGs collected from healthy volunteers. The FDA's industry guidance[3] describes a battery of studies to evaluate a drug's potential to prolong ventricular repolarization, termed Thorough QT (TQT) studies. The purpose of the TQT study, as stated by regulators, is to decide whether more extensive ECG monitoring is necessary in subsequent development program. In reality, however, a positive TQT study or even QT prolongation detected in preclinical studies most often leads to termination of the drug development program, as both sponsors and regulators have become increasingly risk-averse in the wake of the recent, high-profile, market withdrawals of several blockbuster drugs.

Prolonged QT as a biomarker has been widely-criticized for its high rate of false-positives and false-negatives. Consider the case of cisapride (Propulsid), a drug for gastrointestinal motility disorder. When the drug was evaluated for cardiotoxicity in humans using FDA-required testing, cisapride exhibited a small prolongation of the QT interval and consequently was considered safe for marketing. Once on the market, cisapride was associated with numerous arrhythmic events, including 341 cases of life-threatening cardiac arrhythmias with 15 sudden-cardiac arrests over a period of six years.[4,5]

Although the litigation costs of false-negatives can be astronomical—class action suits and legal fees alone for cisapride exceeded $100 million. The conservative regulatory guidance has now dramatically reduced the probability of a false- negative QT study. However, false-positive QT studies produce an enormous "silent" burden on society. A false-positive QT study may cause an unnecessary termination or adverse labeling for an inherently safe drug and thus lead to lack of access to new medicines for patients that need them while at the same time contributing to the skyrocketing costs of new drugs. Some examples of false-positive QT drugs that did make it to market include moxifloxacin (an antibiotic), amiodarone (an anti-arrhythmic), tamoxifen (anti-neoplastic) and ziprasidone (an antipsychotic). All are associated with significant QT prolongation but do not have pronounced arrhythmogenic properties at therapeutic doses.

Drugs that change a subject's heart rate or blood pressure are more likely to cause a false-positive QT finding because of significant limitations in current methods of measuring QT prolongation in ECGs.[6] The QT interval is known to be dependent on both heart rate

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[3] E-14 guidance titled "Clinical Evaluation of QT/QTc Interval Prolongation and Pro-Arrhythmic Potential for Non-Arrhythmic Drugs" (http://www.fda.gov/cber/gdlns/iche14qtc.htm)

[4] Van Haarst AD, van 't Klooster GA, van Gerven JM et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clin Pharmacol Ther 1998 November;64(5):542-6.

[5] Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001 June;96(6):1698-703.

[6] Fossa A, Wisialowski T, Magnano A, et al. Dynamic Beat-to-Beat Modeling of the QT-RR Interval

(represented by the RR period on the ECG) as well as history of heart rate. The heart rate varies, adjusting to different levels of physical activity or changes mediated by the autonomic nervous system. As heart rate increases or decreases, the QT interval changes its duration. This change, however, is not instantaneous. In some cases, it takes several minutes for the QT-RR relationship to stabilize at the new heart rate. The highly complex and dynamic relationship makes it difficult to quantify precisely the drug's effect on the QT interval without taking into account the changes in the RR interval and the history of the QT-RR relationships several minutes prior to the point of measurement.

Simple mathematical formulae developed for heart rate correction prior to the invention of computers and still widely used today, work well only when the subject's heart rate does not significantly deviate from approximately 60 beats per minute. This condition is hard enough to achieve in a well-controlled clinical trial setting, much less when heart rate or autonomic state is affected by a drug. Linear correction methods are not able to distinguish QT changes brought on by drug-induced delayed repolarization (which signifies potential arrhythmia risk) from autonomic-mediated normal physiological responses (which may not pose a safety concern).

Improving the Precision of the QT Prolongation Measurement

Today's more sophisticated signal processing technologies make it possible to compensate for instead of correcting for heart rate. The accuracy and reproducibility of ECG-based measurements for clinical trials can be significantly improved with analysis guided by advanced ECG signal processing algorithms. For example, software algorithms can evaluate continuous Holter recordings to identify the periods of QT-RR adaptation due to significant changes in heart rate and flag those periods as unsuitable for the ECG extraction and QT measurement. Drug-developers can then be assured that the QT measurement was performed at the stable QT-RR relationship. Another software-based technique, known as "RR-bin" method measures the QT interval at narrowly-defined ranges of heart rate ("RR bins"). This technique is especially useful when the drug is known to change heart rate, as it evaluates the QT interval without relying on the mathematical correction methods. With use of these techniques, drug- developers can gain more reliable cardiac safety evaluation that not only fulfills the regulatory requirements but also provide greater confidence in the cardiac safety data.

Advanced ECG Biomarkers

Dynamic QT Assessment Beat-to-Beat (QTbtb):

The standard QT measurement method fails to distinguish the effect of a drug on the repolarization process from the effect on heart rate and autonomic tone on that same measurement. For example, this inability to differentiate often leads to unnecessary termination of drug programs, particularly situations that affect the central nervous and cardiovascular system disorders such as drugs commonly affect both heart rate, blood pressure or autonomic state.

Relationship: Analysis of QT Prolongation during Alterations of Autonomic State versus Human Ether a-go-go-Related Gene Inhibition. JPET 312:1–11, 2005

.Dynamic assessment of ECG data beat-to-beat (QTbtb) allows quantification of QT interval changes under varying conditions of heart rate and autonomic tone, which may not be possible with the use of standard QT correction formulae. This advanced ECG biomarker relies on a set of sophisticated algorithms for dynamic data visualization, providing drug-developers with an ability to actually see how the sequential set of QT-RR measurements or "cloud" of beats changes over time or with drug. Once the statistical boundaries around these normal clouds are established the QTbtb method utilizes anapproach called bootstrapping, which is more appropriate for studying comparisons between clouds for drug or autonomic responses in the large, non-uniformly-distributed data samples, such as QT-RR measurements from Holter recordings.

Morphological ECG Biomarkers:
The repolarization process and its abnormalities underlie the vast majority of dangerous drug-induced arrhythmia problems. The ability to study the repolarization process, represented by the T-wave interval within the QT interval itself, provides critical information that enables proper characterization of a drug's safety profile. Changes to the morphology of the T-wave have been linked to the Long QT Syndrome[7], a rare congenital disorder that is highly analogous to drug-induced repolarization abnormality. The same T-wave morphology changes have been shown to reliably identify drug-induced I_{kr} blockade on ECG, and are present in the ECGs of the patients with the history of drug-induced TdP. Thus a series of advanced morphological ECG markers has been developed to provide secondary or investigative endpoints in cardiac safety studies. Some drugs, for instance, affect the morphology of the T-wave, leading to significant variability in the QT measurement. The additional information can potentially prevent termination of an inherently safe compound associated with benign QT changes, or ensure compounds with minute QT prolongation do not possess torsadogenic properties.

The advanced ECG biomarkers described in this article are available from advanced cardiac safety service providers. Greater precision improves the quality of data in the study and allows clinical researchers to reduce—in some cases by as much as 40 percent—the number of subjects required to reach statistical significance. Greater clarity regarding the drug's effect on QT interval provides an increased confidence in moving the compound to the next phase of development. Drug companies that integrate advanced biomarkers can potentially accelerate drug development programs, reduce false-positive and false-negative results, and pharmaceutical development costs.

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[7] JP Couderc, W Zareba, AJ Moss. Discrimination of HERG Carrier from Non-Carrier Adult Patients with Borderline Prolonged QTc Interval. Computers in Cardiology 2005;32:125−128.