Safety assessment of pediatric drugs

Roy Forster, CIT

ENFANT et TOXIQUES
(Environnement, Médicaments, Tabac, Alcool, Drogues, Dopage, Aliments)

Cassis, 16 et 17 Octobre 2003
Are children just small adults?

Can drug safety for pediatric patients be adequately assessed from adult studies?
Children differ from adults in significant ways

- Allometric differences
- Rapid growth
- Immature organ systems
- Developmental processes
- Higher metabolic rate
- Unique exposure routes

<table>
<thead>
<tr>
<th></th>
<th>Surface area (m²)</th>
<th>Mass (kg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>0.20</td>
<td>3</td>
<td>0.067</td>
</tr>
<tr>
<td>Toddler</td>
<td>0.47</td>
<td>10</td>
<td>0.047</td>
</tr>
<tr>
<td>Child</td>
<td>1.00</td>
<td>33</td>
<td>0.033</td>
</tr>
<tr>
<td>Adult</td>
<td>1.73</td>
<td>70</td>
<td>0.025</td>
</tr>
</tbody>
</table>
Ontogeny of drug disposition

- Allometrics
- Changing body composition
- Maturation of
  - GI physiology (gastric pH and emptying, bacterial flora)
  - blood composition (high bilirubin levels, lower albumin levels)
  - xenobiotic metabolism
  - renal function and GFR

<table>
<thead>
<tr>
<th></th>
<th>% bw</th>
<th>Total body water</th>
<th>ECF</th>
<th>ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>75</td>
<td>40</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>60</td>
<td>23</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Puberty</td>
<td>60</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>50</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>
# Altered toxicity in children

| ↑   | Chloramphenicol                  | “Gray baby” syndrome in newborn babies |
| ↓   | Acetaminophen                    | Children resistant to overdose toxicity up to age 6 - 9 years |
| ↑   | Benzyl alcohol                   | Babies susceptible to “Gasping syndrome” |
| ↑   | Valproic acid                    | Incidence of fulminant hepatotoxicity higher in children |
| ↓   | Isoniazid                        | Prevalence of hepatotoxicity greater in adults |
| ↓   | Aminoglycosides                  | Newborns are resistant to aminoglycoside nephrotoxicity |
Regulatory guidance

- ICH Guideline E11: Clinical investigation of medicinal products in the pediatric population (Dec 2000)
- ICH Guideline M3: Timing of preclinical studies in relation to clinical trials
- Concept paper on the development of a CPMP Note for Guidance on the need for pre-clinical testing of human pharmaceuticals in juvenile animals (Nov 2001)
When are juvenile studies needed?

- Where (pediatric) clinical studies involve long term exposure, juvenile animal studies should be conducted before initiation of long term clinical trials.

- Where clinical studies do not involve long term exposure, such studies can be conducted in conjunction with clinical trials...however, it may be more efficient to complete juvenile (animal) studies early....to clinically evaluate the relevance of identified potential hazards.

- Where there is minimal prior adult and pediatric (clinical) experience, juvenile (animal) studies should be completed before the initiation of pediatric clinical trials.
Choice of species

- Rodents, rabbits, dogs, nonhuman primates “are considered appropriate models”

- Choice of species should take into account the pharmacology, pharmacokinetics, and toxicology of the therapeutic agent, and the comparative developmental status of the major organs of concern between juvenile animals and pediatric patients

- “A study…in one species can be sufficient to evaluate toxicity endpoints for therapeutics that are well characterised in both adult humans and animals”.

Nonclinical Safety Evaluation of Pediatric Drug Products,
FDA CDER, Feb 2003
### Definitions

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Duration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term newborn infants</td>
<td>-</td>
<td>Immature renal and hepatic function, incomplete blood-brain barrier, unique susceptibilities. Requires expert know-how.</td>
</tr>
<tr>
<td>Term newborn infants</td>
<td>0 to 27 days</td>
<td>Change from placental alimentation and excretion to autonomy; adaptation to lung breathing; rapid maturation. High bodywater content.</td>
</tr>
<tr>
<td>Infants and toddlers</td>
<td>28 days to 2 years</td>
<td>Rapid maturation of CNS, immune system development and total body growth.</td>
</tr>
<tr>
<td>Children</td>
<td>2 to 11 years</td>
<td>Developing cognitive and motor skills.</td>
</tr>
<tr>
<td>Adolescents</td>
<td>12 to 16/18 years</td>
<td>Period of sexual maturation, commencing with puberty. Increased in muscular strength, acceptance of delayed gratification.</td>
</tr>
</tbody>
</table>
## Correspondence across species

<table>
<thead>
<tr>
<th></th>
<th>Term neonatal</th>
<th>Infants and toddlers</th>
<th>Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>&lt; 28 days</td>
<td>1 – 24 months</td>
<td>2 – 12 years</td>
<td>12 – 18 years</td>
</tr>
<tr>
<td>Rat</td>
<td>9 – 10 days</td>
<td>10 – 21 days</td>
<td>21 – 45 days</td>
<td>45 – 90 days</td>
</tr>
<tr>
<td>Dog</td>
<td>3 – 21 days</td>
<td>3 – 6 weeks</td>
<td>6 – 20 weeks</td>
<td>20 – 28 weeks</td>
</tr>
<tr>
<td>Macaque monkey</td>
<td>&lt; 15 days</td>
<td>2 – 26 weeks</td>
<td>6 – 36 months</td>
<td>36 – 40 months</td>
</tr>
</tbody>
</table>

Kimmel (1994)
Organ systems develop at different rates in different species!

