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REVIEW: FRONTIERS IN PHARMACOLOGY

Moving towards better predictors of drug-induced torsades de pointes

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Drug-induced torsades de pointes (TdP) remains a significant public health concern that has challenged scientists who have the responsibility of advancing new medicines through development to the patient, while assuring public safety. As a result, from the point of discovering a new molecule to the time of its registration, significant efforts are made to recognize potential liabilities, including the potential for TdP. With this background, the ILSI (HESI) Proarrhythmia Models Project Committee recognized that there was little practical understanding of the relationship between drug effects on cardiac ventricular repolarization and the rare clinical event of TdP. A workshop was therefore convened at which four topics were considered including: Molecular and Cellular Biology Underlying TdP, Dynamics of Periodicity, Models of TdP Proarrhythmia and Key Considerations for Demonstrating Utility of Pre-Clinical Models. The series of publications in this special edition has established the background, areas of debate and those that deserve scientific pursuit. This is intented to encourage the research community to contribute to these important areas of investigation in advancing the science and our understanding of drug-induced proarrhythmia.
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Abbreviation: TdP, torsades de pointes

Recognizing the cardiac safety of promising new drugs is an important aspect of assuring the expeditious advancement of the best candidates targeted at unmet medical needs while assuring the safety of clinical trial subjects and patients. Torsades de pointes (TdP), a potentially life-threatening ventricular arrhythmia is associated with prolonged cardiac repolarization and can be drug-induced (Figure 1). TdP is extremely rare with non-antiarrhythmic drugs (Strnadova, 2005), but when it occurs may lead to syncope, ventricular fibrillation and sudden death of essentially healthy individuals who are treated for minor illnesses, such as the use of antihistamines in the treatment of allergy. The list of drugs associated with TdP is now extensive and TdP has become one of the major causes for withdrawal of drugs from the market (Shah, 2002a, b; Strnadova, 2005). The fact that a potentially life-threatening proarrhythmia can escape undetected during both non-clinical and clinical drug development must be regarded as a severe shortcoming, but has several explanations: (1) the incidence is extremely low and was, as an example, estimated to be 1.2 cases in 100 000 patients on cisapride (Barbey *et al*., 2002); (2) the background incidence of TdP is also very low in most patient populations, whereas the incidence of other forms of polymorphic ventricular tachycardias in patients with pre-existent cardiovascular disease is at least two order-of-magnitude greater (Darpo, 2001); (3) different forms of polymorphic ventricular tachycardias can often be difficult to differentiate and (4) clinical studies are grossly underpowered to detect adverse events as rare as TdP. It can be calculated that to exclude a fivefold increased risk of TdP with a 'cisapride-like' drug studied in the same population, it would take approximately one-half million patients studied during 1 year (Brass *et al*., 2006). Even though very large observational studies can be conducted once a drug is marketed and a sufficient number of patients have used it (see for example (Pratt *et al*., 1996)), it has proven very difficult to conclusively confirm a drug's proarrhythmic liability using a pharmaco-epidemiological approach. (Hanrahan *et al*., 1995; Staffa *et al*., 1995; Pratt *et al*., 1996; de Abajo and Rodriguez, 1999; Tooley *et al*., 1999;

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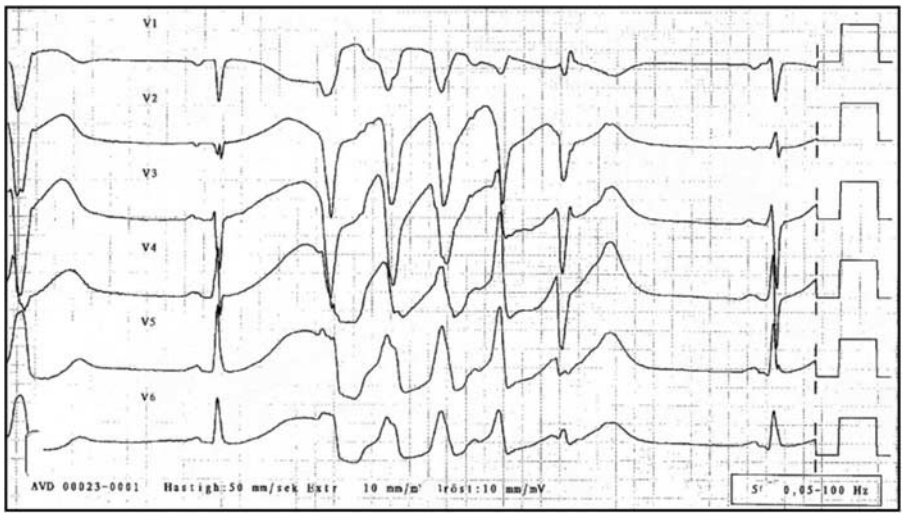

