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Safety First

Boaz Mendzelevski, a Cardiac Safety Consultant, examines drug-induced repolarisation abnormalities and proarrhythmia with regard to improving cardiovascular safety in drug development

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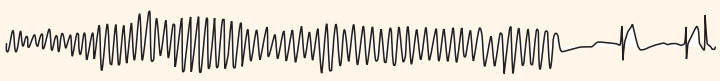
Cardiac safety is a relatively new field in drug development clinical research. It first emerged as a regulatory focus after the high-profile withdrawals of drugs such as terfenadine and cisapride in the 1990s, and became synonymous with drug-induced QT prolongation and its associated cardiac arrhythmia – *torsades de pointes* (TdP). Recent regulatory guidance, most notably ICH-E14, brought cardiac safety into the forefront of regulatory medicine. Since 2000, cardiac safety became the primary reason for drug withdrawals and non-approval of new drugs. Early detection of potential QT prolongation and TdP liability is now an essential component of the drug development paradigm. Most recently, the scope of cardiac safety drug development has expanded and now covers three major areas of potential drug-induced cardiac toxicity: cardiac repolarisation, or drug-induced QT prolongation leading to cardiac arrhythmia; vascular thrombosis leading to myocardial ischemia and infarction; and direct myocardial toxicity leading to loss of cardiac tissue and heart failure. This article will provide an up-to-date overview of the evolving field of drug cardiac safety and the science behind drug-induced cardiotoxicity, current regulatory requirements and drug development strategies to improve management of drug cardiac safety and bring safer medicines to market.

HISTORICAL AND EPIDEMIOLOGICAL BACKGROUND

Recent high-profile cardiovascular adverse drug reactions (ADRs) of newly-approved drugs have triggered public concerns, and resulted in increased regulatory focus and the development of new regulatory guidance concerning cardiac safety of drugs under development. Terfenadine, the first non-sedating antihistamine, also became the first non-antiarrhythmic drug to be formally associated with a rare but serious cardiac arrhythmia, TdP (see Figure 1). This life-threatening arrhythmia was reported when terfenadine was taken concomitantly with certain other drugs, including certain antibiotic and antifungal agents with intrinsic metabolic inhibitory (Cytochrome P450 isozyme 3A4) and QT prolongation properties.

Cisapride, a gastrointestinal prokinetic (antihemetic) drug, was also associated with QT interval prolongation and fatalities due to

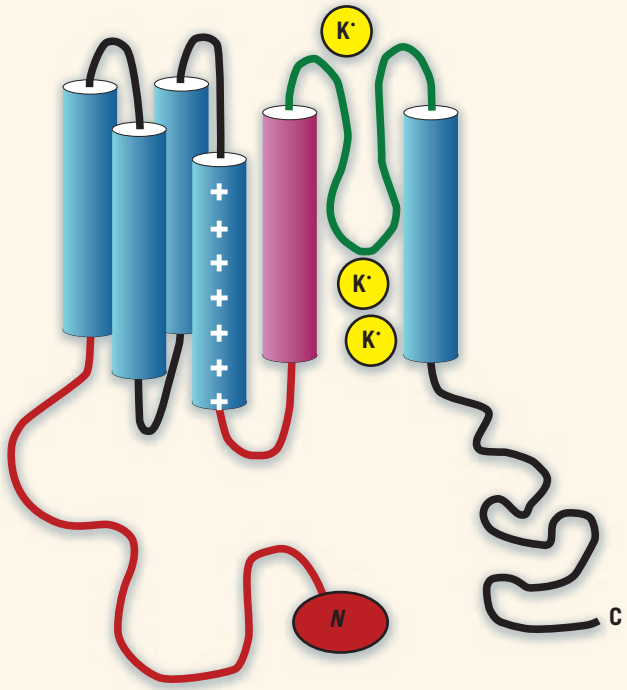
Figure 1: *Torsades de pointes* (TdP) in a patient with acquired long QT syndrome



TdP arrhythmia. Most of the patients who suffered cisapride-induced arrhythmia were treated concomitantly with other drugs that interfered with the cisapride metabolism, primarily macrolide antibiotics and imidazole antifungals. Similar to terfenadine, cisapride was shown to be essentially metabolised by the hepatic CYP3A4 isozyme, and is also a potent blocker of the rapid delayed rectifier (Ikr) potassium channel, also known as the hERG (human ether-a-go-go-related gene) channel.

