Proarrhythmic Assessment of Drugs: The Need For a New Paradigm

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Industry Relationships

Member of DSMB, Adjudication Committee, or Consultant

- Genentech
- Orexo
- Aerpio
- Akebia
- Balance
- Medtronic
- Biomedical Systems
- ICardiac
- Heart Metabolics

- Milestone
- Theravance
- Lilly
- Viamet
- Shire
- Helsinn
- Celgene
- SNBL
- Pharmaclics
- Anthera
Drug-Induced TdP

- Quinidine syncope with drug-induced LQTS (Selter and Wray, 1964)
- Ventricular arrhythmia Torsades de Pointes – TdP (Desserterenne, 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 $K_v11.1$ alpha subunit of $I_{Kr}$) related current is used
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*

Conduct normal ECG monitoring in development

Evidence of QT increase/TdP

+ve (>5ms)

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
• 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: 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
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

Key currents and elements:
- Na\(^+\) current
- Ca\(^{2+}\) current
- Transient outward current
- Delayed rectifiers (\(I_K\))
- \(I_{K1}\)
- Pacemaker current, \(I_f\)
- \(Na^+\)-\(Ca^{2+}\) exchange
- \(Na^+\), \(K^+\)-ATPase
Strong genetic data illustrating potential impact of non-hERG-mediated changes in QT interval with drug examples for most

<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>$QT\uparrow$</td>
<td>$QT\uparrow$</td>
<td>$QT\uparrow$</td>
<td>$QT\downarrow$</td>
<td></td>
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<tr>
<td>Gain of function</td>
<td>$QT\downarrow$</td>
<td>$QT\downarrow$</td>
<td>$QT\downarrow$</td>
<td>$QT\uparrow$</td>
<td>$QT\uparrow$</td>
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C. Pollard
### Acquired LQTS: APD/EAD/QT Interval Prolonging Models

<table>
<thead>
<tr>
<th>Drug/Gene Defect/Intervention</th>
<th>Principal Target</th>
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<tbody>
<tr>
<td>Veratridine, ATX II, anthopleurin A, alfuzosin, <em>(mutations in Na(^+) channels)</em></td>
<td>Enhance late (I_{Na})</td>
</tr>
<tr>
<td>Bay K 8644 <em>(mutations in Ca(^{2+}) channels)</em></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, desmethylenastemizole, cisapride, haloperidol, droperidol, halofantin, erythromycin, fluoxetine, etc. <em>(mutations in Kv11.1 K^+ channels)</em></td>
<td>Suppress (I_{Kr})</td>
</tr>
<tr>
<td>Azimilide, Chromanol 293B <em>(mutations in Kv7.1 K^+ channels)</em></td>
<td>Suppress (I_{ks})</td>
</tr>
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**Conclusions:**

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

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*Modified from January: CSRC Mtg 2013*
Development of TdP

- Early afterdepolarizations (EADs)
  - Trigger
  - Substrate
  - Torsade de pointes

- \( \text{Net repolarizing current} \) decreases
- \( \text{Action potential duration and QT interval} \) increases
- \( \text{Dispersion of ventricular repolarization (ΔAPD)} \)

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
American Heart Journal

Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium

Philip T. Sager, MD, FACC, FAHA, a Gary Gintant, PhD, b J. Rick Turner, PhD, c Syril Pettit, MEM, d and Norman Stockbridge, MD, PhD c Palo Alto, CA; North Chicago, IL; Durham, NC; Washington, DC; and White Oak, MD

• 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: Two Component Proposal

Ionic Currents / In Silico Based Approach

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

<table>
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<th>Myocyte-Based Approach</th>
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<td>Effects on Human Ventricular Myocytes (<em>In Vitro</em> Studies)</td>
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- Complementary approaches
- Not designed to reproduce arrhythmia

Define a gradation of risk instead of a binary approach
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
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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