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The allometric exponent for scaling clearance varies with age: a study on seven propofol datasets ranging from preterm neonates to adults

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SUMMARY

*Aim:* For scaling clearance between adults and children, allometric scaling with a fixed exponent of 0.75 is often applied. In this analysis, we performed a systematic study on the allometric exponent for scaling propofol clearance between two subpopulations selected from neonates, infants, toddlers, children, adolescents and adults.

*Methods:* Seven propofol studies were included in the analysis (neonates, infants, toddlers, children, adolescents, adults1, and adults2). In a systematic manner, two out of the six study populations were selected resulting in 15 combined datasets. In addition, the data of the seven studies were regrouped into five age-groups (FDA Guidance 1998), from which four combined datasets were prepared consisting of one paediatric age-group and the adult group. In each of these 19 combined datasets, the allometric scaling exponent for clearance was estimated using population pharmacokinetic modelling (NONMEM 7.2).

*Results:* The allometric exponent for propofol clearance varied between 1.11 and 2.01 in case the neonate dataset was included. When two paediatric datasets were analysed, the exponent varied between 0.2 and 2.01, while it varied between 0.56 and 0.81 when the adult population and a paediatric dataset except for neonates were selected. Scaling from adults to adolescents, children, infants and neonates resulted in exponents of 0.74, 0.70, 0.60 and 1.11 respectively.

*Conclusions:* For scaling clearance, $\frac{2}{3}$ allometric scaling may be of value for scaling between adults and adolescents or children, while it can neither be used for neonates nor for two paediatric populations. For scaling to neonates an exponent between 1 and 2 was identified.
3.1. Introduction

In paediatric pharmacokinetic (PK) modeling, scaling of pharmacokinetic parameters and in particular of clearance is a major issue, as it provides the rationale for tailoring suitable doses in children [1-3]. Scaling is required both in paediatric drug development for dose finding and selection of new drugs and in clinical practice where dose optimization and individualization is being performed when treating children. Accordingly, in paediatric drug development scaling of PK parameters between adults and the target paediatric population is highly relevant, while in clinical practice it may be relevant to scale within the paediatric population, i.e. a dose from children to neonates. For both purposes, currently the $\frac{3}{4}$ allometric scaling approach is nowadays propagated.

Allometric scaling was originally brought up to describe metabolic rates between different species [4]. The allometric scaling function for clearance can be described as

$$CL_i = CL_{std} \times \left(\frac{BW_i}{BW_{std}}\right)^{\exp{CL}}$$  \hspace{1cm} (1)

where $CL_i$ represents clearance for an individual with bodyweight $BW_i$, $CL_{std}$ represents clearance for a standard individual with bodyweight $BW_{std}$ and $\exp{CL}$ is the allometric scaling exponent which was proposed to be $\frac{3}{4}$ for metabolic rate [4]. Later on, for the purpose of scaling clearance from adults to children, this allometric exponent was also proposed to be fixed to a value of 0.75 [5], which leads to an over-prediction of clearance values for young children [6, 7]. In order to account for this discrepancy, a maturation function on the basis of age was proposed and applied in many studies [5]. More recently, a bodyweight-dependent exponent model was reported to cope with over-prediction of clearance at youngest age ranges by allowing the exponent value to vary with bodyweight [8]. Without the need for an age-based function, this approach was reported to capture changes in clearance from preterm neonates to adults for propofol [8] and from 1 month infants to adults for busulfan [9]. Even though the exact value for the exponents slightly varied between these drugs, typically higher values for the exponent were identified at younger age ranges, representing higher maturation rates at lower bodyweights.
In absence of specific information on the age-based maturation function required for the application of the allometric scaling theory [5] or on specific values of the bodyweight dependent exponent function [8, 9], allometric scaling based on bodyweight alone may be applied during paediatric drug development or when analysing data from clinical practice. In literature, both a fixed value of 0.75 [10-12] and an estimated value [13-15] for the allometric exponent have been reported for scaling clearance in children.

In this study, we did a series of hypothetical analyses by applying the allometric scaling function for clearance on two types of combined datasets from seven previously published propofol studies consisting of neonates, infants, toddlers, children, adolescents and adults. Combined datasets could consist of two study populations (type I models) or two age groups according to FDA Guidance 1998 [16] (type II models). In these combined datasets, the allometric exponents for clearance were estimated and the performances of the scaling function were evaluated in order to investigate the feasibility and boundary of the allometric scaling method without an age-based maturation function in both clinical practice situation and paediatric drug development situation.

