Interpreting Adult Human Thorough QT Studies: Are They Relevant to Pediatric Safety?

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Outline

• Introduction
• Key issues
• Case study
• Take-home message
Introduction

QT/QTc prolongation may cause ventricular arrhythmias
  • torsade de pointes (TdP)

Thorough QT studies (TQTS), the standard approach to evaluate QTc prolongation, are conducted in adults

Can TQTS results be applied to pediatric patients?

• It is infeasible to conduct a thorough/dedicated QTc evaluation in each patient population at different age groups.
• Information obtained from adults can / should be served as the basis for safety evaluation in pediatric patients.
Key Issues

• Concentration-QTc modeling and simulation is a useful tool to bridge the information.

• To translate the study results from adults to pediatric patients:
  – How to adjust exposure difference between adult and pediatric patients? (different dosing regimen and different abilities for body to handle drugs)
  – Is there age-dependant sensitivity towards QTc prolongation? (Slope of concentration-QT relationship)
  – Do we expect baseline QTc differences between pediatric and adult patients?
Exposure Difference

- Under the same dose, the exposure difference between adults and children due to body size, organ, and tissue maturation is well-known.
  - PK samples are typically taken during drug development.
  - Population Pharmacokinetics has been applied to adjust the difference.

A typical renal maturation process
Age-dependant Sensitivity

- A key issue/question lack of adequate experience.
- Example: Sotalol (BETAPACE ®)

Patients: Age > 2: Class III potency in children is not very different from that in adults. (Package insert of Sotalol)

Neonate: The smallest children (BSA < 0.33 m²) showed a tendency for larger Class III effect (ΔQTc). (Package insert of Sotalol and Lear et al. JACC 46(7): 1322-30)
Baseline QTc Difference

- Shorter baseline QTc interval is expected in male adolescents.

- Confirmed by increased QTc interval in patients receiving Degarelix or Leuprolide.
Case Study: Thorough ECG Study for Drug X

• Drug X QTc effect was evaluated in a cross-over, single-dose, placebo- and positive-controlled thorough ECG study.

• Treatment arm:
  – Drug X 100 mg IV (represents the highest approved adult dose)
  – Drug X 300 mg IV (adequately covers the worst clinical scenario)
Thorough ECG Study Results

Drug X prolongs QTc, QRS, and PR interval in a dose-proportional manner.

<table>
<thead>
<tr>
<th>Drug X</th>
<th>Mean Cmax* [ng/mL]</th>
<th>ΔΔQTcF Mean [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 X Dose</td>
<td>1 X Conc</td>
<td>~ 10 ms</td>
</tr>
<tr>
<td>3 X Dose</td>
<td>3 X Conc</td>
<td>~ 30 ms</td>
</tr>
</tbody>
</table>
Concentration~ QT Relationship

<table>
<thead>
<tr>
<th>Concentration (ng/mL)</th>
<th>QTc (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Supratherapeutic</strong></td>
<td></td>
</tr>
<tr>
<td>Model Prediction</td>
<td></td>
</tr>
</tbody>
</table>

**Parent Compound**  

**Metabolite**
Simulation Results

Assumption: Similar sensitivity between healthy adults and pediatric patients

<table>
<thead>
<tr>
<th>Route</th>
<th>Indication</th>
<th>Patient</th>
<th>Predicted QTc Interval: Mean (Upper90% CI) [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>CINV</td>
<td>Adults (healthy)</td>
<td>~ 14 (~ 16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peds cancer patients</td>
<td>~ 22 (~ 24)</td>
</tr>
<tr>
<td></td>
<td>PONV</td>
<td>Adults</td>
<td>3 (~ 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peds</td>
<td>~ 4. (~ 5.)</td>
</tr>
</tbody>
</table>

Regulatory action:

Contraindicating pediatric patients for CINV indication
Take-Home Message

• Information obtained from adult TQTS can be served as the basis for safety evaluation in pediatric patients.

• Concentration-QTc modeling and simulation is a useful tool to bridge the information.

• Experience in evaluating QTc interval change in pediatric patients is still limited:
  
  – Whether age-dependant sensitivity towards QTc interval change exists is an important question, lack of adequate experience.
  
  – The relationship between QTc prolongation and the arrhythmic risk in pediatric patients is unclear.
Thank you for your attention!

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