The list of drugs associated with QT prolongation and TdP, some of which were also withdrawn from the market or denied approval due to cardiac safety concerns, has rapidly extended. It involves drug categories such as antihistamines, antibiotics (including quinolones, macrolides, antimalarials and imidazole antifungals), antipsychotics (neuroleptics), antidepressants, antimagrains (triptans) and other drugs. See (1) for a comprehensive list of drugs associated with QT interval prolongation, with or without evidence for pro-arrhythmia (TdP).

Figure 2: Schematic diagram of the cardiac hERG/Ikr channel alpha-subunit



The incidence of drug-induced TdP in the general population is largely unknown. One population study recently estimated the annual incidence of drug-induced TdP in the Swedish population at four per 100,000 (2). It has also been estimated that only one per cent of serious ADRs are ever reported (3).

Drug-Induced Cardiac Toxicity

The field of drug-induced cardiac toxicity has taken a sharp turn in recent years and is no longer limited to drug-induced aberration of repolarisation and proarrhythmia. The key issues influencing the current state of the extended cardiac safety field are summarised below.

Delayed Ventricular Repolarisation

Virtually all drugs that prolong the QT interval and cause TdP also block the hERG channel, or reduce the IKr current in cardiac myocytes (4). Unfortunately, this finding is not specific, since many drugs that do not appear to cause TdP also block this current. The promiscuity of the hERG channel to drug interaction is quite intriguing given the diversity of the drugs that have been shown to interact with the channel. The hERG potassium channel is composed of four identical tetrameric subunits (alpha-subunits), each consisting of six trans-membrane domains, labelled S1 to S6, with the S5-S6 segment serving as the pore (entrance) area (see Figure 2). It is expected that a better understanding of the channel properties, with the appropriate technology, may lead to the future development of safer drugs with lower affinity to the hERG channel, hence presenting a more favourable cardiac safety profile.

However, cardiac ventricular repolarisation is a much more complex physiological phenomenon than the one represented by a single ion channel, as critical as it may be. The repolarisation process happens at multiple functional-anatomical levels. These are typically described as the molecular level, the cellular level and the whole organ and body level. At the molecular level, multiple ionic currents, modulated by highly specialised ion channels such as the hERG channel, generate electrical currents and trans-membrane electrical potentials. At the cellular level, groups of cells, functioning together as a tissue, generate action potentials which are vital for the propagation of the cellular electrical currents throughout the heart. Finally, at the whole organ level, the heart acts in a well-coordinated electromechanical process to convert the electrical energy onto contractile energy, thus providing the pump action that forces oxygenated blood into the major arteries and throughout the body's organs.

Mechanism of Delayed Repolarisation -Related Arrhythmogenesis

The ventricular myocardium in larger mammals has been shown to comprise three distinct cell types organised in layers: epicardial cells in the outer cardiac myocardium layer; the recently described M cells in the mid-myocardial layer; and endocardial cells in the inner layer. The M cell action potential duration (APD) is longer, and they have a steeper APD-rate relationship. Reduction in net repolarising current (by drug block or genetic mutation of the potassium channel) generally leads to a preferential prolongation of the M cell action potential, responsible for a prolongation of the QT interval and an increase in transmural dispersion of repolarisation (TDR) (5). Amplification of spatial dispersion of repolarisation within the ventricular myocardium is thought to generate the principal arrhythmogenic substrate. The accentuation of spatial

dispersion is typically secondary to an increase of transmural and transseptal dispersion of repolarisation, and the development of early after depolarisation (EAD), an induced triggered activity which underlies the substrate and trigger for the development of TdP arrhythmias (see Figure 3) observed in drug-induced and congenital long QT syndromes (6).

Short QT Syndrome

The short QT syndrome (SQTS) is a new clinical entity that is associated with a high incidence of syncope, atrial fibrillation, ventricular arrhythmia and sudden cardiac death. The syndrome usually affects young and healthy people with no structural heart disease and may be present in sporadic cases as well as in families (7). Patients with this congenital electrical abnormality are characterised by rate-corrected QT intervals of less than 320 milliseconds and peaked tall T waves on the resting electrocardiogram (ECG). The prevalence of the SQTS is currently unknown; however, less than 50 affected families have been reported worldwide.