### 3.2. Methods

#### 3.2.1. Subjects of the original studies

A total of 174 subjects from seven previously published studies on propofol PK were included in the current study, including neonates (1-25 days) [17], infants (3.8-17.3 months) [18], toddlers (12-31 months) [19], children (3-11 years) [20], adolescents (9.8-20.1 years) [21], adults I (33-57 years) [22], adults II (26-81 years) [23]. Detailed information on the studies is summarized below.

**Neonates [17]**

Twenty-five cardiovascularly and respiratory stable neonates with a median of bodyweight of 2.82 (range 0.68-4.03) kilograms, postnatal age of 8 (1-25) days and gestational age of 37 (26-40) weeks were given an intravenous bolus dose of propofol (3 mg·kg\(^{-1}\)) for the elective removal of chest tubes, (semi)elective chest tube placement or endotracheal intubation.
Infants [18]
Twenty-two non-ventilated infants after major craniofacial surgery with a median bodyweight of 8.9 (4.8-12.5) kilograms, aged 10 (3.8-17.3) months received 2-4 mg×kg⁻¹·h⁻¹ propofol during a median of 12.5 (6.0-18.1) hours.

Toddlers [19]
Twelve toddlers with minor burns, who had a median bodyweight of 11.2 (8.7-18.9) kilograms and age of 17.8 (12-31) months, were administered 4 mg×kg⁻¹ propofol just before bathing.

Children [20]
Fifty-three healthy unpremedicated children with a median bodyweight of 23.3 (15-60.5) kilograms and median age of 7 (3-11) years participated in this study. Twenty children received an intravenous loading dose of 3 mg×kg⁻¹ propofol. In the remaining 33 children, an intravenous loading dose of 3.5 mg×kg⁻¹ was followed by a maintenance infusion. In 18 of the 33 children, a single infusion rate of 0.15 mg×kg⁻¹×min⁻¹ was administered, while 15 children received an infusion of 0.20 mg×kg⁻¹×min⁻¹ for 30 minutes, followed by an infusion of 0.125 mg×kg⁻¹×min⁻¹ until the end of the procedure.

Adolescents [21]
Fourteen adolescents with a median bodyweight of 51 (36.6-82) kilograms and median age of 14.7 (9.8-20.1) years were anaesthetized with propofol-remifentanil (2-10 mg×kg⁻¹·h⁻¹) for scoliosis surgery during 6.8 (3.3-7.7) hours with an intra-operative wake-up test followed by re-induction of anesthesia.

Adults I [22]
Twenty-four women undergoing gynaecological surgery, with a median bodyweight of 68.5 (55-80) kilograms and a median age of 45.5 (33-57) years, received 2.5 mg×kg⁻¹ propofol over 60 seconds for induction of anesthesia.

Adults II [23]
Twenty-four healthy volunteers with a median bodyweight of 79.4 (44.4-122.7) kilograms and median age of 53 (26-81) years were administered a bolus dose of propofol, followed 1 hour later by a 60 minutes infusion with an infusion rate of 25, 50, 100, or 200 mg×kg⁻¹·min⁻¹ in a study which investigated the influence
of the method of administration, infusion rate, patient covariates, and EDTA (ethylenediaminetetraacetic acid) on the pharmacokinetics of propofol.

3.2.2. Combined datasets that were analysed
Two types of combined datasets were prepared from the data of the seven previously published propofol studies [17-23]:

Type I models: For the type I models, six study populations, i.e. neonates [17], infants [18], toddlers [19], children [20], adolescents [21] and adults [22, 23], were identified from the data of the seven original studies by merging datasets Adults I [22] and Adults II [23] into one adult population. In a systematic manner, two out of these six study populations were selected resulting 15 combined datasets.

Type II models: For the type II models, the data of the seven propofol studies [17-23] were regrouped into five age groups as defined by FDA Guidance for industry of 1998 [16]:

1) neonates (birth to 1 month)
2) infants (1 month to 2 years)
3) children (2 to 12 years)
4) adolescents (12 years to 16 years)
5) adults (above 16 years)

Four combined datasets were then prepared consisting of one of the four paediatric age groups and the adult group.

