Proarrhythmic Assessment of Drugs: The Need For a New Paradigm

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Industry Relationships

Member of DSMB, Adjudication Committee, or Consultant

- Genentech
- Abviee
- Aerpio
- Akebia
- Balance
- Medtronic
- Biomedical Systems
- ICardiac
- Heart Metabolics
- Milestone
- Theravance
- Lilly
- Viamet
- Shire
- Helsinn
- Celgene
- SNBL
- Pharmacyclics
- Anthera
Drug-Induced TdP

• Quinidine syncope with drug-induced LQTS (Selter and Wray, 1964)

• Ventricular arrhythmia Torsades de Pointes – TdP (Dessertenne, 1966)

• Terfenadine

Mean QT change over 12 hours: 6ms
Mean change at Tmax: 12ms
Mean change with metabolic inhibition: >82ms

Problem not clearly identified after 100,000,000 prescriptions

• Quinidine, d,l-sotalol, dofetilide, ibutilide 1-4% TdP incidence
QT Prolonged/Drug-Induced Torsade

- QT prolongation/TdP – single most common cause of withdrawal or restriction on marketed drugs
  - Terfenadine, astemizole, cisapride, droperidol, grepafloxacin, levomethadyl, lidoflazine, sertindole, terodiline

- This has resulted in the need for regulatory guidance.

- TdP rarely observed during clinical development

- Focus on surrogates- HERG and QTc testing
  - QTc- sensitive but not very specific
S7B: Nonclinical Testing Strategy

Chemical/Pharmacological Class

In vitro $I_{Kr}$ assay*

In vivo QT assay

Other nonclinical and **clinical** information

Integrated Risk Assessment

Follow-up studies

Evidence of Risk

None  Weak  Strong

*The hERG (gene for $K_v$11.1 alpha subunit of $I_{Kr}$) related current is used
Potential follow-up assays

- **Purkinje Fibre action potential**
- **Dog ECG** (multiple ascending doses; anaesthetised dog; paced dog)

Other ion channels/receptors:
- hERG channel trafficking
- Pro-arrhythmia model

Other ion channels/receptors include:
- SCN5a
- L-type calcium
- T-type calcium
- hERG
- KCNQ1/KCNE1
- Kv1.5
- Kv4.3/KCIP2

**In Silico Modeling, Stem Cells**
Forming an integrated risk assessment

Combine data and plot relative to predicted peak free drug levels at clinically effective dose

![Graph showing % inhibition hERG tail current vs. % change QTc against concentration of compound]
Forming an integrated risk assessment

Combine data and plot relative to predicted peak free drug levels at clinically effective dose

Predicted human efficacious $C_{\text{max}}$
free

% inhibition hERG tail current

% change QTc

$\mu$M

$hERG$
Animal QTc

[compound] (µM)

% inhibition hERG tail current

% change QTc

hERG

Animal QTc
Forming an integrated risk assessment

Combine data and plot relative to predicted peak free drug levels at clinically effective dose

Predicted human efficacious $C_{\text{max}}$ free

% inhibition hERG tail current

% change QTc

hERG Animal QTc

[compound] (μM)
Clinical QT Update

Guidance document – ICH E14

Applicable to all new drugs with systemic bioavailability

Gather basic clinical data (e.g. tolerability, PK)

Relatively early in development design and conduct “Thorough QT Study” at substantial multiples of anticipated maximum therapeutic exposure

-ve*

+ve (>5ms)

Conduct normal ECG monitoring in development

Evidence of QT increase/TdP

Stop development or

Fully describe QT effect in target patient population; Extensive QT evaluation in Phase 2/3

* Positive represents an approximately 1.5% increase in the QTc
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.
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
Phase 1 Exposure Response Model-Based Approach In Lieu of the TQT

The IQ-CSRC Prospective Clinical Phase 1 Study: “Can Early QT Assessment Using Exposure Response Analysis Replace the Thorough QT Study?”

