Preclinical ECG Biomarkers of Cardiac Toxicity: Are They Relevant to Pediatric Safety?

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Pediatric Drug-Induced QT Prolongation: Broad Range of Pathological Consequences

- Multiple clinical case reports of QT prolongation in children

**Incidence of QTc > 440 ms**
- Cisapride: 12-48%
- Doxapram: 15%
- Ziprasidone: 15%

**Isolated case reports**
- Sevoflurane
- Droperidol
- Atomoxetine
- Quetiapine

**Toxicological trends**
- Strong correlation between ΔQTc and age
- 8% incidence of QT dispersion
- Lack of $T_{\text{peak}} - T_{\text{end}}$ dispersion
- Bradycardia, 2:1 AV block

- Very low rate of confirmed TdP (~2 cases reported)

- Multiple factors could drive a low rate of ventricular tachycardia
  - Increased rate of monitoring
  - Medical care could lead to a lower risk of polypharmacy e.g. with CYP450 drugs
  - Medical intervention: dose titration or drug discontinuation

- Could the development of the heart also play a role in determining risk?
Consistent QT Effects Seen in Animal Studies; Do the Underlying Mechanisms Vary?

• *In vivo* canine recordings validate clinical findings

• Canine cellular studies highlight the maturation of the heart’s electrophysiological profile

**Neonate**  
**Adult**

Dof: Dofetilide ($I_{Kr}$)  
Azi: Azimilide ($I_{KS}$)

Adapted from Obreztchikova M, 2003
Could the Evolution of Repolarization Gradients Drive a Drug’s Torsadogenic Potential?

• Transmural recordings demonstrate that a repolarization gradient develops with age.

- Neonate
- Young
- Adult

- Dofetilide-induced amplification of TDR is strongly correlated with age.

$\Delta APD_{90} \text{ (ms)}$

Adapted from Obreztchikova M, 2003
Increased Susceptibility of Young Hearts to Premature Depolarizations Increases Risk of Drug-Induced TdP

- Higher rates of triggered beats in young animals lead to a greater incidence of TdP

- The maturation of Ca$^{2+}$ handling proteins/regulation of Ca$^{2+}$ channels could confer a higher risk of EADs in young hearts

- Critical developmental overlap of maturing calcium homeostatic processes and a small, but sufficient, TDR could underlie the higher rate of TdP

Adapted from Obreztchikova M, 2003
How do Preclinical Findings Correlate With Clinical Reports?

**Preclinical**

**Neonate**

- EADs
- ↓ TDR
- Large ∆QT_c but no TdP

**Clinical**

- Despite high risk of QT prolongation, drug-induced TdP is very rare
- Multiple reports of bradyarrhythmias
- AV block reported with cisapride, amiodarone, and sotalol

• Neonatal proarrhythmia: potentially strong correlation between preclinical and clinical findings

**Preclinical**

**Young (~90 days)**

- EADs
- ↑ TDR
- Large ∆QT_c + TdP

**Clinical**

- High risk of QT prolongation
- No reported cases suggesting an increased risk of TdP in this age range

• Discordance between preclinical and clinical findings could point to important species-related differences
Can Zebrafish Serve as a Useful Model for Detecting Pediatric Cardiotoxicity?

• Zebrafish studies reveal potential mechanisms underlying reports of 2:1 AV block
  • QT prolonging drugs significantly reduce heart rate in embryonic fish
  • Breakdance mutants (lacking HERG) recapitulate these findings

Action potentials from isolated hearts

2:1 infranodal AV block despite regular atrial rhythm: prolonged ventricular APD increases refractoriness

Milan D, 2003
What are the Implications of These Findings and Where do we go From Here?

• Findings suggest that arrhythmia risk and phenotype evolves with age

<table>
<thead>
<tr>
<th>Stage of development</th>
<th>Embryonic</th>
<th>Neonatal</th>
<th>Juvenile</th>
<th>Adult</th>
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<tbody>
<tr>
<td>TDR</td>
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<td>Low</td>
<td>Med</td>
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<tr>
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<td>VT risk</td>
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<td>Bradycardia/ asystole</td>
<td>Bradycardia/ AV block</td>
<td>VT/TdP</td>
<td>VT/TdP</td>
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Remaining questions

• Are pediatric patients less susceptible than adults to drug-induced TdP?

• What are the consequences of QRS and PR prolongation in pediatric patients?

• Can immature hepatic enzymes lead to drug accumulation and further raise the risk of cardiac toxicity?