

Neonatal/Juvenile Toxicology – Why babies are not just “little adults”



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Background

- Until ~10 years ago, lack of targeted paediatric drug development – extensive “off-label” use.
- Assumes that paediatric patients will exhibit similar disease progression and respond similarly to the intended therapeutic intervention.
- Estimated 50% - 90% of drugs never specifically evaluated for paediatric use.
- How can we be sure that adult/paediatric toxicity profiles are the same?

Background

- Inherent differences between mature and immature systems » risk of:
 - Unique tox profile in children
 - Poor efficacy
 - Exaggerated pharmacology
 - Unexpected adverse effects, even death.
- 2002 – EU consultation paper “*Better Medicines for Children*” – proposed new legislation.

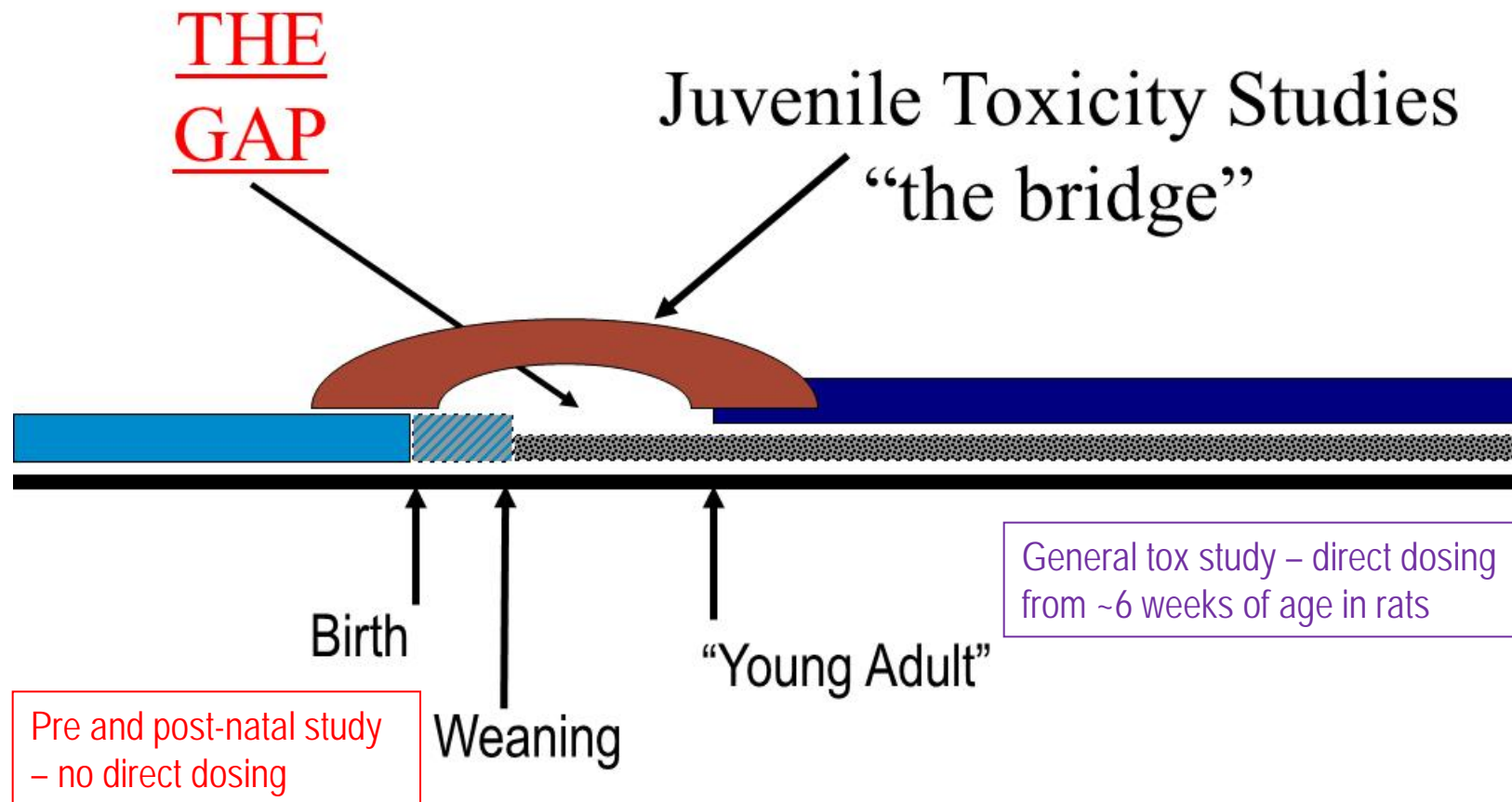


Guidance/Guidelines

- FDA issued formal guidance in 2006: *“Guidance for Industry – Nonclinical Safety Evaluation of Pediatric Drug Products”*.
- EMA guideline issued in 2008: *“Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications”*
- Now, drug dvlpt programs for a paediatric population **must** take into consideration possible effects on developmental processes specific to the relevant age groups.

Why are they needed?

- To obtain information on potentially different safety profiles from those seen in adults – bridging the gap between reprotox and repeat dose tox studies.



When are they needed?

- Situations that would justify toxicity studies in juvenile animals include, but are not limited to:
 - When the indication is specifically targeted for children