Borje Darpo, M.D., Ph.D.,¹,* Nenad Sarapa, M.D.,²,† Christine Garnett, Pharm.D.,³,* Charles Benson, M.D., Ph.D.,⁴,† Corina Dota, M.D.,⁵,* Georg Ferber, Ph.D.,⁶,‡ Venkateswar Jarugula, Ph.D.,⁷,† Lars Johannesen, M.Sc.,⁸,⁹ James Keirns, Ph.D.,¹⁰,† Kevin Kudys, Ph.D.,¹¹ Catherine Ortemann-Renon, Pharm.D., Ph.D.,¹²,* Steve Riley, Pharm.D., Ph.D.,¹³,‡ Danise Rogers-Subramanian, Ph.D.,⁴,† and Norman Stockbridge, M.D., Ph.D.¹⁴


Primary Objective:
• Study 6 marketed drugs on the QTc interval using concentration effect modeling.
  • Ondansetron, Quinine, Dolasetron, Moxifloxacin, Dofetilide, Levocetirizine, Placebo

Primary endpoint:
• Change-from-baseline QTcF (ΔQTcF)
Criteria for QT Assessment

**Positive QT assessment**
- The upper bound of the 90% CI of the projected placebo-corrected ΔQTcF is above 10 ms at the observed peak plasma level of the drug.
- *In addition*, the confidence interval for the slope with respect to concentration is above zero.

**Negative QT assessment**
- The upper bound of the confidence interval of the predicted placebo-corrected ΔQTcF at the geometric mean C_{max} of the drug is below 10 ms.

Results Will Be Presented on Dec 12
Torsade de Pointes

- Graph showing the number of cases of Torsade de Pointes from 1993 to 2011.
  - Cases of Torsade de Pointes:
    - All drugs:
      - Peak in 2003
    - Excluding anti-arrhythmics:
      - Steady trend with fewer peaks

Year of report:
Torsadogenic Drugs

- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved

**Success!**

- 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
  - Drug development in specific areas- CNS
  - Many drugs with QT labeling are unlikely proarrhythmic
  - Engineering-out hERG- applicability/other effects
Ventricular Repolarization

- **P** wave
- **QRS** complex
- **T** wave

Time intervals:
- **80 ms**
- **400 ms**

**Currents and channels**:
- **Na⁺ current**
- **Ca²⁺ current**
  - **L-type**
  - **T-type**
- **Transient outward current**
  - **I_{TO1}** (4-AP-sensitive)
  - **I_{TO2}** (Ca²⁺-activated)
- **Delayed rectifiers (I_K)**
  - **I_{Kr}**
- **Inward rectifier, I_{K1}**
- **Pacemaker current, I_f**
- **Na⁺-Ca²⁺ exchange**
- **Na⁺, K⁺-ATPase**
Evidence of Alternative Mechanisms

Strong genetic data illustrating potential impact of non-hERG-mediated changes in QT interval with drug examples for most K⁺,K⁺,K⁺,Ca²⁺,Na⁺

<table>
<thead>
<tr>
<th>Current</th>
<th>(I_{Kr})</th>
<th>(I_{Ks})</th>
<th>(I_{K1})</th>
<th>(I_{Na})</th>
<th>(I_{Ca,L})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of function</td>
<td>QT↑</td>
<td>QT↑</td>
<td>QT↑</td>
<td>QT↓</td>
<td>QT↓</td>
</tr>
<tr>
<td>Gain of function</td>
<td>QT↓</td>
<td>QT↓</td>
<td>QT↓</td>
<td>QT↑</td>
<td>QT↑</td>
</tr>
</tbody>
</table>
### Acquired LQTS: APD/EAD/QT Interval Prolonging Models

<table>
<thead>
<tr>
<th>Drug/Gene Defect/Intervention</th>
<th>Principal Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veratridine, ATX II, anthopleurin A, alfuzosin, (mutations in Na^+ channels)</td>
<td>Enhance late (I_{Na})</td>
</tr>
<tr>
<td>Bay K 8644 (mutations in Ca^{2+} channels)</td>
<td>Enhance (I_{Ca-L})</td>
</tr>
<tr>
<td>Cs(^+), quinidine, procainamide, bepridil</td>
<td>Suppress (K^+) currents</td>
</tr>
<tr>
<td>E-4031, dofetilide, ibutilide, sotalol, terfenadine, astemizole, desmethylastemizole, cisapride, haloperidol, droperidol, halofantin, erythromycin, fluoxetine, etc. (mutations in Kv11.1 K^+ channels)</td>
<td>Suppress (I_{Kr})</td>
</tr>
<tr>
<td>Azimilide, Chromanol 293B (mutations in Kv7.1 K^+ channels)</td>
<td>Suppress (I_{ks})</td>
</tr>
</tbody>
</table>

