Plasma concentration observations (µg/ml) vs Time (min)
Young children (age < 3 years)
Children (3 ≤ age < 18 years)

- Observed / population predicted concentration
- Observed / posthoc predicted concentration

- Observed concentration (µg/ml)
- Population predicted concentration (µg/ml)
- Posthoc predicted concentration (µg/ml)
Adults (18 ≤ age < 70 years, BMI < 30)
Elderly (age ≥ 70 years)

Observed / population predicted concentration

Time (min)

Observed / posthoc predicted concentration

Time (min)

Observed concentration (µg/ml)

Population predicted concentration (µg/ml)

Observed concentration (µg/ml)

Posthoc predicted concentration (µg/ml)
High BMI (BMI ≥ 30)
Evaluating model performance during model development

All data
10927 observations

NONMEM estimation

2-fold Cross-validation

Dataset 1
5562 observations

Dataset 2
5365 observations

NONMEM estimation

Predict Dataset 2

Predict Dataset 1

Patients only
0.5 ≤ Cobs ≤ 8 µg/ml
Time > 2 min
5492 observations

AIC
Median APE

Young children
409 observations

Performance metric

Children
915 observations

Performance metric

Adults
3381 observations

Performance metric

Elderly
334 observations

Performance metric

High BMI
465 observations

Performance metric

Average performance metric

Performance comparison during model development
Evaluation of intra-operative predictive performance (Table 5)

All data
10927 observations

Predict using PK model

Patients only
0.5 ≤ Cobs ≤ 8 µg/ml
Time > 2 min
5492 observations

Young children
409 observations
Median PE
Median APE
Performance metric

Children
915 observations
Median PE
Median APE
Performance metric

Adults
3381 observations
Median PE
Median APE
Performance metric

Elderly
334 observations
Median PE
Median APE
Performance metric

High BMI
465 observations
Median PE
Median APE
Performance metric
Evaluation of overall predictive performance (Table 6)

All data
10927 observations

Predict using PK model

Young children
569 observations

Median PE
Median APE
Performance metric

Children
1378 observations

Median PE
Median APE
Performance metric

Adults
6685 observations

Median PE
Median APE
Performance metric

Elderly
1127 observations

Median PE
Median APE
Performance metric

High BMI
1244 observations

Median PE
Median APE
Performance metric
Bootstrap resampling and Likelihood profiles

Uncertainty in the estimated population typical parameters was evaluated using bootstrap resampling and likelihood profiles. For bootstrap resampling 350 resamples were evaluated. The results of estimations were used regardless of NONMEM termination criteria. The red line is the NONMEM estimated population typical value. In the likelihood profiles the dark shaded area indicates the p<0.05 region and the light shaded area indicates the p<0.01 region.

\[
f_{\text{sigmoid}}(x,E\frac{50}{\lambda}) = x^\lambda / (x^\lambda + E^50^\lambda)
\]

\[
\text{ADLT} = f_{\text{sigmoid}}(\text{WGT},\Theta_{13},\Theta_{14})
\]

\[
f_{\text{aging}}(x) = e^{-0.001 \cdot (\text{AGE} - 35) \cdot x}
\]

\[
\text{CLAG} = 1 - f_{\text{sigmoid}}(\text{PMA},\Theta_{16},8)
\]

\[
\text{PMAL} = \begin{cases} 
  f_{\text{sigmoid}}(\text{PMA},\Theta_{15},8), & \text{male} \\
  0, & \text{female}
\end{cases}
\]

\[
\text{KGEN} = e^{\Theta_{22} \cdot \text{CLAG} \cdot (1 - \text{PMAL}) + 1 - \text{CLAG} \cdot \text{PMAL} \cdot \text{ADLT}}
\]

\[
\text{V1}(l) = \begin{cases} 
  \Theta_1, & \text{healthy} \\
  \Theta_7, & \text{patient}
\end{cases}
\]

\[
\text{V2}(l) = \begin{cases} 
  \Theta_2, & \text{healthy} \\
  \Theta_8, & \text{patient}
\end{cases}
\]

\[
\text{V3}(l) = \begin{cases} 
  \Theta_3, & \text{healthy} \\
  \Theta_9, & \text{patient}
\end{cases}
\]

\[
\text{CL}(l/\text{min}) = \begin{cases} 
  \Theta_4, & \text{healthy} \\
  \Theta_{10}, & \text{patient}
\end{cases}
\]

\[
\text{Q2}(l/\text{min}) = \begin{cases} 
  \Theta_5, & \text{healthy} \\
  \Theta_{11}, & \text{patient}
\end{cases}
\]

\[
\text{Q3}(l/\text{min}) = \begin{cases} 
  \Theta_6, & \text{healthy} \\
  \Theta_{12}, & \text{patient}
\end{cases}
\]

\[
C_{\text{observed}} = C_{\text{predicted}} \cdot [1 + \text{RES}^2 \cdot \epsilon_1 \cdot e^{\Theta_6}] + \epsilon_2
\]