 - Findings in non-clinical studies that indicate target organ or systemic toxicity relevant for developing systems.
 - Possible effects on growth and development in the intended age group.
 - If a pharmacological effect of the test compound could/would affect developing organs.
 - Unique chemical class or unique combination product.

Regulatory involvement

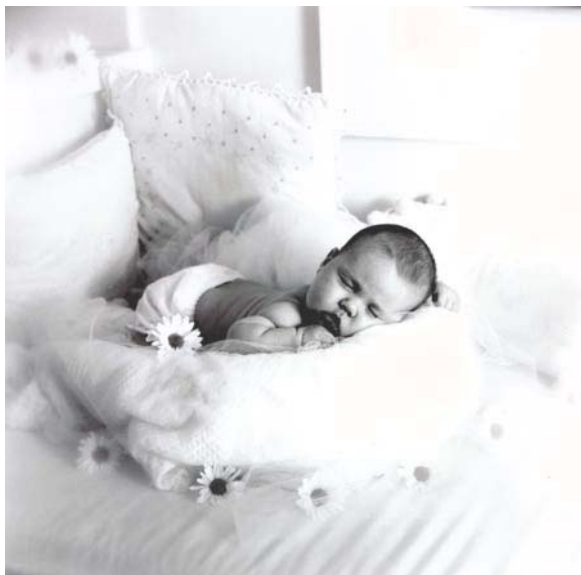
- The original proposal was that the conduct of juvenile toxicity studies should be considered on a case-by-case basis.
- The emphasis has changed though. Rather than questioning whether studies need to be conducted, there is now an assumption that these are required unless you can justify why they are not!
- Study design/content must be discussed with, and approved by, the Regulatory Agencies (FDA/EMA).

Paediatric Investigation Plan (PIP)

- Submitted to Regulatory Agency:
 - Includes detail of timing/measures proposed to demonstrate quality, safety and efficacy in the paediatric population.
 - Specifies which population subsets need to be studied, by what means and by when.
 - Is the basis upon which compliance with the requirement to present either results of studies, or a waiver, or a deferral is judged.
 - ◆ Exemptions
 - Generics
 - Biosimilars
 - Well-established medicinal use
 - Homeopathics
 - Herbals

Challenges

- Children are not “miniature adults”
- Predicting responses in children based on adult data is hard.
- Known cases of different sensitivity between children and adults exist.



Examples of different sensitivity

Chloramphenicol (broad spectrum antibiotic)

- Associated with “Grey baby syndrome” in premature babies because of limited clearance » exposure increased due to a longer $T_{1/2}$ (26 h) compared to adults (4h).