SQTS is a genetically heterogeneous disease; missense mutations in KCNH2 (hERG) linked to a gain-of-function of the IKr channel have been identified in the first two reported families with familial sudden cardiac death (8). Recently, two further gain-of-function mutations were described in the KCNQ1 gene (encoding the IKs channel) and in the KCNJ2 gene (encoding the Kir2.1 protein). As in the LQTS, the possible substrate for the development of ventricular tachyarrhythmias may be a significant transmural dispersion of the repolarisation due to a heterogeneous abbreviation of the action potential durations.

The implantable cardioverter defibrillator (ICD) has been suggested as the therapy of choice in patients with syncope and a positive family history of sudden cardiac death. However, ICD therapy in patients with SQTS has an increased risk for inappropriate shock therapies due to possible T wave over sensing. Since shortening of the QT interval is likely due to an increase in the outward current, blocking the current with antiarrhythmic drugs which are known to increase the QT interval may be a therapeutic approach for treating SQTS. However, to date, only quinidine has shown some effectiveness in suppressing the inducibility of ventricular tachycardia or ventricular fibrillation in some patients, and may therefore be considered as an adjunct to ICD therapy in selected patients.

This association between QT interval modulation (in this case shortening) and proarrhythmia, in some cases involving the hERG channel, attracted some attention within the pharmaceutical scientific community. The assumption is that, similar to the implications of the congenital LQTS to drug development, SQTS may also prove relevant for drug safety due to drug-induced proarrhythmia by a gain-of-function modulation of the IKr channel (eg. potassium channel openers).

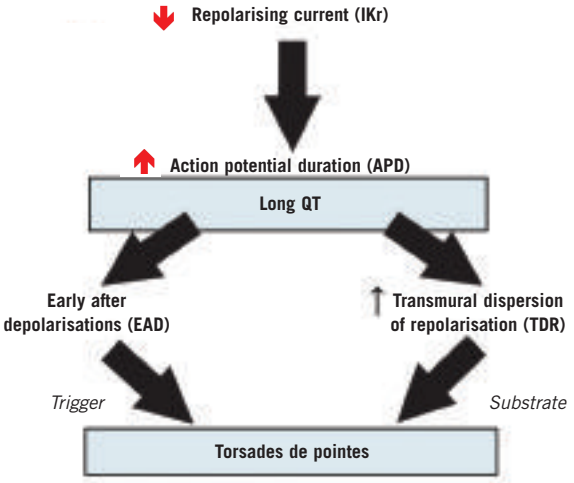
THE REGULATORY PERSPECTIVE

The CPMP and ICH Initiatives

In December 1997, the EU Committee for Proprietary Medicinal Products (CPMP) was the first regulatory agency to issue a formal guidance document underlining the strategy for assessing the propensity of new (non-antiarrhythmic) medicinal products to prolong the QTc interval (9). This guidance includes recommendations for non-clinical testing as well as clinical investigations, required to demonstrate a favourable cardiac safety profile of new chemical entities (NCEs).

Nearly five years later, on 15th November 2002, the US Food and Drug Administration (FDA) and Health Canada (HC) issued a joint preliminary concept paper on clinical strategies for evaluating the effects of NCEs on QT/QTc interval prolongation (10). The concept paper was adopted by the International Conference on Harmonization (ICH) for global implementation, and entered the ICH Step 1 process in February 2003, as ICH topic E14. The ICH E14 document was finally approved by the ICH steering committee on 12th May 2005 (11).

Figure 3: Postulated mechanism of drug-induced arrhythmogenesis



ICH topic S7B, which is primarily concerned with the non-clinical investigation of the effects of new drugs on cardiac repolarisation, was in the ICH development pipeline well before E14. However, the increased regulatory interest in cardiac safety through E14 has renewed the interest in S7B and both documents were developed and finalised simultaneously.

ICH-S7B

Topic S7B of the ICH is dedicated to the non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals (12). The objectives of these non-clinical safety pharmacology studies are to identify the potential of the test substance and its metabolites to delay ventricular repolarisation and induce cardiac arrhythmia.

