Characterizing and Forecasting Individual Weight Changes in Term Neonates

Mélanie Wilbaux PhD, S. Kasser MD, S. Wellmann MD, O. Lapaire MD, J.N. van den Anker MD, Marc Pfister MD

Pediatric Pharmacology & Pharmacometrics
Division of Neonatology, Children’s Hospital Basel (UKBB)
Obstetrics and Gynecology, University Hospital Basel (USB)

25th PAGE Meeting
8 June 2016
Pediatrics – A Heterogeneous Population

Pediatrics – A Heterogeneous Population

Body Composition

Proportion of body weight

- mineral
- fat
- protein
- water

Motivation

• **Weight changes** during the first week of life in **term neonates**:

  • Excessive weight loss (>10%) has negative effects on development and increases the risk for serious **clinical long term complications**

  ➢ To further **improve care of neonates** by clinicians, nurses, midwives, and mothers
Objectives

• **Develop** a pharmacometric model characterizing weight changes in healthy term neonates exclusively breastfed

• **Identify and quantify** effects of maternal and neonatal factors

• **Forecast** individual weight changes up to 7 days of life

• **Provide a user-friendly online monitoring tool** to support neonatologists and other caregivers
Data

- Retrospective single-center study at University Hospital of Basel & University Children’s Hospital Basel: maternal and neonatal data
- A total of 1335 healthy term neonates exclusively breastfed
- Longitudinal body weight data up to the first 7 days of life
- Neonatal and maternal characteristics:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median [min - max]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female / Male</td>
<td>50% / 50%</td>
</tr>
<tr>
<td>Delivery Mode: C-section / Vaginal Delivery</td>
<td>16% / 84%</td>
</tr>
<tr>
<td>Mother’s Age (years)</td>
<td>32 [17 - 47]</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>40 [37 – 42]</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>3390 [2410 - 4610]</td>
</tr>
</tbody>
</table>

- A total of 300 additional neonates for advanced evaluation
Development of a **pharmacometric model** by characterizing weight changes as a net balance between weight gain and weight loss rates.

\[
\frac{d\text{Weight}}{dt} = Kin - Kout \times \text{Weight}
\]
Development of a **pharmacometric model** by characterizing weight changes as a net balance between weight gain and weight loss rates

\[
\frac{d\text{Weight}}{dt} = Kin(t) - Kout(t) \times \text{Weight}
\]

*Kin* and *Kout* describe using **time-dependent** mathematical functions.
Methods – Model Development

\[
\frac{d\text{Weight}}{dt} = \text{Kin}(t) - \text{Kout}(t) \times \text{Weight}
\]

**Kin vs. Time**

- Weight gain rate (Kin, g.day\(^{-1}\))
- Onset of milk production

**Kout vs. Time**

- Weight loss rate (Kout, day\(^{-1}\))
- Initial loss of fluid
Methods – Modeling Method

- Non-linear mixed effects modeling:
  - NONMEM 7.3 (FOCEI algorithm)

- Model selection & evaluation:
  - Maximization of the likelihood
  - Standard error (SE)
  - Goodness-of-fit (GOF) plots
  - Simulation-based diagnostics (Visual predictive Check: VPC)

- Search for covariates:
  - Clinical relevance
  - Standard stepwise forward selection – backward deletion approach
Results - Final Model

\[ \frac{d\text{Weight}}{dt} = K\text{in}(t) - K\text{out}(t) \times \text{Weight} \]
\[ \text{Weight}(t = 0) = WT0 \]

- **Kin(t):** Weight gain rate:

  - IF \( t < TLag \): \( Kin(t) = 0 \)
  - IF \( t \geq TLag \): \( Kin(t) = Kin_{Base} \times \exp^{Kin_{PNA} \times t} \)

  \( TLag = 2 \text{ days} \) for vaginal delivery
  \( TLag = 3 \text{ days} \) for C-section