In total, 19 models were built on those 19 datasets, each of which either comprised two study populations (type I models) or two FDA age groups (type II models).

3.2.3. Pharmacokinetic modelling
The population pharmacokinetic analysis was performed with the non-linear mixed effects modelling software NONMEM version 7.2. (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method with the interaction option (FOCEI). Tools like S-PLUS interface for
Allometric exponent for clearance varies with age

NONMEM (LAP&P Consultants BV, Leiden, NL), S-Plus (version 8.1, Insightful Software, Seattle, WA, USA), XPose and R (version 2.10.0) were used to visualize the output and evaluate the models.

Model Building & Assessment
Propofol concentrations were logarithmically transformed and fitted simultaneously, since the range in concentrations was more than 1000 fold. Model building was performed in three steps: (1) selection of structural model, (2) selection of statistical sub-model, (3) covariate analysis. A difference in objective function (OFV) between models of more than 3.8 points was considered as statistically significant (p<0.05 assuming a Chi-square distribution). Furthermore, the goodness-of-fit plots (observed versus individual predicted concentrations and versus population predicted concentrations, and conditional weighted residuals versus time and versus population prediction concentrations) were evaluated [24]. In addition, improvement of the individual concentration-time profiles, the confidence intervals of the parameter estimates, and the correlation matrix were assessed. Besides, stratified observed versus population predicted goodness-of-fit plot and post hoc clearance versus bodyweight plots were considered, as in each of the 19 analyses two populations with a different human age range were analysed [24]. According to Karlsson et al., a high value for shrinkage of the inter-individual variability (\( \eta \)), named as \( \eta \)-shrinkage, may distort the true relationship between the parameters and covariates when empirical Bayes Estimates (EBE), sometimes referred as post hoc estimates of parameters, are used [25]. As the post hoc clearances were used in our study in the covariate analysis, we evaluated the \( \eta \)-shrinkage for clearance, for which a maximum percentage of 20% was considered acceptable.

Structural Model
Based on previous reports [26-28], the time-course of propofol concentrations in most combined datasets were modelled with a three-compartment model, which was parameterized in terms of total clearance (CL), volume of distribution of the central compartment (V1), volume of distribution of the rapid-equilibrating peripheral compartment (V2) and slow-equilibrating peripheral compartment (V3), and inter-compartmental clearances between central compartment and two peripheral compartments (Q2,Q3). In two models that were built on the datasets that included individuals from the infant study [18],
a two compartment model was the most suitable structural model because, due to the lack of samples in that period, the very fast distribution process could not be identified.

**Statistical Model**

Inter-individual variability in the pharmacokinetic parameters was tested in the model assuming log-normal distributions, expressed as

\[ \theta_i = \theta_{TV} \times e^{\eta_i}, \quad \eta_i \sim N(0, \omega^2) \]  

where \( \theta_i \) is the individual pharmacokinetic parameter value for the \( i \)th individual, \( \theta_{TV} \) is the population pharmacokinetic parameter value or typical value, and \( \eta_i \) is a random variable for the \( i \)th individual from a normal distribution with mean zero and variance \( \omega^2 \). While the inclusion of inter-individual variability on the different PK parameters was tested, model improvement by inclusion of covariance between these variability parameters was tested as well.

For the residual error, an additive model for log-transformed concentrations was used which corresponds to proportional error on untransformed data, expressed as:

\[ \log C_{ij} = \log C_{pred_{ij}} \times \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2) \]  

where \( C_{ij} \) is the value of the observed propofol concentration of \( i \)th individual at time \( j \), \( C_{pred_{ij}} \) is the value of the predicted propofol concentration of the \( i \)th individual at time \( j \), and \( \varepsilon_{ij} \) is a random variable for this observation from a normal distribution with mean zero and variance \( \sigma^2 \).

**Covariate Model**

In all 19 combined datasets, post hoc propofol clearances were described by bodyweight using the allometric scaling function of equation (1). For the other pharmacokinetic parameters, bodyweight was also incorporated in an allometric manner (equation 4) if this would decrease the OFV significantly (\( p<0.005 \)).

\[ P_i = P_{TV} \times \left( \frac{BW_i}{BW_{median}} \right)^k \]
In this equation, $P_i$ is the individual parameter; $P_{TV}$ is the population parameter; $BW_i$ and $BW_{median}$ are corresponding to the individual and median bodyweight; $k$ is the allometric exponent. Allometric scaling functions for clearance and/or covariate functions for other parameters were accepted if the criteria described under Model Building & Assessment were met ($p<0.05$).

