Dose selection
in early paediatric development

Oscar Della Pasqua
Clinical Pharmacology Modelling & Simulation
Outline

- Decision tree for the clinical programme
  - Bridging studies
  - PKPD and Efficacy studies
    (location and shape of the exposure-response curve)

- Recent experience - First time in children
  - scaling for function not for size!

- Cultural and scientific bias
  - demographic covariates versus PKPD relationships

- Relevance of a model-based approach
  - integration of adult data
  - consideration about paediatric issues during the development programme in adults

- Conclusions
Paediatric development strategy

1. Will the drug be used in children?
   - Yes
     2. Is the indication the same as for adults?
       - Yes
         3. Is the disease process similar to that seen in adults?
           - Yes
             4. Is the outcome of therapy likely to be similar in children and adults?
               - Yes
                 5. Does efficacy correspond with blood levels in adults?
                   - Yes
                     6. Does the dose-concentration relationship likely match that of adults?
                       - Yes
                         PD PK & safety data
                         (Efficacy extrapolated from adult data)

   - No
     No paediatric development

2. Is the indication the same as for adults?
   - Yes
     3. Is the disease process similar to that seen in adults?
       - Yes
         4. Is the outcome of therapy likely to be similar in children and adults?
           - Yes
             5. Does efficacy correspond with blood levels in adults?
               - Yes
                 6. Does the dose-concentration relationship likely match that of adults?
                   - Yes
                     PK & safety data
                     (Efficacy extrapolated from adult data)
## Experience in Early Paediatric Development

<table>
<thead>
<tr>
<th>Indication /Study objective</th>
<th>Age</th>
<th>Dose in adults</th>
<th>Dose in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLS - Open label, single dose, dose rising, multi-centre study to assess the tolerability and PK of Ropinirole in adolescent patients</td>
<td>12-17 years old</td>
<td>0.25mg</td>
<td>start dose 0.125mg (0.25 mg if 0.125 well tolerated)</td>
</tr>
<tr>
<td>Seasonal Rhinitis - Double blind comparison of Fluticasone Propionate aqueous spray in children</td>
<td>4-11 years old</td>
<td>200ug od</td>
<td>100 /200 ug od</td>
</tr>
<tr>
<td>Seasonal Allergic Rhinitis (SAR) - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of GW685698X Aqueous Nasal Spray in children</td>
<td>2 to &lt;12 years</td>
<td>100 mcg</td>
<td>50 &amp; 100 mcg</td>
</tr>
<tr>
<td>Migraine - Long-Term Safety Study of a Combination Product Containing Sumatriptan Succinate and Naproxen Sodium in Adolescents</td>
<td>12-17 years old</td>
<td>100 mcg sumatriptan/naproxen 250-500mg bd</td>
<td>85mcg sumatriptan in combination/Naproxen 500mg</td>
</tr>
<tr>
<td>Chemotherapy Antiemetic - An evaluation of the pk properties of IV Ondansetron in children</td>
<td>4-18 years</td>
<td>0.15mg/kg - 3 daily doses at 4 hour intervals</td>
<td>0.15mg/kg - 3 daily doses (4 &amp; 8hrs after initial dose)</td>
</tr>
<tr>
<td>VZV infection - An open-label, multiple-dose, multicenter, pharmacokinetic, safety and tolerability study of Valaciclovir oral suspension in infants and children</td>
<td>1 - &lt;12 years</td>
<td>1000 mg</td>
<td>20mg/kg - 3 times daily</td>
</tr>
<tr>
<td>Eosinophilic esophagitis - A randomised, double-blind, parallel group clinical trial to assess safety, tolerability, PK and PD of mepolizumab (SB240563) (0.55mg/kg, 2.5mg/kg or 10mg/kg) in pediatric patients</td>
<td>2-17 years</td>
<td>Single IV dose up to 100mg/kg - many patients have received up to 10mg/kg</td>
<td>0.55, 2.5, or 10mg/kg</td>
</tr>
<tr>
<td>Anticoagulant - Open label study of Argatroban injection to evaluate the safety and effectiveness in pediatric patients requiring alternatives to Heparin</td>
<td>Birth - 16 years</td>
<td>initial bolus 250-300ug/kg then 20ug/kg/min</td>
<td>initial bolus 100-250 ug/kg then 2 - 3ug/kg/min depending on reason for dosing e.g. cardiac surgery</td>
</tr>
</tbody>
</table>
Key messages

1. The rationale for dosing regimen in clinical trials is often determined by empiricism. Most importantly, medical practice assumes linear relationships between body size, physiological function and clinical response. There is sufficient clinical evidence to revisit this assumption.