- **Kout(t):** Weight loss rate:

  \[ K\text{out}(t) = \frac{K\text{out}_{max} \times t^{-H}}{T50^{-H} + t^{-H}} + K\text{out}_{Base} \times \exp^{K\text{out}_{PNA} \times t} \]

  Saturable Emax with Hill coefficient

  Exponential
Results - Covariates

- 5 covariate – parameter relationships:

  - **Gender** effect on $WT0$: $WT0_{Male} > WT0_{Female}$
Results - Covariates

- 5 covariate – parameter relationships:
  - Positive **GA** effect on $WT_0$
Results - Covariates

- 5 covariate – parameter relationships:
  - Positive **GA** effect on $K_{n_{Base}}$

![Graph showing the effect of gestational age (GA) on KinBase over time.](image-url)
Results - Covariates

• 5 covariate – parameter relationships:

  • Positive **mother age** effect on $WT0$:

    -> **Hypothesis**: age-dependent changes in mother’s glucose metabolism$^1$

Results - Covariates

• 5 covariate – parameter relationships:

  • Negative **mother age** effect on $K_{in_{Base}}$

-> **Hypothesis**: decreased milk production with mother’s age

---

Results - Goodness-of-fit Plots

Individual Predictions, Observations and Population Predictions vs. Time
Results - Goodness-of-fit Plots

CWRES vs. Population Predictions

CWRES vs. Time
**Results - Visual Predictive Check**

**Advanced Validation:** good predictive performance with accuracy (MAE=0.52%) and no bias (MPE=0.01%)
Results - Parameter Estimates

- Typical birth weight: \( WT_0 = 3470 \, g \)
- Typical basal rate of weight gain: \( Kin_{Base} = 41.51 \, g. \, day^{-1} \); \( IIV = 30\% \)
- Maximum rate constant of weight loss (\( K_{out_{max}} \)) slowed by one-half at: \( T_{50} = 1.9 \, days \)
- Variability on \( Kin \) and \( WT_0 \) explained by covariates
- Remaining non-explained variability on \( K_{out} \) (80%)
Clinical Application - Concept

Forecast individual weight changes up to 7 days as soon as possible after birth

- Use of **3 initial weight observations** during first 48 hours of life: birth weight + 2 weight measurements
- **Apply model** to forecast individual weight changes up to 7 days
Clinical Application - Evaluation

Forecast individual weight changes up to 7 days as soon as possible after birth

• Good graphical agreement:

• Predictive performance:
  – Good precision (MAE = 1.54 %)
  – No bias (MPE = -0.74 %)
## NeoWeight Prediction Tool – Input

### General Information
- **Gestational Age**: 39 weeks
- **Sex**: Female
- **Delivery Mode**: C-Section
- **Mother’s Age (years)**: 35

### Birth Weight
- **Observed Weight**: 3660 g
- **Date and Time**: 05/01/2016 10:30 PM

### Subsequent weight measurements

<table>
<thead>
<tr>
<th>Observed Weight</th>
<th>Observed Weight Unit</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3580 g</td>
<td></td>
<td>05/02/2016 9:00 AM</td>
</tr>
<tr>
<td>3400 g</td>
<td></td>
<td>05/03/2016 9:00 AM</td>
</tr>
</tbody>
</table>

---

http://neoweight.mashframe.com/
NeoWeight Prediction Tool – Output

Absolute Weight vs. Time

- Observed weight values
- Forecasted weight change

Percentage Weight Change from Baseline vs. Time

- 8% Weight loss
- 10% Weight loss
Conclusions

- **First pharmacometric model** characterizing weight changes in healthy term neonates exclusively breastfed

- **User-friendly online NeoWeight Prediction tool** allowing caregivers to:
  - Forecast and appropriately monitor individual weight changes
  - Personalize and optimize care of neonates
Outlooks – Model Expansion

- Pre-term neonates
- Sick neonates
- Neonates with additional formula
- Data up to 60 days
- Mother with pregnancy disorder
Thank you!