The Need for a New Approach to Assessing the Proarrhythmic Potential of Drugs and Overview of CiPA

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QT Prolongation/Drug-Induced Torsade

- 2002-2005 ICH Regulatory Discussions
- ICH E14/S7B

- Focus on surrogates- HERG and QTc testing
  - Both are sensitive but not very specific for predicting a drug’s proclivity to be proarrhythmic
    - Relatively low positive predictive value

- HERG/QT Testing has had major impact on drug development
  - Whether drugs progress into humans
  - Whether their development is continued
  - Delays in approval
  - Labeling implications
  - Costs: > 1 Billion $
Consequences: Compound with QT effect

Consequences of developing a compound with QT effect

- Significant development burden
- Increased perceived risk = increased burden to demonstrate benefit
- Increased costs
- Delays in filing and/or approval
- Label warnings and competitive implications
- Licensing/partnering issues
- Often leads to termination of development
Examples of Label Implications of a QT Signal

• Alfuzosin
  – This observation [mild QT prolongation] should be considered in clinical decisions to prescribe UROXATRAL for patients with a known history of QT prolongation or patients who are taking medications known to prolong QT

• Ziprasidone
  – [has a] greater capacity to prolong the QT/QTC interval compared to several other antipsychotic drugs. …raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs ...
  – In many cases this would lead to the conclusion that other drugs should be tried first
QT Prolongation: Dissociation from TdP

- Sodium Pentobarbital
  - Prolongs QT but no TdP
  - Inhibits $I_{kr}$, $I_{ks}$, and late $I_{Na}$

- Amiodarone
  - TdP very rare
  - Inhibits $I_{kr}$, $I_{ks}$, late $I_{Na}$, and $I_{Ca}$

- Verapamil
  - Inhibits $I_{Kr}$ and $I_{Ca}$

- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late $I_{Na}$ and $I_{kr}$
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  - Inhibits $I_{Kr}$ and $I_{Ca}$
  - No QT prolongation or TdP

- **Ranolazine**
  - Prolongs QT but no TdP
  - Inhibits late $I_{Na}$ and $I_{kr}$
  - No EAD’s, reduces dispersion
  - Suppresses E4031 induced TdP

Prolonged QT need not lead to TdP if there is also block of late sodium or calcium currents
Current Proarrhythmia Evaluation

- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved or removed from the market

- Negative impact on drug development
  - Premature discontinuation due to hERG or QT “signal”
    - (Inaccurate) perception of risk leading to drug discontinuation
      - Estimates of up to 60%
    - Concerns regarding development burden, costs, labeling
      - Many potentially good compounds never get evaluated in humans due to a hERG effect
      - Many drugs with QT labeling are unlikely to actually be proarrhythmic
**CiPA: Comprehensive In Vitro Proarrhythmia Assay**

**Goal:** Develop a new *in vitro* paradigm for cardiac safety evaluations of new drugs that provides a more accurate and comprehensive *mechanistic-based* assessment of proarrhythmic potential.

**Focus:** On proarrhythmia (not QT prolongation)

We understand the mechanism of TdP: EADs

Potential significant impact on drug development
Components of CiPA

- **In vitro Assessment of Drug Effects in Multiple Ionic Currents**
  - Sodium
  - Calcium
  - hERG Potassium

- **In silico Computer Modeling to Predict Risk**
  \[ I_{stim} = C \frac{dV_m}{dt} + I_m \]

- **In vivo ECG Biomarker in Phase 1 Clinical Trials**
  - Torsade Metric Score (qNET)
  - ECG
  - Check for unanticipated human effects, confirm mixed channel effects using \( JT_{peakc} \)
  - Can be considered for unanticipated nonclinical effects, or if human ECG data is insufficient

Modified from Jose Vicente
CiPA: Focus on Proarrhythmia

• Reduce the premature termination of drugs with favourable benefit:risk profiles
  – Permit straightforward development and benign labelling of drugs with a low proarrhythmic risk, despite modest QTc prolongation (<20 ms)

• Make drug development more efficient
  – Use preclinical assays to improve candidate selection
  – Move the bulk of proarrhythmic assessment to the discovery phase; simplify clinical development
  – Earlier removal of regulatory uncertainty

• Revise current labels and improve accuracy of how drugs are labelled relative to actual proarrhythmic risks
  – Benign labels for drugs with moderate QT prolongation and low TdP risk
Additional Potential CiPA Benefits

• May be able to reduce the exposure margins in Phase 1 QT assessments

• Permit an alternative risk assessment for drugs with substantial HR increases that confound QT interpretation

• Permit an earlier assessment in Phase 1 of oncology drugs regarding the lack of a concerning proarrhythmic risk
  – Significant opportunity for CiPA to de-risk many oncology drugs
CiPA is Not a Biomarker Validation Project

History of TQT Study

• In 2001, QTc was chosen as the biomarker to assess drug risk for development of Torsade de pointes (TDP)
• QTc is a known biomarker for TdP but its sensitivity and specificity for central tendency changes with respect to TdP development were not well defined
• The TQT Study metrics were not based on clinical data beyond placebo datasets
  • A validation was not performed

• It is appreciated that:
  • TdP risk is somewhat drug-specific, despite similar degrees of QT prolongation
Validation of CiPA

• CiPA is based on a deep understanding of TdP mechanisms
  • The triggering event is EAD’s
  • We understand the ionic factors that result in EAD’s
  • This is directly amenable to study

• Such insights permit the evaluation of an individual drug’s proclivity for causing TdP using an *in silico torsade metric score*

• Validation was based on testing the in silico model’s predictive abilities with respect to a series of reference compounds

• The same compounds were evaluated in IPS cardiomyocytes

• Clinical studies were performed testing ECG analysis of the T-Wave morphology to identify drugs with multi-channel block ($I_{Ca}$ and late $I_{Na}$)
How CiPA Would Likely be Used

1. Drug Discovery - electively to add value to compound selection and preclinical safety assessment

2. To better define potential arrhythmic risk if a drug has a hERG signal or an animal/human QT signal
   - Internal decision making
   - Regulatory purposes- requires standardized CiPA evaluation

3. Alternative to the current S7B/ICH E14 approach
   - Perform standardized CiPA evaluation
   - Drugs with low CiPA proarrhythmic risk, despite anticipated moderate QT prolongation (e.g., 10 to 20 ms at highest clinical exposure), generally need not perform intensive Phase 3 QT evaluation and can expect benign labeling
Data Presentations and How CiPA Would Likely be Used

• In Silico
• Ion Channel
• IPS Cardiomyocytes
• Phase 1 ECGs

• Potential algorithms and roles in preclinical and clinical development
• Regulatory Aspects
Acknowledgments

CiPA Steering Committee
Ayako Takei, Bernard Fermini, Colette Strnadova, David Strauss, Derek Leishman, Gary Gintant, Jean-Pierre Valentin, Jennifer Pierson, Kaori Shinagawa, Krishna Prasad, Kyle Kolaja, Natalia Trayanova, Norman Stockbridge, Philip Sager, Tom Colatsky, Yasunari Kanda, Yuko Sekino, Zhihua Li

CiPA Working groups
• Ion Channel working group
• In silico working group
• Cardiomyocyte working group
• Phase 1 ECG working group

FDA, EMA, PMDA, Health Canada
CSRC, HESI, SPS, JiCSA
In Silico Modelers
Numerous Academic Groups, Pharmaceutical and Device Companies
CRO’s
Thank you

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