<table>
<thead>
<tr>
<th>% adult alveoli</th>
<th>Man (years)</th>
<th>Dog (weeks)</th>
<th>Rat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.5</td>
<td>Birth</td>
<td>Birth</td>
</tr>
<tr>
<td>50</td>
<td>1.5</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>66</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>6.5</td>
<td></td>
<td>28</td>
</tr>
</tbody>
</table>

Completion of nephrogenesis

<table>
<thead>
<tr>
<th>In utero</th>
<th>Man, Primate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks PN</td>
<td>Dog</td>
</tr>
<tr>
<td>3 weeks PN</td>
<td>Pig</td>
</tr>
<tr>
<td>4 to 6 weeks PN</td>
<td>Rat</td>
</tr>
</tbody>
</table>
How do current studies address these concerns?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment I (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segment I (M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segment III (dams)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Endpoints

Medicinal products may affect physical and cognitive growth and development......

Measurements of:

- General toxicology parameters
- Growth and skeletal development
- Developmental landmarks and neurologic development
- Reproductive development
- Physiological parameters (renal and pulmonary)
- Immunological development
Growth and skeletal development

- Growth measures
  - body weight,
  - height and length,
  - rate of change

- Skeletal development:
  - long bone lengths,
  - BMD, detailed bone parameters

- Total body composition
Rat pup development

Birth
- Hairless, blind, toothless & need to keep warm.

PND 5
- Bodyweight has doubled
- Pinna unfolding,

PND 9
- Incisors permit gnawing
- Hair coat present

PND 11
- Cliff avoidance reflex
- First solid food

PND 15
- Eyes open
- Independent thermoregulation

PND 17-18
- Solid food surpasses milk intake

PND 21
- Weaning
Developmental landmarks and behaviour

- Physical landmarks:
  - Incisor eruption, eyelid separation

- Neurological development
  - Reflex development
  - Locomotory activity
  - Neurobehavioural measurements: startle test, passive avoidance tests

Koolhaas (2000)
Reproductive development

- Developmental landmarks:
  - Male: Preputial separation, testicular descent
  - Female: Vaginal patency, onset of estrus
- Organ weights and histopathology of gonads
- Sperm analysis
- Functional evaluation by mating trials
General toxicology and physiological parameters

- Clinical pathology, organs weights, histopathology
- Renal development: urinalysis
- Pulmonary development: plethysmography
Immunological development

Development of immunocompetence and establishment of immune memory

---

**Lymphocyte subsets**

- Total T-cells
- LT CD 4+
- LT CD 8+
- B cells

---

**IgM response to KLH**

- D 22
- D 42
- Adults

---

O.D
Practical issues

- Organisational (time-mated litters)
- Constitution of groups
- Feasibility of dosing procedures
- Blood sampling for investigations and TK
<table>
<thead>
<tr>
<th>Administration Method</th>
<th>Rat</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gavage</td>
<td>PND 1</td>
<td>PND 1</td>
</tr>
<tr>
<td>Subcut</td>
<td>PND 1</td>
<td>PND 1</td>
</tr>
<tr>
<td>IV Bolus</td>
<td>PND 7</td>
<td>PND 1</td>
</tr>
<tr>
<td>Infusion</td>
<td>PND 22</td>
<td>PND 63</td>
</tr>
</tbody>
</table>
Blood volumes

- Problem principally for rat studies
- Satellite groups essential for TK and clinical pathology
- Take advantage of culls and interim sacrifices
- Attention to the impact of manipulations

<table>
<thead>
<tr>
<th></th>
<th>Sample</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>50 ul</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>2</td>
<td>250 ul</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>4</td>
<td>1 ml</td>
<td>10 ml</td>
</tr>
<tr>
<td>6</td>
<td>2 ml</td>
<td>20 ml</td>
</tr>
<tr>
<td>8</td>
<td>3 ml</td>
<td>30 ml</td>
</tr>
<tr>
<td>Clin Path</td>
<td></td>
<td>1.0 ml</td>
</tr>
</tbody>
</table>
Study design considerations

- Age range
- Study duration
- Route of administration
- Husbandry issues?
- Technical issues?
- Endpoints
- Dose-level selection
Example juvenile rat study design

Dosing period
Dose levels
Route & frequency
Group size
Satellite groups
Observations

- PND 10 to PND 84
- Based on range finding and PK data
- Clinical route
- Cross-fostered litters: 5M + 5F
- TK, fertility, reversal groups
  - Bodyweight, growth and skeletal development
  - Neurol. devt & motor activity
  - Reproductive maturation
    - (optional mating trial)
  - TK
  - Organ weights and histopathology
Example juvenile dog study design

Dosing period
- 4 months (aged 2 months at start)

Dose levels
- Based on range finding and PK data

Route & frequency
- Clinical route

Group size
- 3M + 3F plus reversal animals

Observations
- Bodyweight, growth and skeletal development
- Neurological development
- Reproductive maturation
- Clinical pathology
- TK
- Organ weights and histopathology
Conclusion

- Juvenile animal studies present some special issues for safety assessment.

- Appropriate methods for the study of toxic actions in juvenile animal studies are available.

- Design and interpretation of these studies requires sympathetic attention to the special issues relating to growth and development.