Acetaminophen (paracetamol)

- ↓ susceptibility to acute toxicity in children due to
↑ glutathione turnover & more active sulphation
→ ↑ metabolic/ detoxification capacity
compared to adults.



(Quoted in US FDA CDER Guidance 2006)

Examples of different sensitivity

Valproic acid (anti-convulsant - epilepsy)

- In contrast to paracetamol, young children treated with VPA appear disproportionately vulnerable to fatal hepatotoxicity.



Aspirin

- ↑ susceptibility due to abnormal fat accumulation in liver and other organs, and severe increase in intracranial pressure (Reye's syndrome)



(Quoted in US FDA CDER Guidance 2006)

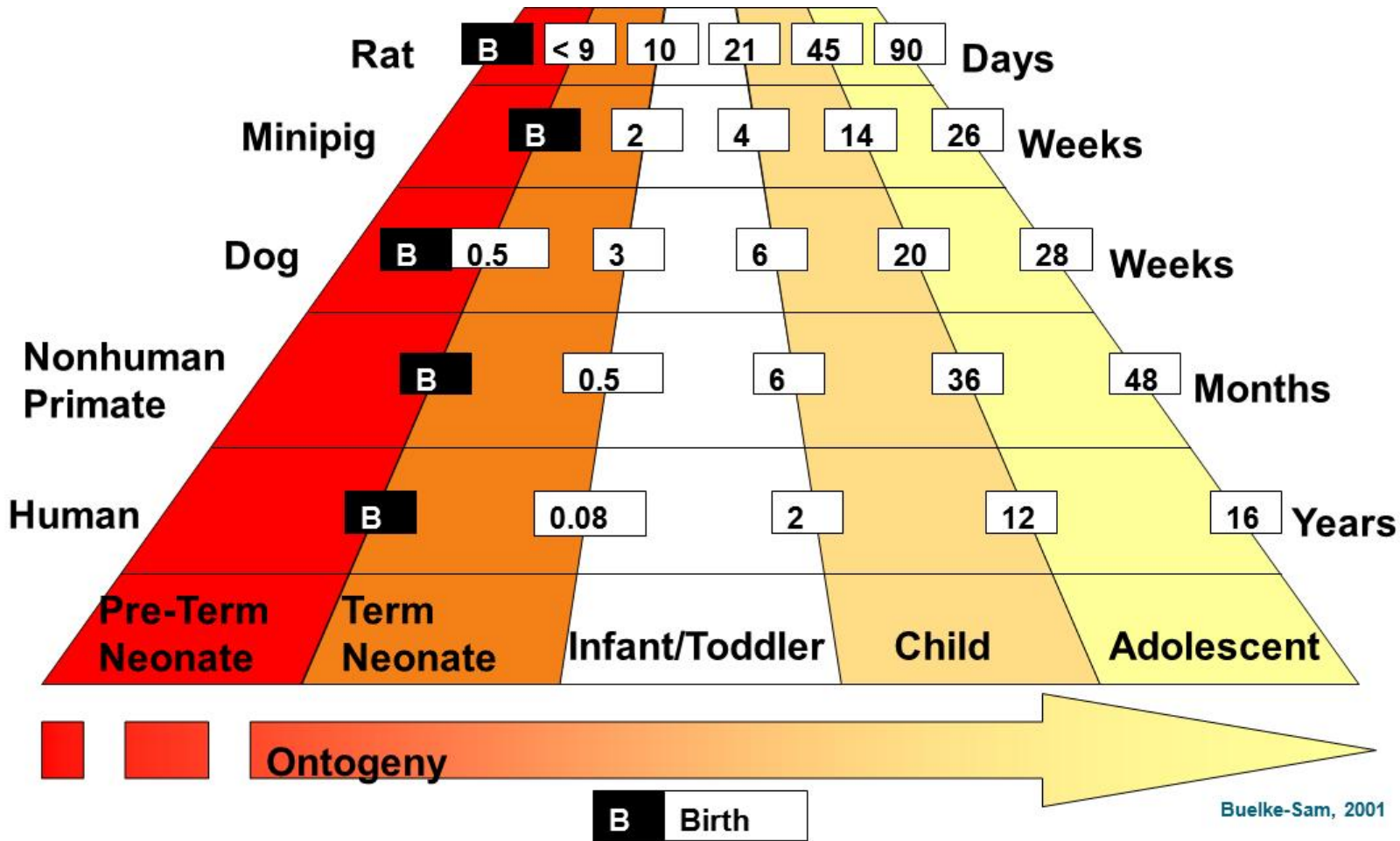
Reasons for sensitivity differences

- Post-natal growth and development can affect drug disposition and action:
 - Metabolism (maturation rate of Phase I/II enzyme activities)
 - Body composition (water and lipid partitions)
 - Receptor expression and function
 - Growth rate
 - Organ functional capacity
- These are all susceptible to modification or disruption by drugs.

Where does a child begin and end?

- Preterm or Newborn
 - Unique pathophysiology
 - Difficult to extrapolate from adults/children
- Infant < 1 month
 - Blood-brain barrier (BBB) immature
 - Altered pharmacodynamics
 - Less predictable absorption
- Infants/Toddlers (1 month - 1 year)
 - Developing CNS, immune system, growth
 - Altered pharmacodynamics
- Children/Adolescents (>2 years)
 - Mainly growth phase
 - Developing repro system
 - ↑compliance issues

Comparative age categories



Structural & functional development

Human

Nervous system: up to adulthood.

Pulmonary system: up to 2 yrs.

Reproductive system: up to adulthood.

Renal system (anatomical): GW35.

Renal system (functional): up to 1 year.

Immune system: up to adulthood.

Liver: depending on the endpoint:
differences in functioning of drug-