Figure 1 Twelve-lead ECG recorded from a woman who was on continuous telemetry in an ICU after having taken an over-dose of thioridazine, a neuroleptic drug. After a pause, the T wave of the sinus beat is markedly abnormal and interrupted on the down slope by a 5-complex run of ventricular extrasystoles with varying morphology. This episode of polymorphic ventricular tachycardia had many of the characteristic features of TdP and was non-sustained. On several other occasions the TdP degenerated into ventricular fibrillation, which required defibrillation. Paper speed: 50 mm s^{-1}. ECG, electrocardiogram; TdP, torsades de pointes.

Walker *et al*., 1999; Enger *et al*., 2002). When these considerations are taken together, it is clear that there is an urgent need for improved non-clinical and/or clinical biomarkers for proarrhythmic risk, which can be applied successfully during the development process.

Over the last 4 years, the Cardiovascular Safety Projects Committee, under the auspices of International Life Sciences Institute—Health and Environmental Sciences Institute (ILSI/HESI), has sanctioned, developed and overseen the execution of a series of prospective studies which evaluated three of the most highly accepted non-clinical assays of prolonged cardiac repolarization (a substrate or risk factor for TdP): potassium repolarizing currents evaluated in heterologously expressed hERG channels, action potential duration assessed in Purkinje fibers isolated from dogs and the QT/QTc interval studied in conscious telemeterized dogs. (ICH Harmonized Tripartite Guideline S7B, 2005; Hanson *et al*., 2006) Each of these assays were evaluated in a blinded fashion using both 'positive' and 'negative' drugs, for which there was strong clinical evidence of their potential for proarrhythmic propensity or lack thereof after many years on the market. A similar initiative was conducted by the 'QT Interval Prolongation: Project for Database Construction Working Group' (QT PRODACT) under the auspices of the Japanese Pharmaceutical Manufacturer's Association. The Japanese investigators tested an expanded list of clinically positive and negative agents and employed additional non-clinical assays of cardiac ventricular repolarization (Omata *et al*., 2005). In each of these projects the sensitivity of the preclinical assays of delayed cardiac repolarization was reaffirmed. The high sensitivity comes at a price of low specificity, however, and it is widely recognized that the uncritical interpretation of the results of these non-clinical assays may cause many potentially valuable drugs to be terminated during either non-clinical or clinical development.

These limitations of non-clinical assays have led to increased requirements on the use of QT prolongation in man as the predictive biomarker of proarrhythmic risk (ICH Harmonized Tripartite Guideline E14, 2005). The 'thorough QT study' in healthy volunteers is now rapidly evolving as the discriminatory tool to differentiate 'safe' from 'unsafe' drugs, despite well known and described limitations with this biomarker; vardenafil, as one example, causes a mild QT prolongation in this study, despite the absence of any non-clinical 'signals' and has been extensively used during several years without any clear association with proarrhythmias. There are also other examples of drugs that mildly prolong the QT interval, but for which either extensive experience from clinical practice (for example, moxifloxacin, sodium pentobarbital and ebastine) (Paakkari, 2002; FDA, 2003) or clinical studies in high risk groups (for example, ranolazine (Morrow *et al*., 2007)) support the lack of proarrhythmic liability. In the case of ranolazine, the lack of proarrhythmia is probably based on other mitigating properties of the drug (Antzelevitch *et al*., 2004); however, the evidence to support this claim will require extensive clinical experience and may always be clouded by the issue of the existent background incidence of TdP in the general patient population.

