Juvenile Animal Toxicology Studies to Support Paediatric Drug Development

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Background

• Setting the scene
• Adult vs juvenile differences
• Study considerations
• Current situation regarding juvenile animal testing
• What are these studies showing?
• The future
• Conclusions
Setting the Scene
The Past - 1

• Until recently information relating to use of medicines in children was lacking
• Thus, substantial unlicensed and off-label use of adult medicines in paediatric population
• Doctors prescribing medicines to children without knowing if they were effective, what dose was appropriate and what adverse reactions the child might suffer
• Off-label use was at the individual physician’s discretion and the individual child patient’s wish
The Past - 2

- Paediatric development not assessed by pharma because of insufficient financial returns to support investment
  - Small patient pool with children representing only about 20% of European population
- Clinical trials in paediatrics are lengthy and therefore costly (due to difficulty in patient recruitment)
- No legal requirement to perform paediatric studies if no intention to develop drug for this population
- Ethical dilemma regarding paediatric recruitment and consent issues
Why Change?

- Long-standing concerns raised by paediatricians, clinical pharmacologists and other health care experts for well-designed clinical trials in children
- View that trials in children are unsafe and unethical has been superseded by realisation that administration of drugs not previously tested in children may pose a greater risk than conducting studies
- Shift in regulatory world and specific legislation for paediatric clinical trials now in place in the US and EU
- Financial rewards
Key Dates - US

- 1998: FDA’s Pediatric Rule which required paediatric studies for drugs in which significant use or benefit in children was expected
- 2002: Best Pharmaceuticals for Children Act (BPCA)
- 2003: Pediatric Research Equity Act (PREA) gave the FDA authority to require research into drugs used in juvenile patients
- 2007: FDA Amendments Act which re-enforced the BPCA and PREA and established the Pediatric Review Committee (PeRC)
- 2012: FDA Safety and Innovations Act made BPCA and PREC permanent and established need to submit paediatric strategy in a Pediatric Study Plan (PSP) including juvenile animal work (if needed)
Key Dates - EU

- 2007: Under an EMEA initiative “Better Medicines for Children” a Paediatric Regulation entered into force
  - As part of Regulation, a Paediatric Investigation Plan (PIP) must be submitted and agreed by a Paediatric Committee (PDCO)
  - The PIP facilitates the development, accessibility and safe use of new drugs in the paediatric population through clinical studies or to provide justification for a waiver/deferral from such studies
  - As well as any proposed paediatric clinical studies, juvenile animal work (if needed) has to be included
Juvenile Animal Testing in PIP

- **Section D.3** sets out the “Strategy in Relation to Non-clinical Aspects” and need to:
  - Highlight what juvenile animal work is planned and specific endpoints eg, neurotoxicity assessment
  - Give outline of study design
  - Provide timelines for work
- **Section D.5** requires an outline of planned or performed non-clinical studies
- **Section D.6** requires timelines for studies
Specific Nonclinical Guidelines


• **Europe**: Non-clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications (2008)

• **Japan**: Guideline on the Nonclinical Safety Study in Juvenile animals for Pediatric Drugs (2012)
  
  • Importance of animal data in predicting the potential drug toxicity in children is recognised
  
  • Comment that juvenile animal studies can provide information that might not be derived from standard adult toxicology studies or from safety information from adult humans
Adults vs Juveniles
Know Your Animal

- Definition of “juvenile” – animal in period between birth and attainment of sexual maturation
- Experimental animals have compressed developmental schedule
## Age Comparison

<table>
<thead>
<tr>
<th>Species</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (week)</td>
<td>0-1</td>
<td>1-3</td>
<td>3-9</td>
<td>9+</td>
</tr>
<tr>
<td>Dog (month)</td>
<td>0-0.75</td>
<td>0.75-1.5</td>
<td>1.5-5</td>
<td>5+</td>
</tr>
<tr>
<td>Primate (year)</td>
<td>0-0.05</td>
<td>0.05-0.5</td>
<td>0.5-3</td>
<td>3+</td>
</tr>
<tr>
<td>Man (year)</td>
<td>0-0.1</td>
<td>0.1-2</td>
<td>2-12</td>
<td>12+</td>
</tr>
</tbody>
</table>

**NOTE:** Does not account for organ maturation
Functional Differences

- Major functional (dynamic) differences between neonates/infants and adults occur
  - Eg CNS, pulmonary, renal, skeletal, immune, reproductive systems
- Development varies among organ systems (and components within each organ system)
  - Differences between mature and immature systems = toxicity in latter that is not seen in mature systems?
  - Therefore, for examination of the toxicity of potential concern need to dose at the appropriate developmental stage in time with maturation of the target organ of concern
Kinetic Differences

- Major kinetic differences between neonates/infants and adults occur and toxic effects in children are often related to altered metabolism compared to adults.

