



In a Heartbeat

In the face of the sensitive variables that constitute the cardiac safety challenge, promising new technologies may offer important solutions, state Susan Boyle of Spacelabs Healthcare and Sasha Latypova of iCardiac Technologies, Inc



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For pharmaceutical companies seeking to improve the productivity of their development pipelines, cardiac safety presents both an obstacle and an opportunity. Most drug developers are familiar with the difficulty of establishing a definitive cardiac safety profile for a compound in development. They may not know, however, that emerging technologies offer a way to significantly reduce uncertainty and curtail the time and cost associated with cardiac safety testing. By providing a solution for what has become a significant hurdle, these new technologies offer the opportunity to accelerate development, reduce false-positive and false-negative results and significantly reduce costs.

THE CARDIAC SAFETY CHALLENGE

That many drugs – whether in development or on the market – have the potential to cause a life-threatening arrhythmia, known as *torsades de pointes* (TdP), is a significant safety concern. It has been estimated that as many as 86 per cent of all new chemical entities tested in pharmaceutical development may show human ether-a-go-go related gene (hERG) inhibitory activity, and thus have a potential to affect the potassium ion channel (I_{kr}) and to prolong the heart's ventricular repolarisation process – the brief period between two heart beats which is known to be a vulnerable point for arrhythmia induction. This prolongation can trigger TdP, which can lead to sudden cardiac death (1).

Drug-induced arrhythmia is one of the leading reasons for withdrawals of marketed drugs. Since 1985, 24 drugs have been withdrawn from the US market because of safety concerns. Of these 24, nine were withdrawn for cardiac safety issues, of which five were dangerous drug-induced arrhythmias. Many

more drugs receive 'black box' warnings on their labels. Such safety warnings understandably discourage physicians from writing prescriptions, but in most cases the drug gets under-utilised relative to the true safety risk that it poses, because there are no precise and objective methods to determine which patients may be at risk for adverse events.

CARDIAC SAFETY TESTING TODAY

The current FDA-required clinical cardiac safety testing consists of measuring for possible drug-induced prolongation of a segment called the QT interval on electrocardiograms (ECGs) collected from healthy volunteers. On 17th October 2005, the FDA published official guidance for industry describing a battery of studies to evaluate a drug's potential to prolong ventricular repolarisation (2). The studies performed according to this guidance have been termed 'thorough QT' (TQT) studies. A 'positive TQT' study means that the drug was found to prolong the QT interval in excess of the threshold for regulatory

concern, and that it would require extensive ECG monitoring in the subsequent development programme. In many cases, however, a ‘positive TQT’ or even some QT signal in earlier drug development stages lead to termination of the development programmes, as both sponsors and regulators have become increasingly risk-averse in the wake of the recent high-profile market withdrawals of several blockbuster drugs.

This situation is of deep concern as QT interval prolongation is known to be a poor surrogate marker of arrhythmia liability. This marker has been widely criticised for its high rate of false-positive and false-negative results. Consider the case of cisapride (Propulsid), a drug for gastrointestinal motility disorders. When the drug was evaluated for cardiotoxicity in humans using FDA-required testing, cisapride exhibited a small prolongation of the QT interval and was thus 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 (3,4).

While the probability of a false-negative QT study is relatively low, the converse – false-positive QT studies – happens more frequently. A false-positive QT study may lead to an unnecessary termination or adverse labelling for a new and inherently safe drug. For instance, moxifloxacin (an antibiotic), amiodarone (an antiarrhythmic) and ziprasidone (an antipsychotic) are all associated with significant QT-prolongation, but do not have strong arrhythmogenic properties. A false-positive QT finding is more likely for drugs that may change the subjects’ heart rate or blood pressure (5). This is due to significant limitations of the current methods for measuring QT prolongation in ECG. The QT interval is known to be dependent on the heart rate (represented by the RR period on ECG) as well as on the history of heart rate. The heart rate itself varies, for example in adjusting to different levels of physical activity or autonomic nervous system state. When the heart rate changes either upward or downward, the QT interval also changes its duration. This change, however, is not instantaneous: in some cases it takes several minutes for the QT-RR relationship to stabilise at the new level of the heart rate. Given this highly complex and dynamic relationship, it is difficult to precisely quantify the drug’s effect on the QT interval without taking into account the changes in the RR interval as well as the history of the QT-RR relationships several minutes prior to the point of measurement.