At present, it could be argued that drugs with any effect on cardiac repolarization, irrespective of its magnitude, will only be progressed through clinical development and to the market, if there exist a substantial unmet medical need and where the risk/benefit is felt acceptable, such as within oncology. Consequently, a major challenge today in pharmaceutical development is to identify experimental models, composite strategies and alternative biomarkers of cardiac risk, which can rank order new drug entities according to their risk of producing proarrhythmias, once a mild effect on cardiac ventricular repolarization has been detected.

The Proarrhythmia Models Projects Committee of the ILSI/HESI was formed to address this important objective. The

urgent need for strategies with markedly improved predictive value was further emphasized by the recent adoption of ICH S7B, which prescribes that all new chemical entities should undergo testing with two standard non-clinical assays (hERG and *in-vivo* QT assessment). A workshop of experts in the field of cardiovascular safety was convened in November 2005; which included individuals from the academic, regulatory and pharmaceutical communities with expertise in molecular and cellular sciences, non-clinical models and scientific approaches to understanding the potential proarrhythmic properties of drugs. The objectives of the workshop were to develop a better fundamental understanding of the emerging science, trends and methods and methodologies that relate to predicting drug-induced TdP. Specific objectives were to: (1) identify the underlying (known or novel) mechanisms for drug-induced TdP arrhythmia to develop better tools for identifying drugs at risk, (2) evaluate and assess emerging non-clinical methodologies for predicting drug induced TdP, (3) identify biomarkers in non-clinical studies that may be applied to clinical testing for drug-induced arrhythmia, (4) identify the critical aspects of non-clinical and clinical methods of evaluating potential for drug-induced TdP in the context of public-health decision-making, and (5) identify short- and long-term priorities for developing better predictors for drug-induced TdP.

The first day of the workshop was devoted to series of brief presentations based on outlines and references provided by each of the speakers to the workshop participants in advance of the meeting (available at: http://www.hesiglobal.org/Events/TdPWorkshop.htm.). The subjects of these presentations are presented as individual manuscripts in this special issue. On the second day of the 2-day meeting, breakout sessions addressing four key topics were convened: (1) molecular and cellular biology underlying TdP; (2) dynamics of periodicity; (3) models of TdP proarrhythmia and (4) key considerations for demonstrating utility of pre-clinical models. The background to each session topic, the salient points of discussion and debate and the important recommendations for further study are also summarized in this special issue.

Drug-induced QT prolongation and TdP represent in two ways a significant issue in relation to human health and medical needs: (1) drugs with this property may cause sudden death in susceptible individuals and must, therefore, be identified (and in most cases abandoned) during clinical development and (2) drugs that target important unmet medical needs are screened out during the development process using assays with inadequate specificity to identify human proarrhythmia risk. Some of these drugs may not be proarrhythmic, but will, nonetheless, never be available for patients with important medical needs. Retrospective studies have suggested that for every 15 new molecular entities entering the clinical phase, one new drug is marketed after many years of testing. Thus, identifying that one promising agent using measures with sufficient predictive value for drug-induced TdP remains of paramount importance. These proceedings will inform the reader of the background to this important area of study and the key topics of discussion and debate. Most importantly, the proceedings will provide direction for further research intended to create and validate improved non-clinical models of drug-induced TdP. A workshop will be convened by the Proarrhythmia Models Project Committee in 2–3 years from now at which the advancements in these promising areas of study will be reviewed. Based on this review, the models and scientific strategies confronting this significant challenge that hold the greatest promise will be considered as future topics of collaborative research under the auspices of ILSI/HESI. It is hoped that the scientific community will be encouraged by the ideas promoted in this workshop proceedings to contribute to these investigations.

Conflict of interest

The authors of this paper are employed in the pharmaceutical industry or serve as consultants to the pharmaceutical industry. However, the subjects presented in the paper do not advocate or support purchase of any of the products offered by the respective organizations.

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