### Table 3-1 Characteristics of the six study populations used in the type I models

<table>
<thead>
<tr>
<th>Study-population</th>
<th>Reference</th>
<th>Number of individuals</th>
<th>Weight (kg)</th>
<th>Age (yrs)</th>
<th>Samples per subject (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>[17]</td>
<td>25</td>
<td>2.82(0.68-4.03)</td>
<td>8(1-25) †</td>
<td>4-14</td>
</tr>
<tr>
<td>Infants</td>
<td>[18]</td>
<td>20</td>
<td>9(4.8-12.5)</td>
<td>10.2(3.8-17.3) ‡</td>
<td>4-15</td>
</tr>
<tr>
<td>Toddlers</td>
<td>[19]</td>
<td>12</td>
<td>11.2(8.74-18.9)</td>
<td>1.25(1-2.6)</td>
<td>11-12</td>
</tr>
<tr>
<td>Children</td>
<td>[20]</td>
<td>53</td>
<td>23.3(15-60.5)</td>
<td>7(3-11)</td>
<td>5-18</td>
</tr>
<tr>
<td>Adolescents</td>
<td>[21]</td>
<td>14</td>
<td>51(36.6-82)</td>
<td>14.5(9.6-19.8)</td>
<td>6-21</td>
</tr>
<tr>
<td>Adults</td>
<td>[22,23]</td>
<td>48</td>
<td>79.4(44.4-122.7)</td>
<td>53(26-81)</td>
<td>18-21</td>
</tr>
</tbody>
</table>

† age in days
‡ age in months

### 3.3. Results

An overview of the data of the seven propofol pharmacokinetic studies [17-23], which were merged into six study populations for the type I models and into five paediatric FDA age groups for the type II models, are summarized in Table 3-1 and Table 3-2, respectively.

Table 3-3 provides an overview of the results of all 19 models (15 Type I models and 4 Type II models) indexed by the model number with their estimated allometric exponent, including the relative standard error (RSE%) and corresponding ninety-five percent confidence interval (95%CI), for propofol clearance. Information on model structure, inter-individual variability on clearance and shrinkage values for the inter-individual variabilities on clearance are also listed in Table 3-3. Shrinkage values for clearance for all models were very low with values varying between 2.06% and 13.45%, indicating acceptable reliability of individual clearance values from the model. Given the designated allometric scaling model for clearance, all models were optimized in the covariate analysis with respect to covariates for pharmacokinetic parameters other than clearance in order to minimize the objective function and obtain
optimal goodness-of-fit plots. Diagnostic plots (observed versus population predicted plots) of the 15 type I models are shown in Figure 3-1, while the diagnostic plots for the 4 type II models are presented in Figure 3-2.

Table 3-2 Characteristics of age groups according to FDA guidance [16] used in the type II models

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of individuals</th>
<th>Weight (kg)</th>
<th>Age (yrs)</th>
<th>Samples per subject (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>25</td>
<td>2.82(0.68-4.03)</td>
<td>8(1-25) †</td>
<td>4-14</td>
</tr>
<tr>
<td>Infants</td>
<td>31</td>
<td>9(4.8-14.2)</td>
<td>304.8(113.7-689) †</td>
<td>4-15</td>
</tr>
<tr>
<td>Children</td>
<td>58</td>
<td>36.6(11.2-74)</td>
<td>9.6(2-11.3)</td>
<td>5-18</td>
</tr>
<tr>
<td>Adolescents</td>
<td>9</td>
<td>53(40-82)</td>
<td>14.5(13.6-15.7)</td>
<td>6-21</td>
</tr>
<tr>
<td>Adults</td>
<td>48</td>
<td>79.4(44.4-122.7)</td>
<td>53(26-81)</td>
<td>18-21</td>
</tr>
</tbody>
</table>

† age in days

Of the type I models, 5 models (model 1-5) included the neonate population. Estimation of the allometric exponent for clearance in those five models resulted in values varying between 1.11 and 2.01 (Table 3-3). The performance of those models (model 1-5) in terms of goodness of fit were quite adequate as shown in Figure 3-1 although there was some bias left. In the log-log scaled post hoc clearances versus bodyweight plot (Figure 3-3 A), all post hoc individual clearances from model 1 to model 5 are shown, with the allometric scaling functions that resulted from these models (see Table 3-3 for estimated exponents). In addition, the ¾ fixed allometric scaling line that was extrapolated from the adult sub-population was inserted to Figure 3-3 as a reference line. Figure 3-3 A shows that for model 1-5, none of the allometric functions estimated in the models was able to capture the change in clearance within the preterm and term neonate subpopulation completely, independently from which other sub-population they were scaled from.