metabolising enzymes, transporters,
etc. during the first months →
ca 3years

Rat

Brain: by ~ 35 days.

Pulmonary system: by 28-35 days.

Reproductive system: ~35/45 days (F/M).

Renal system (anatomical): 4-6 weeks.

Renal system (functional): ~ 21 days.

Immune system: by ~ 60 days.

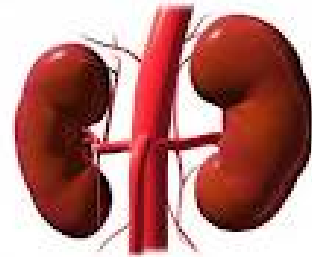
Liver: adult structure reached by ~28 days.
Enzyme/transporter activity still not
clearly understood, but P450
considered to be ~ 45 days.

Specific organ systems - CNS

- Developmental stage of BBB important for:
 - CNS drugs
 - If findings seen post-natally in PPN study
 - If patient population is less than 1 year old.
- BBB laid down in first trimester, permeability varies during development.
- Considered established by 6 months in man, but functional at PND10 in rats with full functionality at ~5 weeks.
- Immaturity → potential for ↑ exposure of developing brain (eg. Oseltamivir, treatment for flu).
 - PND7 - death after 1 x 1000mg/kg dose
 - PND14 - no effects after 1 x 2000 mg/kg dose
 - 1500 fold ↑ brain exposure at PND7 compared to PND14
 - Therefore, comparability of PND21 rat pup and 2yr child not reflected in BBB development (i.e develops later in rat pup).



Specific organ systems - Kidneys



■ Nephrogenesis

- Human - complete by 35 wks gestation – all functional nephrons (~1million) present at birth
 - ◆ Postnatal maturation continues up to 1 year.
- Rats - maturation complete by ~ 6 wks.

■ Glomerular filtration rate

- Man - commences prenatally, increases rapidly from birth to adult levels by 2 years.
- Rats – from birth, rises sharply until 6 wks of age, when adult levels reached.

Study design considerations (1)

There is no such thing as a “standard” study design – each study is uniquely tailored according to the test material, target population, organ system of interest & duration of use.

