Journal of Pharmacological and Toxicological Methods 81 (2016) 15–20

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

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

The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative — Update on progress

Thomas Colatsky [a], Bernard Fermini [b], Gary Gintant [c], Jennifer B. Pierson [d,*], Philip Sager [e], Yuko Sekino [f], David G. Strauss [a], Norman Stockbridge [a]

[a] US FDA, 10903 New Hampshire Ave, Silver Spring, MD 20993, United States
[b] Pfizer, Eastern Point Road MS 4083, Groton, CT 06340, United States
[c] AbbVie, R46R AP-9, 1 North Waukegan Rd, North Chicago, IL 60064-6118, United States
[d] ILSI-Health and Environmental Sciences Institute, 1156 15th Street NW, Suite 200, Washington, DC 20005, United States
[e] Stanford University, 719 Carolina St., San Francisco, CA 94107, United States
[f] NIHS Japan, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158-8501, Japan

ARTICLE INFO

Article history:
Received 31 March 2016
Received in revised form 1 June 2016
Accepted 4 June 2016
Available online 7 June 2016

Keywords:
CiPA
Proarrhythmia
In silico model
Ion channel
Myocyte

ABSTRACT

The implementation of the ICH S7B and E14 guidelines has been successful in preventing the introduction of potentially torsadogenic drugs to the market, but it has also unduly constrained drug development by focusing on hERG block and QT prolongation as essential determinants of proarrhythmia risk. The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative was established to develop a new paradigm for assessing proarrhythmic risk, building on the emergence of new technologies and an expanded understanding of torsadogenic mechanisms beyond hERG block. An international multi-disciplinary team of regulatory, industry and academic scientists are working together to develop and validate a set of predominantly nonclinical assays and methods that eliminate the need for the thorough-QT study and enable a more precise prediction of clinical proarrhythmia risk. The CiPA effort is led by a Steering Team that provides guidance, expertise and oversight to the various working groups and includes partners from US FDA, HESI, CSRC, SPS, EMA, Health Canada, Japan NIHS, and PMDA. The working groups address the three pillars of CiPA that evaluate drug effects on: 1) human ventricular ionic channel currents in heterologous expression systems, 2) in silico integration of cellular electrophysiologic effects based on ionic current effects, the ion channel effects, and 3) fully integrated biological systems (stem-cell-derived cardiac myocytes and the human ECG). This article provides an update on the progress of the initiative towards its target date of December 2017 for completing validation.

1. Introduction

The risk of approving drugs with the potential to produce Torsade de pointes (TdP) in patients has effectively been eliminated by evaluating their ability to block the human ether-à-go-go related gene (hERG) channel in vitro, and prolong ventricular repolarization and the QTc interval of the ECG in preclinical studies and clinical trials (Anonymous, 2005a; Anonymous, 2005b) However, the high sensitivity of this approach comes with low specificity. As a result, many drugs with effects on hERG and QTc prolongation but little actual TdP risk are deprioritized or excluded from further development or, if approved, see their clinical use limited by inappropriate warnings in product labeling.

The cause for the low specificity of the current ICH S7B/E14 approach is generally understood to be the result of focusing on only one of the many ion channels governing ventricular repolarization, and the inadequacy of the QTc interval as a surrogate marker of actual proarrhythmic risk. The duration of ventricular repolarization is determined by a fine balance between inward (depolarizing) and outward (repolarizing

Abbreviations: APD, action potential duration; AERS, adverse event reporting system; CiPA, Comprehensive in Vitro Proarrhythmia Assay; EAD, early after depolarizations; ECG, electrocardiogram; HESI, Health and Environmental Sciences Institute; HT, high throughput; hSC-CM, human cardiac stem cell derived cardiomyocyte; hERG or I_{Kr}, human ether-à-go-go related gene; ISWG, In Silico Working Group; ICWG, Ion Channel Working Group; ICH, International Conference on Harmonisation; JiCSA, Japan iPS Cardiac Safety Assessment; MEA, multielectrode array; ORd, O'Hara-Rudy model; RRT, Rapid Response Team; SPS, Safety Pharmacology Society; TdP, Torsades de pointe; US FDA, United States Food and Drug Administration; VSD, voltage sensitive dye; I_{CaL} (Cav1.2), L-type calcium current; I_{Na} peak and late (Nav1.5), sodium current; I_{TO} (Kv4.3), transient outward current; I_{Ks} (KCNQ1 + KCNE1), delayed rectifier potassium current; I_{K1} (Kir2.1), inward rectifier potassium current.

