The Need for a New Paradigm to Assess Proarrhythmic Effects of Drugs

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- Viamet
- Shire
- Helsinn
- Celgene
- SNBL
- Pharmacyclitics
Drug-Induced Torsade de Pointes
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

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**Integrated Risk Assessment**

- Follow-up studies

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**Evidence of Risk**

- None
- Weak
- Strong

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*The $h_{ERG}$ (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*

+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
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/S&B 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

- $80\text{ms}$
- $400\text{ms}$

- $P$, $QR$, $T$

- Na$^+$ current
- Ca$^{2+}$ current
  - L-type
  - T-type
- Transient outward current
  - $I_{T01}$ (4-AP-sensitive)
  - $I_{T02}$ (Ca$^{2+}$-activated)
- Delayed rectifiers ($I_K$)
  - $I_{Kr}$
- $I_{Kur}$
- $I_{Cl}$ or $I_{Kp}$
- Inward rectifier, $I_{K1}$
- Pacemaker current, $I_f$
- Na$^+$-Ca$^{2+}$ 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

<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>
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<tbody>
<tr>
<td>Loss of function</td>
<td>QT↑</td>
<td>QT↑</td>
<td>QT↑</td>
<td></td>
<td>QT↓</td>
</tr>
<tr>
<td>Gain of function</td>
<td>QT↓</td>
<td>QT↓</td>
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<td>QT↑</td>
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</tr>
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</table>

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

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• 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
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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