2. Current ICH guidelines for age strata ignore important aspects such as incidence of disease, homeostatic mechanisms and (patho)physiological changes which occur within or across the proposed boundaries.

3. Understanding of disease and PKPD relationships should underpin the rationale for dose selection before assigning covariates to adjust for the potential effect of developmental growth on pharmacokinetics, pharmacodynamics and response.

4. Rigid protocols do not meet the needs of this vulnerable population. Flexible study designs are required to ensure optimisation of dosing regimen in early paediatric studies.
ICH Preferences

• **Age strata:**
  – pre-term neonate (<37 weeks gestation)
  – term neonate (0-27 days)
  – infants & toddlers (28 days to 23 months)
  – children (2-11 years)
  – adolescent (12-18 years)

• **Dosing preference:**
  – mg/kg
WHAT IS THE APPROPRIATE DOSE?
WHAT IS THE APPROPRIATE SCALING FACTOR?
Empiricism: problems

Desired clinical response level in adults & children
Approaches for Scaling of Dose

Covariates in PKPD relationships

- Age \[\text{DOSE} = f (\theta \times \text{age})\] mg/year
- Body Surface \[\text{DOSE} = f (\theta \times \text{BSA})\] mg/m²
- Weight \[\text{DOSE} = f (\theta \times \text{weight})\] mg/kg
- Allometric scaling (power function)
  \[\text{DOSE} = f (\theta \times (\frac{\text{wt}_i}{\text{wt}_{std}})^y)\]
- No Normalisation \[\text{DOSE} = \text{Adult dose}\]
What is Allometry?

- From Greek αλλο μετρον (allo metron, ‘other measure’)

- Originally, allometry was first used to define the relationship between size and basal metabolic rate (Kleiber, 1932). He proposed the formula

\[
\text{BMR} = 73.3 \times W^{0.75}
\]

Where BMR is basal metabolic rate, W is weight, 73.3 and 0.75 are two constants (respectively the allometric coefficient and the allometric exponent)
Dose recommendation for marketed drugs with paediatric indication vs. dose adjustment based on allometric scaling

<table>
<thead>
<tr>
<th>brand name</th>
<th>active substance</th>
<th>adult dose (mg, 70 Kg)</th>
<th>paediatric dose (from studies)</th>
<th>WEIGHT (Kg)</th>
<th>dose (mg)</th>
<th>allometric dose (calculated with b=0.75)</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMADINE</td>
<td>emedastine (1 drop = 1/12 ml)</td>
<td>0.083</td>
<td>0.083</td>
<td>20</td>
<td>0.083</td>
<td>0.032</td>
<td>-61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>0.083</td>
<td>0.044</td>
<td>-47%</td>
</tr>
<tr>
<td>EMTRIVA</td>
<td>emtricitabine (HIV)</td>
<td>240</td>
<td>6 mg/Kg</td>
<td>10</td>
<td>60</td>
<td>56</td>
<td>-7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>120</td>
<td>94</td>
<td>-22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>180</td>
<td>127</td>
<td>-29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>240</td>
<td>158</td>
<td>-34%</td>
</tr>
<tr>
<td>ENBREL</td>
<td>etanercept (Rheumatoid arthritis)</td>
<td>25</td>
<td>0.4 mg/Kg</td>
<td>10</td>
<td>4</td>
<td>5.8</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>8</td>
<td>9.8</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>12</td>
<td>13.2</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>16</td>
<td>16.4</td>
<td>3%</td>
</tr>
<tr>
<td>EPIVIR</td>
<td>lamivudine (HIV)</td>
<td>300</td>
<td>4 mg/Kg</td>
<td>10</td>
<td>40</td>
<td>70</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>80</td>
<td>120</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>120</td>
<td>160</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>160</td>
<td>200</td>
<td>25%</td>
</tr>
<tr>
<td>EXJADE</td>
<td>deferasirox (thalassaemia)</td>
<td>1400</td>
<td>20 mg/Kg</td>
<td>10</td>
<td>200</td>
<td>325</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>400 (UP)</td>
<td>550</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>600 (UP)</td>
<td>740</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>800</td>
<td>920</td>
<td>15%</td>
</tr>
</tbody>
</table>
Differences in Exposure and Response