There were 10 type I models (model 1-4, 6-8,10-11,13, Table 3-3) which scaled clearance within two different paediatric populations. The estimated allometric exponent in those models varied largely with values between 0.20 (model 6) and 2.01 (model 1) without a trend (Table 3-3). The diagnostic plots of those 10 models were good except for some small bias when the infant population was included (Figure 3-1). In Figure 3-3, the panels B, C, D and E depict the post hoc individual clearance values and estimated scaling curves of the models scaling
to infants (model 6, 7, 8, 9, Figure 3-3 B), toddlers (Model 10, 11, 12, Figure 3-3 C), children (Model 13, 14, Figure 3-3 D) and adolescents (Model 15, Figure 3-3 E). These subfigures 3B-3E suggest that with increasing age of the target scaling population, the range in post hoc clearances was smaller. In addition, these subfigures show that with increasing age, the scaling lines deviate less from the \( \frac{3}{4} \) allometric line.

Table 3-3 Model results including estimated allometric exponent for clearance \((\text{Exp}_{\text{cl}})\) for type I models on two study populations (model 1-15) and type II models on one paediatric FDA age group and the adult dataset (model 16-19)

<table>
<thead>
<tr>
<th>Model number</th>
<th>Younger subpopulation</th>
<th>Older subpopulation</th>
<th>Structure Model</th>
<th>( \text{Exp}_{\text{cl}} ) (RSE%)</th>
<th>95% Cl</th>
<th>( \eta_{\text{CL}} ) % (RSE%)</th>
<th>Shrink ( \eta_{\text{CL}} ) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neonate Infant</td>
<td>3-COM</td>
<td>2.01 (15.20%)</td>
<td>1.41-2.61</td>
<td>79%</td>
<td>(21.30%)</td>
<td>4.38%</td>
</tr>
<tr>
<td>2</td>
<td>Neonate Toddler</td>
<td>3-COM</td>
<td>1.64 (12.40%)</td>
<td>1.24-2.04</td>
<td>81%</td>
<td>(19.40%)</td>
<td>2.55%</td>
</tr>
<tr>
<td>3</td>
<td>Neonate Child</td>
<td>3-COM</td>
<td>1.39 (6.80%)</td>
<td>1.20-1.58</td>
<td>54%</td>
<td>(16.30%)</td>
<td>2.06%</td>
</tr>
<tr>
<td>4</td>
<td>Neonate Adolescent</td>
<td>3-COM</td>
<td>1.13 (5.40%)</td>
<td>1.01-1.25</td>
<td>75%</td>
<td>(17.40%)</td>
<td>2.31%</td>
</tr>
<tr>
<td>5</td>
<td>Neonate Adult</td>
<td>3-COM</td>
<td>1.11 (5.50%)</td>
<td>0.99-1.23</td>
<td>46%</td>
<td>(17.90%)</td>
<td>2.37%</td>
</tr>
<tr>
<td>6</td>
<td>Infant Toddler</td>
<td>3-COM</td>
<td>0.20 (98%)</td>
<td>-0.18-0.57</td>
<td>34%</td>
<td>(13.60%)</td>
<td>4.20%</td>
</tr>
<tr>
<td>7</td>
<td>Infant Child</td>
<td>3-COM</td>
<td>0.46 (16.60%)</td>
<td>0.31-0.61</td>
<td>28%</td>
<td>(11.60%)</td>
<td>7.43%</td>
</tr>
<tr>
<td>8</td>
<td>Infant Adolescent</td>
<td>2-COM</td>
<td>0.32 (16.30%)</td>
<td>0.21-0.42</td>
<td>24%</td>
<td>(13.90%)</td>
<td>8.25%</td>
</tr>
<tr>
<td>9</td>
<td>Infant Adult</td>
<td>2-COM</td>
<td>0.56 (7.40%)</td>
<td>0.48-0.64</td>
<td>21%</td>
<td>(10.70%)</td>
<td>12.08%</td>
</tr>
<tr>
<td>10</td>
<td>Toddler Child</td>
<td>3-COM</td>
<td>0.88 (9.20%)</td>
<td>0.72-1.04</td>
<td>22%</td>