* Corresponding author.
E-mail addresses: Thomas.Colatsky@fda.hhs.gov (T. Colatsky), Bernard.Fermini@pfizer.com (B. Fermini), Gary.Gintant@abbvie.com (G. Gintant), jpierson@hesiglobal.org (J.B. Pierson), psager@stanford.edu (P. Sager), yukos@nihs.go.jp (Y. Sekino), David.Strauss@fda.hhs.gov (D.G. Strauss), Norman.Stockbridge@fda.hhs.gov (N. Stockbridge).

http://dx.doi.org/10.1016/j.vascn.2016.06.002

currents) that are activated with each heart beat. When the amount of net outward current exceeds the amount of net inward current during the cardiac action potential plateau, repolarization occurs. The risk of proarrhythmia increases when repolarization is delayed to such a degree that inward currents can be triggered and generate new excitatory waveforms. While drug block of the hERG/I_{KR} channel plays a critical role in delaying repolarization (see Rampe and Brown, 2013, for a review), activation of inward late sodium and/or calcium currents are needed to trigger a proarrhythmia response. Drugs that affect both inward and outward cardiac currents (e.g. verapamil, ranolazine) may therefore have effects on repolarization and the QTc interval, but not be associated with the generation of TdP due to the blockade of inward currents. Because experimental studies and in silico reconstructions of ventricular repolarization have shown differences across species in the ionic currents underlying repolarization and proarrhythmia (O'Hara and Rudy, 2012), there is a need to use human-based studies to assess accurately the clinical risk of delayed repolarization and proarrhythmia.

Some pharmaceutical developers now appreciate these issues and, to varying extents, factor ion channel activity beyond hERG into development decisions (Gintant et al., 2016, Polak et al., 2015). However, the premature termination of drugs due to hERG and/or QT effects that might have favorable benefit to risk ratios remains common. The Comprehensive in Vitro Proarrhythmia Assay (CiPA) is being developed to place this integrated, mechanistic assessment of risk on a footing solid enough to inform regulatory decision-making, and efficient enough to be deployed during the drug discovery phase. It is envisioned that drugs that are assessed as being at low likelihood for causing TdP may receive benign labeling even if they have some QT prolonging effects.

The CiPA pathway consists of three main elements, 1) assessment of drug effects on the critical human ventricular ion channel currents, 2) in silico integration of the ion channel effects to determine the net effects on the cardiac action potential, and 3) a check for discrepancies in fully integrated biological systems (stem-cell-derived cardiac myocytes and the human ECG) (Sager et al., 2014).

A Steering Team convenes working groups to address each of the three CiPA elements and drives the initiative forward. The CiPA Steering Team consists of partners from the United States Food and Drug Administration (US FDA), Health and Environmental Sciences Institute (HESI), Cardiac Safety Research Consortium (CSRC), Safety Pharmacology Society (SPS), European Medicines Agency (EMA), Health Canada, Japan National Institute of Health Sciences (NIHS), and Pharmaceuticals and Medical Devices Agency (PMDA). These organizations each provide project administration support as well as scientific experts to populate each working group. Through this complex network of consortia and experts, novel data are being generated for the CiPA initiative. This article describes the progress made to date and the plan to bring CiPA into general use.

2. Compound selection

To support this effort, a set of compounds with well-defined cardiac electrophysiology and known clinical characteristics was identified by a subteam of expert clinicians, safety pharmacologists, and cardiac electrophysiologists who discussed, selected and categorized 28 compounds into high, intermediate and low risk of Torsade de Pointes (TdP) based on published reports, analysis of the FDA adverse event reporting system (AERS) database, other data sources and expert opinion. The set of 28 drugs was divided into a set of 12 drugs to be used for CiPA training and calibration, with the remaining 16 used for CiPA validation.