■ Age of animals at start of dosing

- To match lowest age of target patient group.
(see Buelke-Sam diagram previously)
- Relatively easy to match rats, may be possible for minipigs, but tricky for other species, as difficult to obtain dams with litters or gestating females.
- Once weaned (equivalent to 2yr old), all species can be used.

Study design considerations (2)

- **Duration of dosing period**
 - To cover developing organ system(s) of interest.
 - Link with age that general tox studies started.
 - Will treatment be life-span?
 - Will recovery period be necessary?
- **Route of administration**
 - As intended clinical route, where possible.
 - ◆ ... but not always practical (eg. repeat IV in the rat from Day 4 of age)

Study design considerations (3)

■ Formulations

- Restrictions in rat studies:
 - ◆ Earlier treatment starts, the more restrictions apply.
 - ◆ Solutions only for the youngest rats, whether by gavage or subcutaneous administration.
 - ◆ Smooth, non-viscous suspension suitable for gavage from mid-lactation.
 - ◆ Restricted by the small bore of the dosing catheter.
- Dogs would not have these restrictions, in principle.

Study design considerations (4)

■ Selection of species

- Must be appropriate for evaluating tox endpoints relevant for intended pediatric popⁿ
- Rats and dogs are traditionally the species of first choice.
- Testing in one appropriate species using both sexes will normally be sufficient (but not always!).



Species selection – why the rat?

- Major species in general toxicity data
- Studies run in a short time-frame
- Can synchronise breeding/animal supply
- Pup dosing possible from an early age
- Good statistical power by using a large number of animals
- Established functional/behavioural tests
- Reproductive function easily assessable
- Can easily randomise litters pre-weaning:
 - Spreads genetic pool, eliminating genetic bias
 - Can use all litters born (no wastage due to abnormal sex ratio/litter size)

Species selection – why not the rat?

- May not respond to compounds in similar way to man
- Interspecies differences may affect drug handling
- Small size:
 - may compromise some routes of dose administration
 - makes toxicokinetic and/or clinical pathology sampling difficult:
 - ◆ uses many animals because pre-weaning bleeds are terminal **at the moment!**
 - ◆ achievable blood volumes low, so may need to pool samples

Study design considerations (5)

- **Dose selection**
 - Exaggerated toxicity not desirable, aim is to detect any possible increase in sensitivity of young vs adults.
- **Preliminary study essential**
 - To assess tolerability/dose-range
- **Inclusion of TK essential**
- **Endpoints**
 - Numerous and flexible
 - ◆ Each study has tailor-made design
- **Numbers per sex per group not standard**
 - Depends on endpoints
- **Practical issues... !!**

Practical issues



Study Organization

Husbandry

Formulation

**Practical
Issues ...**

**Dosing
procedure**

**Blood
sampling**

**Laboratory
capabilities**



Main study endpoints (1)

- Growth (bodyweight and limb length)
- Development (external indices of sexual maturation)
- Clinical/post-dosing signs
- Food intake (post-weaning only)
- Haematology/blood chemistry/urinalysis
- Organ weights
- Macropath/micropath investigations
- Reversibility
- Toxicokinetics

Main study endpoints (2)

- Neurotoxicity and immunotoxicity assessments:
 - Triggered if the class of compound or previous studies in humans or animals give cause for concern
 - ◆ Behavioural tests usually in recovery
- Reproductive function:
 - If histopathological changes in male/female reproductive organs in adult studies or delays in attainment of puberty
 - ◆ Needs group size of 16+ (ICH 4.1.1 – 4.1.3 Repro guidelines)
 - ◆ Usually only assessed in recovery

Summary/Conclusion

- Juvenile toxicity studies are an essential part of the drug development programme.
 - Aim is to support safe testing and use of drugs by paediatric patients.
- Study design will depend on:
 - Timing of use in man
 - Intended therapeutic area
 - Suspected target organs - targeted study design is crucial according to organ system of interest
- Must recognise that organ systems differ between babies and adults. So, variation in anatomical and functional maturation is an important consideration in extrapolation of animal data to man.

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Thank you for listening

Any questions?