<td>(10.60%)</td>
<td>9.90%</td>
</tr>
<tr>
<td>11</td>
<td>Toddler Adolescent</td>
<td>3-COM</td>
<td>0.72 (6.20%)</td>
<td>0.63-0.81</td>
<td>17%</td>
<td>(14.30%)</td>
<td>5.64%</td>
</tr>
<tr>
<td>12</td>
<td>Toddler Adult</td>
<td>3-COM</td>
<td>0.81 (4.20%)</td>
<td>0.74-0.87</td>
<td>18%</td>
<td>(9.90%)</td>
<td>6.88%</td>
</tr>
<tr>
<td>13</td>
<td>Child Adolescent</td>
<td>3-COM</td>
<td>0.55 (11.10%)</td>
<td>0.43-0.67</td>
<td>21%</td>
<td>(8.80%)</td>
<td>5.12%</td>
</tr>
<tr>
<td>14</td>
<td>Child Adult</td>
<td>3-COM</td>
<td>0.69 (4.90%)</td>
<td>0.62-0.75</td>
<td>19%</td>
<td>(8.50%)</td>
<td>7.46%</td>
</tr>
<tr>
<td>15</td>
<td>Adolescent Adult</td>
<td>3-COM</td>
<td>0.84 (11.90%)</td>
<td>0.64-1.03</td>
<td>19%</td>
<td>(9.40%)</td>
<td>4.77%</td>
</tr>
<tr>
<td>16</td>
<td>FDA neonate Adult</td>
<td>3-COM</td>
<td>1.11 (5.50%)</td>
<td>0.99-1.23</td>
<td>46%</td>
<td>(17.90%)</td>
<td>2.37%</td>
</tr>
<tr>
<td>17</td>
<td>FDA infant Adult</td>
<td>2-COM</td>
<td>0.60 (6.00%)</td>
<td>0.53-0.67</td>
<td>22%</td>
<td>(10.70%)</td>
<td>13.45%</td>
</tr>
<tr>
<td>18</td>
<td>FDA child Adult</td>
<td>3-COM</td>
<td>0.70 (4.90%)</td>
<td>0.63-0.77</td>
<td>20%</td>
<td>(7.80%)</td>
<td>7.15%</td>
</tr>
<tr>
<td>19</td>
<td>FDA adolescent</td>
<td>3-COM</td>
<td>0.74 (17.00%)</td>
<td>0.49-0.98</td>
<td>18%</td>
<td>(10.20%)</td>
<td>5.23%</td>
</tr>
</tbody>
</table>

Younger subpopulation = the younger sub-population of the combined dataset of type I or type II models; Older sub-population = the older sub-population of the combined dataset of type I or type II models; 3-COM = three-compartment model; 2-COM = two-compartment model; \( \text{Exp}_{\text{cl}} \) (RSE%) = estimate of the allometric exponent for clearance (equation 1) and corresponding relative standard error in percentage; 95%CI = ninety-five percent confidence interval of the estimate of the allometric exponent for clearance; \( \eta_{\text{CL}} \) % (RSE%) = estimate of inter-individual variability of clearance in percentage and corresponding relative standard error in percentage; Shrink \( \eta_{\text{CL}} \) % = shrinkage of the inter-individual variability of clearance in percentage.

In the four type II models (model 16-19), modelling was performed on combined datasets comprising data from the adult population and data
from one paediatric age group according to the FDA guideline [16] that was extracted from the available merged dataset.

**Figure 3-1** Observed versus population predicted concentration plots for type I models (model 1-15), each of which was based on a combined dataset comprising two out of the six study populations of Table 3-1 (neonates, infants, toddlers, children, adolescents, and adults).

Open circle: younger sub-population of the combined dataset (Table 3-3); Filled triangle: older sub-population of the combined dataset (Table 3-3); neo=neonates, inf=infants, tod=toddlers, chd=children, ado=adolescents, adt=adults.