- For anti-infective drug*
  - Single oral doses in rats of 1 and 15 days resulted in 15 and 7 fold higher exposure, respectively than in adults while oral bioavailability of nearly 100% and day 15 and 24% in adults.
  - Repeated oral dosing showed 3-5 fold higher exposure at day 18 vs 24.
  - Differences due to low capacity of metabolising enzymes and reduced first pass metabolism in younger animals?

Study Considerations

Not Easy Studies

They are toxicology studies in very young animals vs adult data which covers treatment in rats from eg >6 weeks of age and dogs from eg >6 months of age.
Study Considerations - 1

• Species (usually rat)
  • Other species such as dog and monkey have been used
• Age of animals at start of treatment (can commence oral dosing at one day of age – not recommended!)
• Route/administration limitations
  • Eg intravenous dosing into fragile veins
• Toxicokinetic evaluation
  • Sample volumes in young rats are limited so sampling is terminal requiring large numbers of pups
Study Considerations - 2

- Study duration and dose levels
  - May need to cover period from birth in humans to 18 years of age
  - Need to avoid toxic dose levels as can lead to growth retardation with secondary effects on organ systems AND / OR maternal neglect / rejection of offspring
Study Considerations - 3

• Study parameters additional to those used in adult work can include
  • Neurobehavioural testing eg detailed clinical signs/behavioural testing (functional observational battery) / terminal assessment (brain pathology)
  • Specific growth measurement eg femur length and/or specialised study design (eg reproductive, renal or pulmonary system development)
  • Reproductive development eg mating performance
Study Considerations - 4

• Also for pre-weaning animals will need to consider developmental landmarks eg in rats
  • Physical development (pinna detachment, eye opening, tooth eruption, acoustic startle, vaginal opening, preputial separation)
  • Sensory and reflex development (negative geotaxis, righting reflex, visual placing, papillary reflex)
• Need to be aware that an apparent effect on physical or functional development may solely be due to a drug-induced effect on bodyweight
Current Situation Regarding Juvenile Animal Testing

In Demand!
Juvenile Animal Study Frequency

**PIP Applications***

- Examination of published opinions (to 12 December 2014) showed:
  - 185 drug decisions had juvenile animal work requested (to support paediatric age range of from birth - 12 years to less than 18 years)
  - Species to be used (with main study usually preceded by range-finding work): 125 with rat, 18 with dog, 9 with mouse, 9 with monkey, 3 with pig, 3 with sheep, 1 with rabbit + 30 cases with species not specified
  - Some biologicals were included (at least 6 Mabs and 5 recombinant proteins)
  - Request for 2 juvenile species for 12 drugs

*www.emea.europa.eu/htms/human/paediatrics/decisions.htm
Drug Area With JA PIP Request

- Oncology*
- Cardiovascular diseases*
- Infectious diseases*
- Endocrinology*
- Dermatology
- Gastroenterology
- Haematology
- Ophthalmoscopy
- Pain
- Uro-Nephrology
- Diagnostic
- Neonatology
- Other

*Together make up >50% of the decisions
Study Design – Example - 1

- Juvenile rat study performed with **allergy vaccine Pollinex® Quattro Grass** based on recommendation from PDCO to allow use in children*
- Contained grass pollen extract + immunostimulatory adjuvant monophosphoryl lipid A
- Study designed to cover dosing from 5 years and to bridge to adult rat data
  - One weekly subcutaneous dosing for 3 weeks with full toxicological evaluation followed by a 4 week non-dose recovery period
  - No obvious toxicity seen – as with adult rats, only relatively minor immunostimulatory effects along with injection site reaction

*Baldrick et al (2011) Repro Tox 322-328
Study Design – Example - 2

- Combination of 2 antifungal agents anidulafungin and voriconazole
- Juvenile rat study performed to support paediatric clinical trials with the combination as follows*
  - Daily dosing from PND 21-56 with a recovery period to PND 84 of each drug alone or in combination
  - Doses chosen to target exposures at or above adult rat NOAELs
  - Results showed
    - Systemic exposure at juvenile animal NOAEL comparable to that seen in adults
    - Similar study findings with no novel, additive or synergistic toxicities

