In Silico Proarrhythmia Risk Assessment under the CiPA Initiative

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Disclaimer

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## Drugs Withdrawn from Market Due to QTc Prolongation or Torsade de Pointes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Class</th>
<th>Year of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenylamine</td>
<td>Antianginal</td>
<td>1988 (EU, not marketed in US)</td>
</tr>
<tr>
<td>Terodiline</td>
<td>Antianginal/urinary incontinence</td>
<td>1991 (EU, not marketed in US)</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>1998</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Antipsychotic</td>
<td>1998 (not marketed in US, EU reintroduction in 2002)</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Antihistamine</td>
<td>1999</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>Antibiotic</td>
<td>2001</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Gastric prokinetic</td>
<td>2000</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Tranquilizer/analgesic</td>
<td>2001</td>
</tr>
<tr>
<td>Levacetylmethadol</td>
<td>Methadone substitution</td>
<td>2003</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Antipsychotic</td>
<td>2005 (ex-US)</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Opioid analgesic</td>
<td>2010</td>
</tr>
</tbody>
</table>

Adapted from Table 1 in Stockbridge et al. Drug Safety (2013) 36:167-82

EU, European Union; US, United States
What do the Torsade Drugs Have in Common?

- Torsade de pointes ...
- Is associated with QT prolongation ...
- Is associated with action potential prolongation ...
- Is associated with hERG channel block
- Potassium ions
Current Regulatory Guidelines

- **S7B: Non-clinical cardiac safety pharmacology**
  - hERG potassium channel block
  - Non-clinical action potential or QT study

- **E14: Human Clinical ‘Thorough QT’ study**
  - Threshold of concern is ~2% increase in QT (very small!)
  - Most intensive and expensive clinical pharmacology study in drug development

- **Primary goal is to inform whether ECG monitoring in patients is required in clinical phase 3 trials**
- **Not to inform whether a drug causes torsade de pointes**

As some QT prolonging drugs do not cause torsade de pointes (More mechanistic marker assessing multichannel pharmacology needed!)
Comprehensive *in vitro* Proarrhythmia Assay (CiPA)

1. *In vitro* Assessment of Ion Channels
2. *In silico* Computer Modeling to Predict Risk
3. *In vitro* Stem Cell Derived Cardiomyocytes
4. *In vivo* ECG Biomarker in Phase 1 Clinical Trials

- Sodium
- Calcium
- hERG
- Potassium

\[ I_{\text{stim}} = C \frac{dV_m}{dt} + I_m \]

Predict clinical risk of arrhythmias
Check for missed or unanticipated effects
# CiPA Drugs Selected for Model Development

## High TdP Risk
**Training:**
- Bepridil
- Dofetilide
- Quinidine
- D,l Sotalol

**Validation:**
- Azimilide
- Ibutilide
- Vandetanib
- Disopyramide

## Intermediate TdP Risk
**Training:**
- Chlorpromazine
- Cisapride
- Terfenadine
- Ondansetron

**Validation:**
- Astemizole
- Clarithromycin
- Clozapine
- Domperidone
- Droperidol
- Pimozide
- Risperidone

## Low TdP Risk
**Training:**
- Diltiazem
- Mexiletine
- Ranolazine
- Verapamil

**Validation:**
- Loratadine
- Metoprolol
- Nifedipine
- Nitrendipine
- Tamoxifen

Clinical Translational Working Group
O’Hara-Rudy (ORd) Cardiomyocyte Model

Improving the ORd Model for CiPA

• Making the IKr/hERG component temperature dependent
• Modeling dynamic drug-hERG interactions rather than using simple IC50s
• Optimizing model parameters based on experimentally recorded drug effects on human ventricular myocytes
Development of a Temperature Sensitive hERG Model

• Because O’Hara-Rudy model operates at physiological temperature, while industry-generated hERG data are often obtained at room temperature, a dynamic, temperature-sensitive hERG model is required.

• We developed a modified hERG model that can reproduce temperature-induced changes in major channel gating processes.
Modeling Dynamic drug-hERG Interactions

Original Article

Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG (Human Ether-à-go-go-Related Gene) Channel–Drug Binding Kinetics and Multichannel Pharmacology

Zhihua Li, PhD; Sara Dutta, PhD; Jiansong Sheng, PhD; Phu N. Tran, PhD; Wendy Wu, PhD; Kelly Chang, PhD; Thembi Mdluli, PhD; David G. Strauss, PhD; Thomas Colatsky, PhD


- Because the same drug may show different block potency under different conditions (i.e. heart rate), a novel model was developed to capture this dynamic drug-hERG interaction.
- This model can distinguish between hERG blockers with similar IC50s but different TdP liabilities because of some drugs’ tendency to be trapped in closed hERG channel.
Modeling Dynamic drug-hERG Interactions

- The model allows drugs to be trapped in closed-bound state with varying propensities, a realistic feature often missing from published hERG models.