### Conclusions:
- Most LQTS drugs cause rapid direct channel block of \(I_{kr}\), but this is not the exclusive mechanism

Modified from January: CSRC Mtg 2013
EAD Generation and TdP

Similar results with quinidine, anenome toxin (ATX II), E-4031
Development of TdP

↓ Net repolarizing current

↑ Action potential duration and QT interval

Early afterdepolarizations (EADs)

↑ Dispersion of ventricular repolarization (ΔAPD)

Torsade de pointes

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 $I_{Kr}$ but also Ca influx

- **Ranolazine**
  - Prolongs QT but no TdP
  - Inhibits late $I_{Na}$, $I_{kr}$, and $I_{NaCa}$
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- Verapamil
  - Inhibits $I_{Kr}$ but also Ca influx
    - No QT prolongation or TdP

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

Thus QTc Prolongation need not cause TdP
Issues

• QT prolongation ≠ Proarrhythmia
• HERG block ≠ Proarrhythmia
• Negative impact on drug development
• New paradigm
New Paradigm

A new cardiac safety paradigm focused on non-clinical measurement of proarrhythmia proclivity

Focus on the real issue: Proarrhythmia

• Reduce the premature termination of drugs with favourable benefit:risk profiles
• Make drug development more efficient
  – Move the bulk of proarrhythmic assessment to the discovery phase
  – Use the assays to potentially guide candidate selection
  – Obviate the TQT study
• Enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrhythmic risks
Proarrhythmic risk can be determined by pre-clinical assessments

- Proclivity to develop EAD’s
  - Ionic Currents
    - in silico modeling
  - Cell-Based Approach

- Focus on high throughput approaches

- ECG Phase 1 Assessment
CiPA: Three Component Proposal

Ionic Currents / In Silico Based Approach

- Effects on Multiple Cardiac Currents (Voltage Clamp Studies)
- Reconstruction of Cellular Electrophysiology (In Silico Studies)

+ Myocyte-Based Approach

- Effects on Human Ventricular Myocytes (In Vitro Studies)

Human Phase 1 ECG’s

Effects on Human ECG morphology/waveforms

Not designed to reproduce arrhythmia

Define a gradation of risk instead of a binary approach
Work Streams

**In Silico** – model design, execution, feedback and vetting Tom Colatsky (Thomas.Colatsky@fda.hhs.gov)

**Ion Channel** – channel selection, protocol development, novel data generation to test model; (Bernard.Fermini@pfizer.com and Najah.AbiGerges@astrazeneca.com)

**Stem Cell Myocyte** – protocols, platforms and validation; (Gary.Gintant@abbvie.com)

**Compound Selection and Clinical Translation/Regulatory** – Compound selection, arrhythmia metrics, ECG assessment, regulatory interactions (Psager@Stanford.edu)

**Steering Team** – Coordination and integration
Comprehensive

*In Vitro* ProArrhythmia Assay (CIPA)

- Potential to make drug development more efficient
- Move arrhythmia risk assessment to the discovery phase
- Reduce the premature termination of drugs with favorable benefit:risk ratios
- Re-label some current drugs with warnings related to QT prolongation
Day 1: December 11, 2014

CSRC/HESI/SPS/FDA Meeting
DoubleTree Hotel, Silver Springs, Maryland

Day 2: December 12, 2014
Registration is now open!

Sharing Results from Novel Research Symposium
10903 New Hampshire Avenue, Silver Spring, Maryland 20993
White Oak Facility, FDA Headquarters • Silver Spring, MD • December 12, 2014
Collaborators

- Drs. Stockbridge, Gintant, Petit, and the Steering Comm.
- FDA
- EMA
- PMDA
- Health Canada
- CSRC
- HESI
- SPS
- In Silico Modelers
- Pharmaceutical and Device Companies
- CRO’s
- Numerous Academic Groups
Thank you

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