As described above, the complex repolarisation process happens at multiple functional-anatomical levels. Consequently, no single assay can test the entire repolarisation process and predict which drugs will produce TdP in humans. Instead, multiple assays were designed to test the functionality at each level, including *in vitro* ion channel (hERG/Ikr) tests, tissue (purkinje) repolarisation tests and whole animal *in vivo* tests (typically in dog). In addition, whole heart preparations designed to provide pro-arrhythmia models (for example the Langerdorf-perfused rabbit heart) were also developed. S7B suggests a continuous integrated risk stratification system, grading the integrated risk as low, medium or high.

Unfortunately, the applicability of non-clinical studies to clinical risk assessment and their ability to predict drug-induced arrhythmia in humans are still under intensive debate. It has been shown that many of the drugs that prolong the QT interval *in vitro* or *in vivo* are not associated with drug-induced TdP (13). This has led to the assumption that some drugs prolong the QT interval homogeneously across the myocardium, meaning they do not increase TDR, therefore producing a 'safe' QT prolongation, while others do so in a non-homogeneously pattern, therefore increasing TDR and producing a potentially 'arrhythmogenic' QT prolongation. Nonetheless, even with the ongoing controversy, non-clinical safety assessments are an important component of the current cardiac safety paradigm, regardless of the scepticism currently expressed by some regulatory agencies, primarily the US FDA.

ICH-E14

The ICH-E14 guidance calls for the majority of NCEs to undergo a thorough assessment of their effect on the QTc interval. At the heart of the guidance is a single clinical pharmacology trial, the 'thorough QT/QTc (TQT) study', typically conducted in healthy volunteers. The study is designed and powered to detect a small, mean change of up to five milliseconds in the QTc interval and an upper 95 per cent confidence limit of less than 10 milliseconds. The results of the TQT study are primarily used to define the intensity of ECG monitoring during the subsequent drug development programme.

ICH-E14 Implementation – Regional Variations

The ICH process concludes in Step 5, the implementation period, during which an implementation working group (IWG) monitors the implementation process, provides advice and support, and collects questions and responses. The E14 implementation process has been completed in the US and Europe, but is still ongoing in Japan, the third ICH region. Interestingly, in March 2007 the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) unveiled an initiative that is aimed at closing the West-to-East 'drug lag', meaning the long delay (of up to five years) in the regulatory approval and commercial availability of new drugs in Japan (14). The PMDA is promising pharmaceutical companies a more streamlined and transparent regulatory process in return for conducting studies in Japan simultaneously with the West, to shorten the time to approval and market (15). It is expected that as part of this initiative the PMDA will also release their much anticipated version of the E14 guidance, to allow companies to better prepare for the new requirements.

PRINCIPALS OF THOROUGH QT STUDIES

At the centre of the new regulatory initiatives is the need for a well-designed, appropriately powered and well-executed 'thorough QT/QTc (TQT) study'. The study should have the power to provide a categorical answer to the potential pro-arrhythmic risk of drugs in development. However, experience with the new TQT study is still limited and its impact on the late stage development and regulatory approval process is not yet fully understood.

The hallmarks of the TQT study are the requirements to test the investigational product at the expected therapeutic dose and at a supratherapeutic dose, aimed to test the worst-case exposure scenario. In addition, the study should incorporate two control arms – placebo and active control – the latter used to establish assay sensitivity and prove that negative studies are genuine and not false. The statistical design and power considerations have been the subject of intensive discussions within the industry and regulatory agencies, however it has generally been accepted that for drugs with short half-life, a single-dose administration, cross-over design is preferred and will result in a substantially smaller sample size compared with multiple-dose, parallel group study. The analysis of the TQT data has also attracted significant attention and is still evolving with increasing emphasis on concentration-effect analysis methods.

PLACE OF CARDIAC SAFETY IN THE DRUG DEVELOPMENT CYCLE

With the current regulatory focus and new guidelines concerning cardiac safety in drug development, most NCEs under development are required to demonstrate a favourable cardiac safety profile. For small molecular entities this requires a well-designed and performed TQT study, typically conducted before end of Phase II. It is the experience of the author that the US FDA would not usually allow sponsors to progress into Phase III without the required TQT data, unless they agree to continue with intensive ECG monitoring during Phase III, until their TQT data is available.

The lack of clear advice regarding the applicability of the new requirements for large molecules, including peptides, vaccines and other biological compounds, as well as cytotoxic drugs, is causing considerable confusion within the industry. While large peptides are not expected to block the hERG/Ikr channel, there are examples of such drugs being associated with QT prolongation via other mechanisms. Consequently, no general

regulatory advice is available and each drug is considered on its own merits.

