Journal of Pharmacological and Toxicological Methods 68 (2013) 7–12

Contents lists available at SciVerse ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Original article

A public–private consortium advances cardiac safety evaluation: Achievements of the HESI Cardiac Safety Technical Committee

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ARTICLE INFO

Article history:
Received 6 March 2013
Accepted 26 March 2013

Keywords:
Animal models
Cardiac repolarization
Cardiac safety
Cardiac biomarkers
FDA
ILSI/HESI
Integrated risk assessment
Stem cells

ABSTRACT

Introduction: The evaluation of cardiovascular side-effects is a critical element in the development of all new drugs and chemicals. Cardiac safety issues are a major cause of attrition and withdrawal due to adverse drug reactions (ADRs) in pharmaceutical drug development. **Methods**: The evolution of the HESI Technical Committee on Cardiac Safety from 2000-2013 is presented as an example of an effective international consortium of academic, government, and industry scientists working to improve cardiac safety. **Results and Discussion**: The HESI Technical Committee Working Groups facilitated the development of a variety of platforms for resource sharing and communication among experts that led to innovative strategies for improved drug safety. The positive impacts arising from these Working Groups are described in this article.

1. Introduction

The ILSI Health and Environmental Sciences Institute (HESI) was established in 1989 to engage scientists from academia, government, industry, and other research institutes to identify and move towards resolution of global health and environmental issues of common and critical concern (www.hesiglobal.org). HESI serves as a coordinating resource for these public–private partnerships by forming scientific committees. Through the HESI committee mechanism, scientists share responsibility for identifying research topics, developing the research program and study design, and interpreting and applying the study results.

Cardiac safety issues have been and continue to be a major cause of attrition and withdrawal due to Adverse Drug Reactions (ADRs) in pharmaceutical drug development (Lasser et al., 2002; Laverty et al., 2011; Piccini et al., 2009; Redfern et al., 2010; Stevens & Baker, 2009; Stummann et al., 2009). This attrition occurs in both the nonclinical and clinical phases of development and can extend to the post-market approval phase (Laverty et al., 2011; Redfern et al., 2010). Furthermore, cardiovascular safety liabilities cause delays in development, labeling restrictions, and negative impacts on physician prescribing preferences, which reduce patient benefit and limit the potential for product success (Laverty et al., 2011; Redfern et al., 2010). Effective cardiovascular evaluation is also critical in assessing risk and subsequently protecting public health in the context of exposure to environmental chemicals. A WHO report on the global composite impact of chemicals on public health reported that 16% (7–23%) of the total burden of cardiovascular disease was attributed to environmental chemical exposure, corresponding to

Abbreviations: ADRs, adverse drug reactions; CDER, Center for Drug Evaluation and Research; cTn, cardiac troponin; CV, cardiovascular; EMA, European Medicines Agency; EWG, Expert Working Group; ECG, electrocardiogram; HESI, Health and Environmental Sciences Institute; hERG, human ether-á-go-go related gene; ICH, International Conference on Harmonization; IKr, delayed rectifier potassium current; ILSI, International Life Sciences Institute; IND, investigational new drug; JPMA, Japanese Pharmaceutical Manufacturer Association; NDA, new drug application; PRODACT, project for database construction; PSTC, Predictive Safety Testing Consortium; QTc, corrected QT interval; SC-CM, stem-cell derived cardiac myocytes; TdP, torsades de pointes; TQT, thorough QT study; US FDA, United States Food and Drug Administration.

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http://dx.doi.org/10.1016/j.vascn.2013.03.008

2.5 million deaths per year (Prüss-Üstün & Corvalan, 2006; Weinhold, 2011). In the context of both drug and environmental safety concerns, the Cardiac Safety Technical Committee is working to develop improved predictors of adverse cardiac events.

Drug cardiovascular safety has been a priority at HESI for over a decade. In the year 2000, the need to better understand the scientific basis for drug-induced delayed ventricular repolarization (QTc prolongation) and Torsades de Pointes (TdP) was proposed as a timely and important area of focus for HESI and the drug safety community. An exploratory meeting was held in August of 2001 at ILSI headquarters in Washington D.C. and later that year, HESI initiated an experimental program to better characterize nonclinical models as predictors of QTc prolongation. While this work matured and evolved from 2000 to 2008, a cardiac biomarker (i.e. troponin) research program was initiated within the context of a broadly based HESI Biomarker development committee. In 2008, the present-day Cardiac Safety Technical Committee was endorsed by the HESI Board of Trustees to centralize cardiac-focused efforts at HESI and synergize resources, expertise, and outcomes. Since its inception, the Cardiac Safety Technical Committee has expanded its program of work to support an improved understanding of cardiovascular structure and function and its assessment for safety and risk. This work can serve as an important resource in reducing unanticipated adverse drug effects and evaluating the potential impact of environmental or chemical exposures.