- Modeling shows that High TdP Risk compounds tend to have a higher propensity to be trapped within hERG channel during repolarization.
Dynamic hERG Protocol

Voltage protocol

hERG Current (I)

Fractional Block

\[ 1 - \frac{I_{drug}}{I_{control}} \]

Block Development for Drugs with Different Trapping Propensity

**Dofetilide** (highly trapped):
- No block recovery during channel closing

**Cisapride** (less trapped):
- Almost complete recovery during channel closing
After incorporating the hERG model into ORd, conductance parameters need to be adjusted (optimized).

- Human cardiomyocyte action potential duration (APD) was recorded under L-type calcium current (ICaL) blocker (1 µM nisoldipine).

- The optimized model was able to reproduce the experimental data better than the original model.

- Similar improvement seen for other major potassium currents (IKr/hERG, IKs, IK1) and also late sodium current INaL.

Key Mechanism of TdP: imbalance of Inward and Outward Currents

Major currents modulating repolarization

<table>
<thead>
<tr>
<th>Inward</th>
<th>Outward</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICaL (L type calcium)</td>
<td>IKr (potassium)</td>
</tr>
<tr>
<td>INaL (late sodium)</td>
<td>IKs (potassium)</td>
</tr>
<tr>
<td>IK1 (potassium)</td>
<td>Ito (potassium)</td>
</tr>
</tbody>
</table>

The net current between inward and outward currents reflect their balance.

\[ \text{Inet} = ICaL + INaL + IKr + IKs + IK1 + Ito \]

qNet: Amount of electronic charge carried by Inet
Performance of qNet on 12 CiPA Training Compounds

- **Red**: CiPA TdP High Risk
- **Blue**: CiPA TdP Intermediate Risk
- **Green**: CiPA TdP Low/No Risk

ציעוד ה- EAD: Induced

**qNet**: Net amount of electronic charges passing through the membrane carried by selected currents

Drug separation is good along all concentrations from 1x to 25x Cmax
Comparison of the New Metric(s) with All Other Tested Markers

- qNet is the only metric with 0 training error across all concentrations.
- Metrics based on action potential duration (APD), the cellular basis for QT interval, failed to classify all training drugs.
qNet vs APD: A Case Study

Q: Which cell is in a more dangerous status (closer to EAD generation)?
• APD: The cell with ranolazine (black)
• qNet: The cell with cisapride (grey)

- Applying the same pro-EAD “push”
- Added 91.6% IKr conductance reduction (perburbation)

- qNet, but not APD, correctly predicts the distance from EAD
- qNet, but not APD, independently supports the rank order of the two drugs in CiPA categories
Recent Publication about the qNet Metric and Its Physiological Significance

Optimization of an *In silico* Cardiac Cell Model for Proarrhythmia Risk Assessment

Sara Dutta, Kelly C. Chang, Kylie A. Beattie, Jiansong Sheng, Phu N. Tran, Wendy W. Wu, Min Wu, David G. Strauss, Thomas Colatsky\(^*\) and Zhihua Li\(^*\)

Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States
Incorporating Experimental Uncertainty

• Experimental data have intrinsic (i.e. inherent randomness) and extrinsic (i.e. cell-to-cell variability) uncertainty

• This will lead to uncertainty in metric calculation and TdP risk assessment

• A method was developed to incorporate experimental uncertainty and calculate a probabilistic distribution of the metric
• According to uncertainty quantification analysis, qNet calculation can only be reliably made at up to 4x Cmax.

• For each drug, the averaged qNet from 1 to 4x Cmax across the uncertainty distribution is used as the characteristic metric value.

• Note that even if a drug’s Cmax is unknown, qNet can still be calculated in a concentration-dependent manner and compare to other reference drugs.
Summary of In Silico Work

• The consensus cardiac model (ORd) is further enhanced with temperature-dependent dynamic drug-hERG interaction, and optimized model parameters based on human cardiomyocyte data
• A promising metric identified using training drugs; its performance to be assessed using independent validation drugs
• Method to incorporate experimental uncertainty established;
• The experimental quality criteria, data format standard, and efficient route for sponsor data submission are being developed in collaboration with industry collaborators.
Validation and Implementation Progress

- CiPA Model and Metric had been developed using manual patch clamp data for 12 CiPA training compounds.
- The usability of High Throughput patch clamp Systems is being tested using 12 CiPA training compounds.
- An FDA Advisory Committee Meeting was held in 2017 to seek external expert opinions about CiPA strategy.
- An independent set of 16 drugs are being assessed by both manual and HTS systems.
- The model and metric will be evaluated based on their performance on two tasks:
  - Rank order the TdP risk levels of the 16 validation compounds.
  - Assign each of the 16 validation compounds into one of the three risk categories.
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**All CiPA Working groups**
- Ion Channel working group
- In silico working group
- Cardiomyocyte working group
- Phase 1 ECG working group

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- Many pharmaceutical, CRO, and laboratory device companies
- Academic collaborators

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