Drugs that do not lend themselves to the TQT study design due to high toxicity or low tolerance may still be required to undergo cardiac safety assessment using alternative approaches. These approaches may include pooling or meta-analysis of data from early development studies, collecting ECG data from large late development studies or applying more robust PK:PD analyses. It is also expected that the development of new, innovative and highly-sensitive testing tools and methods will allow more drugs to be assessed for cardiac safety despite their inability to undergo the TQT study as defined today.

FUTURE TRENDS AND STRATEGIES

While the QT interval continues to be highly criticised as a relatively poor assay due to its low predictive value, it remains the only widely acceptable biomarker for drug-induced proarrhythmia. New diagnostic tools and highly sensitive biomarkers of proarrhythmia are under development and it is widely anticipated that new validated and approved methods and biomarkers may soon be available to replace, or as adjunct, to the good old QT interval.

CONCLUSION

The evolution of drug safety assessments, and the regulations enforcing them, gained a significant momentum during the past decade following experience with high profile pharmaceutical disasters, some of which caused considerable harm and even loss of human lives. It is expected that while the tools and methods available for assessing drug cardiac safety will continue to evolve and their development be facilitated, the regulatory requirements may also advance to maintain the newly-established safety standards reflecting the new technologies and methods to assess cardiac safety. ◆

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References

1. The University of Arizona Center for Education and Research on Therapeutics, Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia, http://www.torsades.org/medical-pros/drug-lists/drug-lists.htm
2. Darpo B, Spectrum of Drugs Prolonging QT Interval and the Incidence of Torsades de Pointes, *European Heart Journal*, Supplement K; 3: K70-K80, 2001
3. http://www.torsades.org/medical-pros/research-focus.htm
4. Sanguinetti MC, Jiang C, Curran ME and Keating MT, A Mechanistic Link Between an Inherited and an Acquired Cardiac Arrhythmia: HERG encodes the IKr potassium channel, *Cell*; 81: pp299-307, 1995
5. Antzelevitch C, Modulation of Transmural Repolarization, *Ann NY Acad Sci*; 1,047: pp314-323, 2005
6. Antzelevitch C and Shimizu W, Cellular Mechanisms Underlying the Long QT Syndrome, *Curr Opin Cardiol*; 17: pp43-51, 2002
7. Brugada R, Hong K, Cordeiro JM and Dumaine R, Short QT Syndrome (Review), *CMAJ*; 173(11): pp1,349-1,354, 2005
8. Gaita F, Giustetto C and Bianchi F *et al*, Short QT syndrome: a Familial Cause of Sudden Death, *Circulation*; 108: pp965-970, 2003
9. Committee for Proprietary Medicinal Products, Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products (CPMP/986/96) *EMEA*, 17th December 1997
10. US Food and Drug Administration/Health Canada, The clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs, Preliminary Concept Paper, 15th November 2002, http://www.fda.gov/ohrms/dockets/ac/03/briefing/pubs%5Cprelim.pdf
11. ICH Harmonised Tripartite Guideline, The Clinical Evaluation of QT/QTc Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs, E14, Current Step 4 version, http://www.ich.org/LOB/media/MEDIA1476.pdf, 12th May 2005
12. ICH Harmonised Tripartite Guideline: The Non-Clinical Evaluation of The Potential For Delayed Ventricular Repolarization (QT Interval Prolongation), by Human Pharmaceuticals S7B, Step 4 of the ICH Process, 12th May 2005
13. Redfern WS, Carlsson L and Davis AS *et al*, Relationships Between Preclinical Cardiac Electrophysiology, Clinical QT Interval Prolongation and Torsade de Pointes for a Broad Range of Drugs: Evidence for a Provisional Safety Margin in Drug Development, *Cardiovasc Res*; 58: pp32-45, 2003
14. Yoshiaki U, Pharmaceuticals & Medical Devices Agency (PMDA), Perspectives for Global Drug Development Strategies – Introduction of a Draft Paper, 'Basic Principles on Global Clinical Trials', Presentation at the PMDA Session in the EURO DIA Annual Meeting, Vienna, Austria, 28th March 2007
15. McCurry J, Japan Unveils 5-Year Plan to Boost Clinical Research, *The Lancet*; 369, 21st April 2007