Introduction to population PKPD modelling in paediatric clinical pharmacology

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What is the problem?

- Drugs dosing in children is largely empirical
- Frequent under- and overdosing problems
- Efficacy and safety of drugs, in particular in (premature) newborns is largely unknown

Body weight is used for dose adjustment instead of the PKPD relationships
PKPD MODELING: What is it?
Clinical Questions

• How to identify a **safe and effective** dosing regimen in children in different age groups?
  - First time in kids (early drug development)
  - Change in indication or age group, including neonates (clinical practice)

• **Which** factor(s) should be used to adjust the dose for the individual child in different age groups?
  - dosing recommendation in the label
Paediatric Research Issues

Unbalanced vs balanced designs:
- 100 observations for subject A
- 1 observation for subject B

Sparse vs. serial data:
- 2 measurements per subject
Population approach

Simultaneous analysis of all available data:

PK and/or PD parameters are simultaneously estimated taking into account differences between patients

1. POPULATION PK and/or PD parameters (fixed effects)
2. Inter-individual variability
3. Residual error
Population PKPD modelling

![Graph showing predictions and observations over time.](image)

- Residual error
- Inter-individual variability

**Predicted**

**Observed**

- ID=1 (pred)
- ID=1 (obs)
- ID=2 (pred)
- ID=2 (obs)
- ID=3 (pred)
- ID=3 (obs)
• Applicable to sparse and unbalanced data sets (neonates, children, etc)

• **Scientific basis for study/trial simulations, dose adjustment or labeling extensions in other populations (intra and interspecies)**

• **Covariate analysis for identification of predictors of variability in PK and PD (genetics, body weight, age, interactions etc)**
Ventilated children (1-5 yrs) following cardiac surgery in the ICU

Knibbe et al., Br J Clin Pharmacol 2002

6 samples of 250 ul per child
6 children

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min)</td>
<td>35*</td>
<td>2.3</td>
</tr>
<tr>
<td>(ml/kg/min)</td>
<td></td>
<td>28*</td>
</tr>
<tr>
<td>V1 (l)</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>(l/kg)</td>
<td>0.78*</td>
<td>0.26*</td>
</tr>
<tr>
<td>Q (l/min)</td>
<td>0.35</td>
<td>1.4</td>
</tr>
<tr>
<td>(l/kg/min)</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>V2 (l)</td>
<td>24</td>
<td>139</td>
</tr>
<tr>
<td>(l/kg)</td>
<td>1.54</td>
<td>1.88</td>
</tr>
</tbody>
</table>
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• Covariate analysis for identification of predictors of variability in PK and PD (genetics, body weight, age, interactions etc)
Propofol in non-ventilated children

Peeters MYM et al., Anesthesiology 2006; 104(3):466-474
Propofol in nonventilated children

Knibbe, observed conc, Rigby-Jones, Schuttler, current study

Peeters MYM et al., Anesthesiology 2006 Mar; 104(3):466-474
COMFORT-B

6 behaviour items

- alertness
- Calmness/agitation
- Respiratory response / crying
- Physical movement
- Muscle tone
- Facial tension

**Alertness**
- Deeply asleep (eyes closed, no response to changes in the environment)
- Lightly asleep (eyes mostly closed, occasional responses)
- Drowsy (child closes his/her eyes frequently, less responsive to the environment)
- Awake and alert (child responsive to the environment)
- Awake and hyper-alert (exaggerated responses to environmental stimuli)

**Calmness/agitation**
- Calm (child appears serene and tranquil)
- Slightly anxious (child shows slight anxiety)
- Anxious (child appears agitated but remains in control)
- Very anxious (child appears very agitated, just able to control)
- Paralyz (severe distress with loss of control)

**Respiratory response**
- No coughing and no spontaneous respiration
- Spontaneous respiration with little or no response to ventilation
- Occasional cough or resistance to ventilator
- Actively breathes against ventilator or coughs regularly
- Fights ventilator, coughing or choking

**Crying**
- Quiet breathing, no crying sounds
- Occasional sobbing or moaning
- Whining (monotonous sound)
- Crying
- Screaming or shrieking

**Physical movement**
- No movement
- Occasional (three or fewer) slight movements
- Frequent (more than three) slight movements
- Vigorous movements limited to extremities
- Vigorous movements including torso and head

**Muscle tone**
- Muscles totally relaxed; no muscle tone
- Reduced muscle tone; less resistance than normal
- Normal muscle tone
- Increased muscle tone and flexion of fingers and toes
- Extreme muscle rigidity and flexion of fingers and toes

**Facial tension**
- Facial muscles totally relaxed
- Normal facial tone
- Tension evident in some facial muscles (not sustained)
- Tension evident throughout facial muscles (sustained)
- Facial muscles contorted and grimacing

**VAS (Visual Analogue Scale)**
Put a mark on the line below to indicate how much pain you think the child has at this very moment.