- Anatomy/Physiology
  - Structure & function
  - Homeostasis

- Disease
  - Co-morbidities

- Pharmacodynamics
  - Sensitivity

- Pharmacokinetics
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

- Pharmaceutics
  - Formulation and delivery
The size of the liver relative to total body weight decreases from infancy to adolescence.

Liver blood flow (as a proportion of cardiac output) changes with body size (and hence age):
Co-morbidities

Paediatric Bipolar Disorder and ADHD

Comorbidities have impact on:

- Inclusion and exclusion criteria
- Different AE profile from adults
- Different Effect size and variability
- Drug-drug interactions

**TABLE 2. Scores on Measures of Mania and Attention Deficit Hyperactivity Disorder (ADHD) Severity for Patients With**

<table>
<thead>
<tr>
<th>Study Phase and</th>
<th>Treatment</th>
<th>With</th>
<th>response to treatment %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label trial</td>
<td>Baseline (N=40)</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Crossover trial</td>
<td>Last visit while divalproex sodium</td>
<td>89.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=30)</td>
<td>10.0</td>
<td></td>
</tr>
</tbody>
</table>

a) Treatment response was defined as a CGI improvement score of 1 or 2.
b) Treatment response was defined as a CGI improvement score of 1 or 2.

c) Patients received 8 weeks of treatment with open-label divalproex sodium (median dose=750 mg/day at the end of the open-label phase).
d) Patients with a ≥50% reduction in the baseline Young Mania Rating Scale score at the end of the 8-week open-label phase were randomly assigned to receive, in addition to divalproex sodium, either mixed amphetamine salts (5 mg by mouth b.i.d.) or placebo for 2 weeks under double-blind conditions and then the alternative treatment (in addition to divalproex sodium) for 2 weeks.
e) N=29 for CGI improvement score for ADHD symptoms.
f) N=28 for Young Mania Rating Scale score.
Factors affecting rate and extent of absorption

Inhaled drugs
Operational Considerations
Study Design

• Staggered X Sequential Paediatric Programme

• Chronic X Acute Indication

• PK Differences Only

• Different PK/PD Relationship and AE profiles
Operational Considerations

Study Design

• Clinical endpoints
  – validation of assessment scales
  – tailored equipment

• Sampling techniques
  – sparse population sampling
  – sensitive assays
  – collection methodology

• Data Analysis
“Bridging” Studies

• Criteria for extrapolation from adult data
  – same indication as adults
  – disease process similar to adults
    (i.e., similar PKPD relationships)
  – outcome of therapy likely to be comparable

• In addition:
  – PK in adult patient population available
Sumatriptan for Migraine Attacks in adolescents and children

Similar exposure to adult migraineurs treated with 20mg sumatriptan nasal spray

- 9, 10 or 11 years of age
  - 10 mg of sumatriptan NS unless weight > 40 kg
  - Children with weight > 40 kg: 20 mg.

- 6, 7 or 8 years of age
  - 5 mg of sumatriptan NS unless weight > 25 kg
  - Children with weight > 25 kg: 10 mg.