Prior to the invention of computers and sophisticated signal processing technologies, it was almost impossible to formulate control for heart rate and its adaptation given the amount of data

that would need to be processed for every QT measurement. Since the early 1900s, several authors have proposed simple mathematical correction methods that measure QT interval, given the heart rate in the preceding heart beat. These methods – Bazett’s, Fredericia and individual correction formulae, just to name a few popular ones – are still in wide use. The simplicity of these methods is an obvious advantage. Unfortunately, they work well only when the subject’s heart rate does not significantly deviate from approximately 60 beats-per-minute. This is hard to achieve even in a well-controlled clinical trial setting, and it becomes even more problematic when the heart rate or autonomic state is changed by the drug. In addition, these methods ignore inter-subject QT-RR interval relationship differences. These limitations pose a significant challenge when trying to distinguish the changes in the QT interval by either drug-induced delayed repolarisation (which signifies potential arrhythmia risk) or from autonomic-mediated normal physiological responses (which should not lead to a cardiac safety concern). Fortunately, in the current climate of drug development, new technological solutions are helping to overcome the limitations of early cruder methods.

TECHNOLOGIES TO MAKE THE MOST OF QT PROLONGATION TESTING

The methodologies employed by the various ECG core labs to evaluate and measure the QT interval vary depending on the processes, hardware and software used. Approximately 75 per cent of TQT studies are now conducted using 12-Lead Holter monitors, which record and store continuous ECG data. The so-called ‘semi-automated’ approach to interval measurement is usually employed, which involves the placement of the fiducial points by the computer algorithm, with adjustment by the operator as deemed necessary. The operator’s training and experience vary widely from lab to lab, from individuals with only minimal training and supervision to board-certified cardiologists. Regardless of their experience, the operators may perform the measurements without much regard for heart rate or morphological changes, rendering the critical data less than optimal.

Since the methods of measurement, training and quality standards vary across the industry, it is crucial for sponsors to carefully evaluate the technological capabilities of the ECG core lab. 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 the continuous Holter recording to identify the periods of QT-RR

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adaptation due to significant changes in heart rate, and flag those periods as unsuitable for the ECG extraction and QT measurement. The drug developers can then be assured that the QT measurement was performed at the stable QT-RR relationship. This ECG data processing technique has been shown to reduce the variability of the QT measurement by up to 25 per cent. Another software-based technique, known as 'RR-bin' method, measures the QT interval at narrowly defined ranges of the heart rate ('RR bins'). This technique is especially useful when the drug is known to change the 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 evaluations that not only fulfill the regulatory requirements but also provide greater confidence in the cardiac safety data.

ADVANCED MORPHOLOGICAL ECG BIOMARKERS

The repolarisation process and its abnormalities underlie the vast majority of dangerous drug-induced arrhythmia problems. Thus the ability to study the repolarisation process, which is represented by the interval called T-wave within the QT interval, is very important for a proper characterisation of the drug's safety profile. The changes in the morphology of the T-wave have been linked to long QT syndrome – a rare congenital disorder that is highly analogous to the drug-induced repolarisation abnormality (6). 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 a history of drug-induced TdP.

It is recognised that some drugs may affect the morphology of the T-wave, and thus lead to significant variability in the measurement of the QT interval. In such development programmes, it is important to consider incorporating advanced morphological ECG markers. Collecting this data as secondary or investigative endpoints in a cardiac safety study, along with the standard QT/QTc parameters, is likely to provide important additional information as well as improve the precision of QT measurement. This supplementary information can potentially help to avoid the cessation of development for an inherently safe compound associated with 'benign QT' changes, or ensure that compounds with very small QT-prolongation do not actually have torsadogenic properties.

FUTURE OUTLOOK FOR ADVANCED ECG TECHNOLOGIES IN CARDIAC SAFETY STUDIES

The increased interest in advanced technologies utilising Holter and telemetric ECG recordings was highlighted at the recent meeting led by Drs Couderc (University of Rochester Medical Center, Rochester, New York) and Stockbridge (FDA-CDER, Silver Spring, Maryland). On 16th January 2008, a group of over 40 industry, academia and regulatory experts gathered at the FDA's campus in Silver Spring, Maryland, to discuss the future of these technologies and to initiate the telemetric and Holter ECG warehouse project. The initial purpose of this

warehouse – for validation of the novel ECG biomarkers and technologies – demonstrates the growing interest in tools that improve the quality of the TQT data submitted to the FDA.

Recently, to address the limitations of the current cardiac safety testing process, a group of specialist companies have joined forces to create the drug development industry's most comprehensive and technologically advanced solution for determining how drugs affect the heart. The Cardiac Safety Network integrates preclinical and clinical cardiac safety analysis services, and offers a suite of advanced ECG biomarkers and analytical software tools that greatly improve the precision of TQT studies and provide the ability to study the drug's effect on the QT interval independently from its effect on the heart rate or blood pressure. Greater precision improves the quality of the data in the study and allows clinical researchers to reduce – in some cases by as much as 40 per cent – 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. ♦

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