Juvenile Animal Studies: When can they contribute to cardiovascular safety assessments?

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What is the concern

Are you more or less concerned about safety in a neonate or a child or an adolescent?

Better question

What is your confidence level to generalize existing data to a neonate a child or an adolescent?
Pediatric Drug Development - Toxicology

- Same expectations as for adults
- Integrated assessment of available data
  - Prior toxicology
  - Adult clinical studies

Juvenile animal studies are performed on a case-by-case basis

- Is there a signal of concern?
  - If yes, does the existing data characterize the signal sufficiently?
    - If no, what additional data are needed?
Juvenile Animal models for cardiac toxicity

• What do you want to know?
  – What aspect of cardiovascular toxicity?

• Choosing your model
  – Which species were used in the adult studies
  – Most relevant or sensitive species

• When to test
  – Comparative species development
Comparative Age Categories Based on Overall CNS & Reproductive Development

- **Pre-Term Neonate**
  - Rat: Birth (< 9)
  - Minipig: Birth (2)
  - Dog: 0.5 weeks (3)
  - Nonhuman Primate: 0.5 weeks (3)
  - Human: 0.08 weeks (2)

- **Term Neonate**
  - Rat: 4 weeks (14)
  - Minipig: 4 weeks (14)
  - Dog: 0.5 weeks (3)
  - Nonhuman Primate: 0.5 weeks (3)
  - Human: 0.08 weeks (2)

- **Infant/Toddler**
  - Rat: 21 weeks (45)
  - Minipig: 4 weeks (14)
  - Dog: 6 weeks (20)
  - Nonhuman Primate: 6 weeks (20)
  - Human: 2 weeks (12)

- **Child**
  - Rat: 26 weeks (52)
  - Minipig: 14 weeks (28)
  - Dog: 16 weeks (32)
  - Nonhuman Primate: 14 weeks (28)
  - Human: 12 weeks (24)

- **Adolescent**
  - Rat: 20 weeks (40)
  - Minipig: 14 weeks (28)
  - Dog: 20 weeks (40)
  - Nonhuman Primate: 14 weeks (28)
  - Human: 12 weeks (24)

**Ontogeny**
- Pre-Term Neonate
- Term Neonate
- Infant/Toddler
- Child
- Adolescent

Critical Windows for Development

Buelke-Sam, 2001
## Heart Parameters

### Human Infant

<table>
<thead>
<tr>
<th>Age</th>
<th>1 day</th>
<th>6 days</th>
<th>1 month</th>
<th>2 month</th>
<th>6–11 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>133</td>
<td>135</td>
<td>155</td>
<td>150</td>
<td>140</td>
</tr>
<tr>
<td>RV pre-ejection period (msec)</td>
<td>71</td>
<td>59</td>
<td>51</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>RV ejection time (msec)</td>
<td>199</td>
<td>203</td>
<td>193</td>
<td>204</td>
<td>232</td>
</tr>
<tr>
<td>LV pre-ejection period (msec)</td>
<td>65</td>
<td>59</td>
<td>55</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>LV ejection time (msec)</td>
<td>197</td>
<td>192</td>
<td>184</td>
<td>192</td>
<td>200</td>
</tr>
</tbody>
</table>

### C57bl/6 Mouse

<table>
<thead>
<tr>
<th>Age</th>
<th>3 days</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>10 weeks</th>
<th>16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>372</td>
<td>422</td>
<td>390</td>
<td>442</td>
<td>360</td>
</tr>
<tr>
<td>LV cardiac output (ml/min)</td>
<td>1.1</td>
<td>8.7</td>
<td>9.3</td>
<td>15.7</td>
<td>14.3</td>
</tr>
<tr>
<td>LV stroke volume (ml)</td>
<td>3.2</td>
<td>20.8</td>
<td>23.9</td>
<td>35.6</td>
<td>40.2</td>
</tr>
</tbody>
</table>

### Sheep

<table>
<thead>
<tr>
<th>Age</th>
<th>Term fetus</th>
<th>Newborn</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>150</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Ventricular output (ml/min/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>150</td>
<td>400</td>
<td>100</td>
</tr>
<tr>
<td>Right</td>
<td>300</td>
<td>400</td>
<td>100</td>
</tr>
</tbody>
</table>

Modified from Hew and Keller, BDR B 2003
What do the studies tell us

Value

• Increased sensitivity
  – Some helped to set age limits for use
• Unique toxicity
• Non specific study designs often replicated toxicities already characterized and were least likely to be of benefit
Case study

Drug A (treatment of 1° and 2° hyperparathyroidism)

- Species - rat and dog
- Rat: age at dosing PND 21–49; recovery to PND 67
  - No unexpected toxicity; adverse effects attributed to pharmacology
- Dog: age at dosing PND 70 – 98 recovery to PND 126
  - Cardiac toxicity
  - Findings drove request for an additional dog study for safety
  - Pediatric studies on hold until completed
- Dog: 6 month study; age at dosing PND 70 with 3 month recovery higher doses used
  - No cardiac toxicity; other findings consistent with excess pharmacology
  - Pediatric studies now underway

Value - unexpected finding in a study with a ‘general toxicity’ design had potential clinical consequence; a second, more directed, study supported resumption of pediatric program
Interpreting the data

More or less sensitive?

Unique toxicity?

JUVENILE ANIMAL  ADULT

JUVENILE HUMAN  ADULT
When can Juvenile Animal Studies contribute to cardiovascular safety assessments?

• What would trigger an expectation for juvenile animal toxicity testing?

• For assessing potential cardiovascular toxicity what are the key parameters?
  - To measure routinely
  - To measure when there is a suggested cardiovascular toxicity signal