Where \(\Theta_{1-23}\) are estimated parameters from the model and \(\eta_1-\eta_8\) represent random variables of variances denoted in Table 4. \(\text{AGE}, \text{WGT} \) and \(\text{PMA}\) represent an individuals age in years, weight in kg and post-menstrual age in years \((\text{AGE}+40/52)\), respectively. \(\text{RES}\) is the proportional residual error for each component dataset. Error variance \(\epsilon_1\) was fixed to a variance of 1 and \(\epsilon_2\) was estimated from the data. Constants with a subscript \(\text{ref}\) are calculated for the reference individual.
Table 1: Estimated model parameters compared to results from bootstrap resampling.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated value</th>
<th>350 Bootstrap resamples</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Percentile</td>
<td>25%</td>
<td>75%</td>
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<tr>
<td>$\Theta_1$</td>
<td>5.74</td>
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<td>5.75</td>
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<td>$\Theta_2$</td>
<td>11.8</td>
<td>11.8</td>
<td>11.8</td>
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<td>12.9</td>
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<td>$\Theta_3$</td>
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<td>223</td>
<td>225</td>
<td>210</td>
<td>238</td>
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<tr>
<td>$\Theta_4$</td>
<td>1.83</td>
<td>1.84</td>
<td>1.84</td>
<td>1.79</td>
<td>1.88</td>
</tr>
<tr>
<td>$\Theta_5$</td>
<td>3.10</td>
<td>3.14</td>
<td>3.11</td>
<td>2.84</td>
<td>3.39</td>
</tr>
<tr>
<td>$\Theta_6$</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>0.99</td>
<td>1.17</td>
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<tr>
<td>$\Theta_7$</td>
<td>9.77</td>
<td>9.65</td>
<td>9.66</td>
<td>9.32</td>
<td>9.97</td>
</tr>
<tr>
<td>$\Theta_8$</td>
<td>29.0</td>
<td>29.1</td>
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<td>27.6</td>
<td>30.6</td>
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<tr>
<td>$\Theta_9$</td>
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<td>133</td>
<td>133</td>
<td>128</td>
<td>139</td>
</tr>
<tr>
<td>$\Theta_{10}$</td>
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<td>1.55</td>
<td>1.54</td>
<td>1.51</td>
<td>1.57</td>
</tr>
<tr>
<td>$\Theta_{11}$</td>
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<td>1.44</td>
<td>1.44</td>
<td>1.39</td>
<td>1.49</td>
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<tr>
<td>$\Theta_{12}$</td>
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<td>0.60</td>
<td>0.60</td>
<td>0.58</td>
<td>0.63</td>
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<tr>
<td>$\Theta_{13}$</td>
<td>16.6</td>
<td>16.5</td>
<td>16.4</td>
<td>15.7</td>
<td>17.2</td>
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<tr>
<td>$\Theta_{14}$</td>
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<td>2.79</td>
<td>2.78</td>
<td>2.63</td>
<td>2.93</td>
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<td>$\Theta_{15}$</td>
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<tr>
<td>$\Theta_{16}$</td>
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<tr>
<td>$\Theta_{17}$</td>
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<td>0.35</td>
<td>0.34</td>
<td>0.30</td>
<td>0.39</td>
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<td>$\Theta_{19}$</td>
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<td>$\Theta_{21}$</td>
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<td>$\Theta_{22}$</td>
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<td>0.864</td>
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<td>$\Theta_{23}$</td>
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<td>0.263</td>
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<tr>
<td>Variance</td>
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<td></td>
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<td>$\eta_1$</td>
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<td>0.037</td>
<td>0.029</td>
<td>0.017</td>
<td>0.049</td>
</tr>
<tr>
<td>$\eta_2$</td>
<td>0.323</td>
<td>0.326</td>
<td>0.330</td>
<td>0.295</td>
<td>0.352</td>
</tr>
<tr>
<td>$\eta_3$</td>
<td>0.294</td>
<td>0.296</td>
<td>0.294</td>
<td>0.267</td>
<td>0.322</td>
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<tr>
<td>$\eta_4$</td>
<td>0.318</td>
<td>0.318</td>
<td>0.316</td>
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<td>0.344</td>
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<tr>
<td>$\eta_5$</td>
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<td>0.068</td>
<td>0.068</td>
<td>0.064</td>
<td>0.072</td>
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<tr>
<td>$\eta_6$</td>
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<td>0.126</td>
<td>0.103</td>
<td>0.147</td>
</tr>
<tr>
<td>$\eta_7$</td>
<td>0.091</td>
<td>0.088</td>
<td>0.087</td>
<td>0.070</td>
<td>0.105</td>
</tr>
<tr>
<td>$\eta_8$</td>
<td>0.044</td>
<td>0.042</td>
<td>0.041</td>
<td>0.037</td>
<td>0.046</td>
</tr>
</tbody>
</table>
Bootstrap distribution of population parameter estimates (350 resamples)