The diverse base of the Cardiac Safety Technical Committee allows HESI to combine resources (intellectual, experimental, and financial) to pursue innovative strategies in a collaborative, non-biased approach. This diversity comes from more than 21 industry organizations and 23 academic and government institutions from North America, Europe and Asia. The members are a cross-disciplinary group of scientific experts from the fields of clinical medicine, pathology, imaging, safety pharmacology, physiology, toxicology, bioinformatics and many more.

The working groups of the Cardiac Safety Technical Committee evolved from the expertise of the members, the need to address cardiac safety issues as a major cause of attrition in drug development, and concern around cardiac effects potentially resulting from environmental exposures. The current working groups include: proarrhythmia, cardiac biomarkers, integrated strategies, and stem cell-derived cardiomyocytes subteam. The evolution and current projects of the working groups are described in more detail below.

Since its inception in 2008, the HESI Cardiac Safety Technical Committee has informed the practice and philosophy of cardiac safety evaluation through a significant body of novel research and expert consultation. For example, the program has already:

- Increased the translational relevance of nonclinical studies by developing data on the utility of cardiac troponin as a marker of cardiac injury in nonclinical models (i.e. animal toxicity testing),
- Supported accurate and efficient safety decision-making by generating and analyzing datasets that inform the selection and interpretation of nonclinical models to predict TdP risk;
- Enriched the field of cardiac safety by creating multi-disciplinary forums for interaction and program formulation between structurally focused cardiac safety scientists (*e.g.*, pathology) and those primarily focused on cardiac functional endpoints (*e.g.*, safety pharmacology); and
- Created a successful, multi-sector and international network of experts that are coordinated through a committee infrastructure capable of identifying and pursuing new challenges to address continued cardiovascular safety issues.

In the last 4 years, this program of work has yielded 13 articles in the peer-reviewed literature, presentations at 32 scientific meetings, and 5 independently convened workshops or meetings. As the Committee maintains several active work streams and is continually adopting new areas of focus, additional impacts and outcomes are anticipated in the months and years to follow (Fig. 1).

2. Committee evolution

At the time of finalization of the ICH-S7A guideline (EMA, 2000), a note was incorporated to the document stating that *"there is no scientific consensus on the preferred approach to, or internationally recognized guidance on, addressing risks for repolarization-associated ventricular tachyarrhythmia (e.g., TdP). A guideline (S7B) will be prepared to present some currently available methods and discuss their advantages and disadvantages. Submission of data to regulatory authorities to support the use of these methods is encouraged."*

At the same time, HESI scientists identified cardiovascular safety as a high priority topic and formed the Cardiovascular Safety Subcommittee. This Subcommittee convened the first working group in 2001 that explored drug-induced cardiac QT interval prolongation and TdP. As a result, the Cardiovascular Safety Subcommittee formed two subteams to further explore nonclinical *in vitro* and *in vivo* assays as well as clinical studies to refine formatting for ECGs, heart rate and QT values.

The Nonclinical Cardiovascular Studies Subteam engaged in comprehensive evaluation to compare the utility of selected nonclinical approaches in assessing ventricular repolarization liability using a panel of 12 drugs with either no association or a strong association to TdP as supported by extensive clinical data on their propensity to elicit QTc prolongation and proarrhythmia in man. These studies demonstrated a high degree of association between hERG blockade potency and clinical QTc prolongation and proarrhythmia. *In vivo* canine electrocardiograms (ECGs) were also shown to be a good predictor of QTc prolongation and arrhythmogenic risk. However, the canine Purkinje fiber assay was found to show a low predictive value towards the clinical outcomes. An additional goal of the studies was to provide information on the interlaboratory variability in hERG assay results. Results of these studies were influential in the subsequent development of the Topic S7B guideline by the ICH Expert Working Group, which requires the hERG assay and *in vivo* non-rodents ECGs but does not require an action potential assay (*e.g.*, the Purkinje fiber assay) (J Koerner, personal communication, February 22, 2013), (Hanson et al., 2006). The Methods and Methodology Subteam developed background information on the strengths and weaknesses of current cardiovascular toxicity assays and determined the extent to which the existing assays worked independently or in tandem to predict clinical outcomes. This document also provided input to the ICH-S7B Cardiovascular Safety Expert Working Group (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002841.pdf).

The Hanson et al. (2006) article was the first of its kind to show that nonclinical safety pharmacology data can be used to understand cardiac safety. Detecting these cardiac risks earlier in the drug development process and distinguishing a drug that prolongs QT interval and is not proarrhythmic from one that leads to TdP has benefits for both the industry and patient safety. The results from that study (Hanson et al., 2006), together with the Japanese Pharmaceutical Manufacturer Association Project for Database Construction (JPMA QT PRODACT) study (Nakaya & Hashimoto, 2005) were instrumental in defining the nonclinical cardiac repolarization assays required before first administration of a drug to humans as outlined in the ICHS7B (EMA, 2005).

The Cardiovascular Pro-Arrhythmia Models Project Committee replaced the previous committee in 2005 to further focus on drug-induced TdP. This project committee convened a workshop that resulted in several publications on improving predictivity based on the workshop recommendations (Bass, Darpo, Breidenbach, et al., 2008; Bass, Darpo, Valentin, Sager, & Thomas, 2008). The main