3. Ion channel

The Ion Channel Working Group (ICWG), sponsored by the Safety Pharmacology Society (SPS), was established in December 2013. Its primary role is to work in close collaboration with the In Silico Working Group (ISWG) in providing ion channel support for the development of a computer model of the adult human ventricular myocyte, to be used as part of the CiPA initiative in predicting the clinical risk of drug-induced TdP. Originally composed of a number of expert electrophysiologists from various pharmaceutical companies, contract research organizations and academic institutions, the ICWG has morphed into a smaller and nimbler Rapid Response Team (RRT) empowered with the task of addressing emerging issues affecting the fluid interaction between the ICWG and the ISWG, while focusing on the timely delivery of supporting data. The original remit of the ICWG was: 1) to select key cardiac ion channels to include in the CiPA evaluation; 2) to develop robust, reliable and reproducible voltage clamp protocols required to generate data allowing the training and validation of the in silico model; 3) to define which biophysical and/or pharmacological properties of the channels to study for drug effects in order to optimize the predictivity of the model (e.g., potency (IC_{50}), kinetic of block, rate/use/voltage dependence) and; 4) to define the requirements needed to transition the various ion channel protocols from manual to automated high throughput (HT) patch clamp platforms, in order to adapt to the screening environment present in most pharmaceutical companies. It is believed that developing a standardized protocol for each ion channel will, in itself, be of significant benefit to the field since many different protocols with varying results are currently in use.

Seven recombinant human channels expressed in replicating cell lines were selected to be studied. The selection was based partly on the knowledge of their fundamental roles in defining the human cardiac action potential duration (APD) and documented contribution to cardiac arrhythmias (Moreau et al., 2013; Belardinelli et al., 2006; Workman et al., 2012; January and Riddle, 1989; Kim et al., 2016; Varro and Baczko, 2011; Lengyel et al., 2007; Stengl et al., 2003; Virag et al., 2009), together with the information obtained from an SPS survey, exploring the diversity of ion channels screened in the pharmaceutical industry as part of cardiovascular safety de-risking strategies. The SPS survey was conducted in 2013 to gather additional information about pharmaceutical practices with regards to ion channel screening in non-clinical drug development phases. Results were presented at the CSRC/HESI/SPS/FDA joint meeting on December 11, 2014, but remain unpublished. The selected channels include: I_{Kr} (hERG), I_{Ca} (L-type; Cav1.2), I_{Na} (Nav1.5 peak and late current); I_{TO} (Kv4.3); I_{Ks} (KCNQ1 + KCNE1), and I_{K1} (Kir2.1). Following the selection, the ICWG set out to design standardized voltage clamp protocols for each of these channels.

In addition to developing protocols, the ICWG and ISWG collaborated to define a "minimally acceptable" dataset needed for modeling. Accordingly, the two groups initially agreed to focus on hERG, and identify a protocol allowing the characterization of potency and dynamic block properties of the compounds included in the test set of 12 drugs selected for training and validation of the model (Table 1). While adopting a single voltage clamp protocol to be used at both room and physiologic

Table 1
CiPA compounds.

A list of the CiPA compound test set and calibration drugs		
High risk	Intermediate risk	Low risk
Azimilide	Astemizole	Diltiazem[a]
Bepridil[a]	Chlorpromazine[a]	Loratadine
Dofetilide[a,b]	Cisapride[a]	Metoprolol
Ibutilide	Clarithromycin	Mexiletine[a]
Quinidine[a]	Clozapine	Nifedipine[b]
Vandetanib	Domperidone	Nitrendipine
Disopyramide	Droperidol	Ranolazine[a]
D,l Sotalol[a]	Terfenadine[a]	Tamoxifen
	Pimozide	Verapamil[a]
	Risperidone	
	Ondansetron[a]	

[a] 12 compound test set.
[b] Myocyte calibration compounds.