- Total score

**Details medication**

**Details child’s condition**

**Type of assessment**

(before or after medication or standard assessment)
Non-agitated children

Peeters et al., Anesthesiology, March 2006
Peeters et al., Anesthesiology, March 2006
Model based advised propofol dose
30 mg/h for a postoperative child of 10 kg

Peeters et al., Anesthesiology, March 2006
• Applicable to sparse and unbalanced data sets (neonates, children, etc)

• Scientific basis for study/trial simulations, dose adjustment or labeling extensions in other populations (intra and interspecies)

• Covariate analysis for identification of predictors of variability in PK and PD (genetics, body weight, age, interactions etc)
Body weight or age?
Identification of potential covariates
(based weight, gender, age, renal function, PGx etc).

Graphical evaluation of each covariate versus
- The individual post-hoc PK or PD parameter estimate
- The weighted residuals

Statistical evaluation using standard techniques
1. Change in objective function
2. Standard error of the additional parameter
3. Improvement of individual fits
4. Diagnostics: B) observed versus model-predicted

Peeters MY et al., Anesthesiology, March 2006 and Dec 2006, CP&T March 2008
When more than one significant covariate for the simple model is found, the covariate-adjusted model with the largest decrease in objection function is chosen as a basis to explore the influence of additional covariates sequentially with the use of the same criteria.

Forward inclusion and backward deletion

Peeters MY et al., Anesthesiology, March 2006 and Dec 2006, CP&T March 2008
Nature of the influence of the covariate

- preferably non-empirical (mechanism/physiologically based)
- Consider the possibility of potential extrapolation or interpolation

Validation confirms the influence of the covariates

Peeters MY et al., Anesthesiology, March 2006 and Dec 2006, CP&T March 2008*
Morphine PK in Children

- 250 children:
  - 70 premature neonates,
  - 60 neonates,
  - 60 < ½ yr,
  - 30 < 1 yr,
  - 30 < 3 yr
- 1-4 samples/24 h/pt
- BW median 2.8 kg

Supported by a grant of the Sophia Stichting voor Wetenschappelijk Onderzoek
Influence of postnatal age >/ < 10 d

Independent of gestational time or body weight at birth
Formation clearance to M3glucuronide observed versus model-predicted

Post natal age < 10 d

Post natal age > 10 d
Validation of sparse data studies

- Diagnostics
  (e.g. observed versus model-predicted)
Validation of sparse data studies

• **Diagnostics** (e.g., observed versus model-predicted)

• **Bootstrap resampling**
  - repeated random sampling to produce another data set (same size but different combination of individuals)
  - Compare parameters (250 times) with estimates from the original data set

• **Visual predictive check**
  - Simulation with final estimates and compare the distribution of the observations with the simulated distribution
  - Plot of the time course of the observations and prediction interval for the simulated values
Validation of sparse data studies

• Diagnostics (e.g. observed versus model-predicted)

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    (same size but different combination of individuals)
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  - Plot of the time course of the observations and prediction interval for the simulated values

• Normalised Prediction Discrepancy Errors (NPDE)

1) Brendel et al. Pharm. Res. 23(9); 2036-49 (2006)
Points to consider

- Use of the population approach (nonlinear mixed effects modelling) in all phases of the investigation

- Validation of population PKPD models

- Infrastructure for data sharing

- Neonates deserve further attention
Neonates, young infants are different!
Conclusions

- Population PK-PD modelling (or non linear mixed effects modelling) should be the PRIMARY ANALYSIS METHOD in paediatric drug development and dosing studies.
- Population PK-PD models can be also be developed based on data from PREVIOUS CLINICAL STUDIES (retrospective studies/meta analyses).
- Dosing regimen based on VALIDATED POPULATION PK-PD MODELS should be included in the LABEL of drugs.
Mechanism-based PK-PD modeling platform

- University-Industry consortium with 6 industrial partners (Eli Lilly, GSK, Johnson & Johnson, Organon, Nycomed, Pfizer)
- Unique infrastructure for data management, data analysis and reporting: sharing of data, models and biological system specific information
- Emphasis on key factors in drug discovery and development
  - Translational pharmacology (efficacy and safety)
  - Developmental pharmacology (pediatrics, elderly)
  - Disease system analysis
Multidisciplinary, multicentre research

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*Supported by NWO/Veni*

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Dr. J. De Jongh  
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