PK model (common to all populations)

1. Depot Cpt
   - $F_1(\theta, \eta) = \text{fraction of Dose}$
   - $K_a(\theta)$

2. Central Cpt:
   - $C_p(\varepsilon)$
   - $V_d(\theta, \eta), Cl(\theta, \eta)$

$F_2 = 1 - F_1$

- **Changes of CL/F with Weight**
  - Children
  - Adolescent
  - Adult

- **Children**
  - **Ado data**
  - **Combined data**

- **Sumatriptan conc (ng/mL)**

- **Time (hr)**

- **Weight (kg)**

- **CL/F (L/h)**

- **Sumatriptan conc (ng/mL)**

- **Time (hr)**
Incorporation of priors (adult PK) - Bayesian hierarchical models -

Use PK parameters in adults to support parameter estimation in children

Priors can also contribute to characterising whether estimates originate from the same parameter distribution

Sparse sampling scheme, mandatory in paediatrics, difficult to fit
Incorporation of priors (adult PK) - Bayesian hierarchical models -

Example of analysis in HIV
Incorporation of priors (adult PK) - Bayesian hierarchical models -

In a bridging study for the HIV indication, dose adjustments are aimed at achieving exposure equivalent to the reference population (i.e., adults). Model-predicted exposure (AUC) for doses of antiviral therapy, which are required to achieve the median adult exposure:

<table>
<thead>
<tr>
<th>Weight (Kg)</th>
<th>Predicted dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>30</td>
<td>260</td>
</tr>
<tr>
<td>40</td>
<td>320</td>
</tr>
</tbody>
</table>
PKPD and Efficacy Studies

There are design possibilities that may be more efficient, i.e., giving a surer answer about the location & shape of the exposure-response curve, providing important data for subsequent regulatory studies.

These include:

• Enrichment approaches - larger effect sizes give surer answers
• Better dose finding - a useful titration design (Sheiner) and attention to dose throughout Phase III
• Reversing the sequence - the randomised withdrawal study
Outcome of antiviral therapy with zidovudine in patients with HIV, comparing RDCT with RCCT. Study duration 52 weeks with PK assessment at week 2 and dose adjustment at week 4.

The Kaplan-Meier survival analysis for the probability of CD4+ cell counts remaining above 90% of the baseline value shows a significantly superior response in the group of patients who were assigned to a target concentration of 0.17 mg/L or greater compared with patients assigned to the 300 mg BID standard dosage.

PKPD Modelling - Sotalol in SVT

PK/PD relationship

Effect of Age on Clearance

Probability of arrhythmia suppression in the 15 children with supraventricular tachycardia vs sotalol trough concentration under steady-state conditions and an 8-h dosing interval.

Filled circles  6 neonates (28 days).

Measured (closed diamonds) and model predicted oral sotalol clearance based on body weight (open diamonds). Median (solid line) and the 10th and 90th percentile (dashed line) of 1,000 simulated data sets.

Dose Recommendation

Age-specific Dose regimen for sotalol in Children with SVT

Black box plots and hatched bars indicate recommended dosing range. (A) Simulated sotalol trough concentrations (125 patients per group and dose level) for paediatric patients with supraventricular tachycardia. Lines indicate 50% and more than 95% efficacy. (B) Patient fraction with 50% and more than 95% probability of arrhythmia suppression. Arrows indicate start and target doses.
Summary

- Decision tree for the clinical programme
  - Bridging studies
  - PKPD and Efficacy studies
    (location and shape of the exposure-response curve)

- Recent experience - First time in children
  - scaling for function not for size!

- Cultural and scientific bias
  - demographic covariates versus PKPD relationships

- Relevance of a model-based approach
  - integration of adult data
  - consideration about paediatric issues during the development programme in adults
Conclusions

1. The rationale for dosing regimen in clinical trials is often determined by empiricism. Most importantly, medical practice assumes linear relationships between body size, physiological function and clinical response. There is sufficient clinical evidence to revisit this assumption.

2. Current ICH guidelines for age strata ignore important aspects such as incidence of disease, homeostatic mechanisms and (patho)physiological changes which occur within or across the proposed boundaries.

3. Understanding of disease and PKPD relationships should underpin the rationale for dose selection before assigning covariates to adjust for the potential effect of developmental growth on pharmacokinetics, pharmacodynamics and response.

4. Rigid protocols do not meet the needs of this vulnerable population. Flexible study designs are required to ensure optimisation of dosing regimen in early paediatric studies.