Study Design – Example – 3a

- **Dolutegravir** - antiviral drug in development (HIV-1 integrase inhibitor) with interest in expanding into paediatric population
- Theoretical developmental immunotoxicity risk identified as mode of action involves inhibition of pathway required for development of mature B and T lymphocyte populations*
- Juvenile rat toxicology study performed:
  - Day 4 to 66 oral dosing
  - Additional endpoints of T cell receptor expression and immunophenotyping of lymphocyte subsets (using flow cytometry) + T cell dependent antibody response (anti-KLH IgM and IgG response)

Results showed:

- No evidence of immunotoxicity (from evaluation of haematology, weight and pathology of immune organs and additional T cell response measurements)
- Confirmed lack of immunotoxicological findings in adult rats
- In addition, related drug raltegravir showed no immunotoxicological findings following dosing of juvenile rats from Day 5-54
- Toxicokinetic examination showed exposure decreased with age, with AUC being 33-89% lower on Day 32 vs 13
What Are These Studies Showing?

The Future
Recent Survey

- Review of 241 JA studies (range-finding / mechanistic and definitive) provided by 24 companies, apparently largely covering the period 1999-2008
  - Majority of studies showed findings comparable to adult data and quantitatively, a general trend for increased sensitivity in terms of general toxicity for rats, but not dogs
  - “Novel toxicity” (defined as a finding in an organ system not previously seen in adult animals) was only seen in 14 studies in rat and 2 studies in dog
  - In many cases findings could have been predicted from either the known pharmacology of the drug or adult data
  - Information from 5 juvenile rat studies considered to have added value by changes examined in the clinic, while the results of 8 studies (4 each in rat and dog) contributed to the product label

Beware Uninterpretable Findings

- **Kalydeco (Ivacaftor)** approved in 2012 for Cystic Fibrosis from 6 years of age
- Cataracts seen in juvenile rats treated day 7-35 at $\geq 10$ mg/kg/day (approximately 1/10 of maximum recommended human dose) but not in toxicology studies in young adult rats or dogs
- Finding stated in US and EU product label with comment on uncertainty of relevance of risk to children since differences in eye development between humans and rats
- FDA requested clinical study in children up to 11 years of age (stated as age in which eye development is complete) followed for at least 2 years with 6 monthly examination for visual acuity + cataracts/eye opacities (www.fda.gov)
Future Considerations / Needs

- Move away from standard toxicology study designs to more focused ones (specifically addressing safety concerns)
- More understanding of cross-species postnatal functional and kinetic development (especially through published data)
- Removal of need for juvenile animal testing for follow-on drugs in the same class
- Need for testing identified post-marketing
- Understanding of regulatory needs and close interaction with agencies (especially to get agreement on study designs)
- Need for consistent advise from cross-region regulatory agencies
- More use if pharmacokinetic modelling to remove / reduce the need for toxicology testing
- Reduced animal use through microsampling toxicokinetic evaluation
Draft concept paper for new “nonclinical testing in juvenile animals for pediatric indications” guideline issued 3 Mar 2014

Recognised that regional differences in approaches by regulatory agencies in determining need for and design of JA studies + conflicting recommendations arise within regulatory bodies
New Guideline - 2

• Key identified concerns include:
  • JA study being required by one region but not another, one design deemed acceptable by one agency but considered insufficient by another, trend away from a case-by-case approach to routine performance + trend for study designs that mirror adult animal studies
  • Timing of regulatory interaction to discuss paediatric plans – early in clinical development in EU and later in clinical development in US
  • Timeline – EWG to meet in Nov 2014, draft guideline in 3Q 2015 and final guideline 2017
Conclusions
Conclusions - 1

- Before embarking on any thoughts of juvenile animal testing, it is important to be clear if there is a real need
  - No “box ticking”!
- Numbers of juvenile animal studies are being requested / performed with vast majority appearing to be toxicology studies, presumably using standard endpoints and / or with additional add-on measurements (such as developmental / reproductive or behavioural endpoints) on occasion
Conclusions - 2

• Undoubtedly, more juvenile animal data are appearing in drug labels

• However, it is still unclear to what extent juvenile animal work is identifying new toxicities / safety concerns not already available from adult data or predictable from exposure / maturation differences

• What would be useful is publication of the rationale with details of why juvenile animal work is being proposed by a drug company or requested by the regulators

• If full information is made available, it is possible that the need to examine a particular maturation concern for further new drugs will not be needed, greatly reducing the number of studies
The End

THANK YOU