The estimated allometric exponent values were relatively close to each other when scaling from FDA adults to infants, children and adolescents (0.60, 0.70...
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and 0.74, respectively), while for scaling from adults to neonates a value higher than 1 was identified (i.e. 1.11) (Table 3-3). Figure 3-3 F illustrates the results of these type II models 16-19 with post hoc clearances and scaling curves estimated in the models versus bodyweight. This figure shows that scaling to infants leads to the lowest value for the allometric exponent (i.e. 0.60) and scaling to neonates to the highest value for the allometric exponent (i.e. 1.11), with the latter having a wide variability in post hoc clearances.

Figure 3-2 Observed versus population predicted concentration plots for type II models (model 16-19), each of which was based on a combined dataset comprising one paediatric FDA age group (neonates: birth-1month, infants: 1 month-2years, children: 2 years-12 years, and adolescents: 12 years-16 years [16]) and one adult (above 16 years) age group (Table 3-2). Open circle: younger sub-population of the combined dataset (Table 3-3); Filled triangle: older sub-population of the combined dataset (Table 3-3); neo=neonates, inf=infants, chd=children, ado=adolescents, adt=adults
Chapter 3

3.4. Discussion

The allometric scaling method is often propagated when scaling for size in paediatric pharmacokinetic modeling [5] while there is more recently also interest for this scaling function when scaling for size in (morbid) obesity [29, 30]. Particularly in early drug development when based on adult data a first-time-in-kids dose needs to be selected, this ¾ allometric scaling approach for scaling clearance seems attractive. In addition, as the fixed value of 0.75 for the allometric exponent of clearance has also lead to acceptable results in children [12, 31-34], its use is increasingly popular for scaling between paediatric populations. However, as this allometric scaling theory is particularly based on the combination of the 0.75 fixed allometric equation together with an age-based maturation function [5], the question is how valid the value of the exponent of 0.75 is in absence of these age-based functions which are often not available. Therefore in this study, where relatively rich pharmacokinetic datasets of propofol were available across the entire human age range, a series of hypothetical analyses were performed to identify the allometric exponent for clearance between populations that varied in age.

The results of this study show that a large variety in the value for the allometric exponent for clearance can be expected ranging from 0.2 to 2.01, when two paediatric populations are analysed (model 1-4, 6-8, 10-11, 13, 15). While the lowest exponent of 0.2 was identified between infants and toddlers (model 6), the highest exponent of 2.01 was found between neonates and infants (model 1). These findings seem in accordance with previous reports stating that the fixed ¾ allometric function is inappropriate to describe and predict drug clearance in preterm and term neonates, infants and young children, as it systematically over-predicts clearance for neonates and under-predicts clearances for infants [6, 21, 35, 36]. In addition, for busulfan clearance across very young neonates to adolescents, Paci et al. also identified two exponents; an exponent of 1.25 for children < 9 kg and an exponent of 0.76 for children > 9 kg [37]. Concerning our finding of an exponent of 0.88 for toddlers and children (model 10), this value seems in good agreement with findings on oxycodone clearance in children 6 months to 7 years reporting a value of 0.875 [13]. It therefore seems from these findings that for scaling clearance between two paediatric populations, the allometric exponent needs to be estimated
rather than fixed to 0.75 in order to account for differences in maturation rates in different age groups. However, as with increasing age the estimated allometric scaling line moved slowly towards 0.75 (Figure 3-3 B to E), it may seem that ¾ allometric scaling function may be of value in older children (>3 or 4 yrs).

In drug development situations, paediatric pharmacokinetic information is necessary if the drug will be prescribed for paediatric population. A decision tree has been proposed by the FDA [38] to determine when and what kind of paediatric study (PK, PD, safety) should be conducted, depending on similarities in disease and response to treatment between children and adults [16, 38]. Adequate selection of the first-time-in-kids dose is thereby highly relevant, which is in early drug development based on results of adult PK studies. Our type II models mimic this situation by studying the allometric exponent between the adult group and one paediatric group defined according to the age range defined by FDA (0-1 month, 1 month-2 years, 2-12 years and 12-18 years) [16]. The results show that among FDA adolescents and children the exponent of the allometric scaling curve is close to 0.75 (0.74 and 0.70, respectively, Figure 3-3 F) at low inter-individual variability in clearance (18% and 20%, respectively). For adolescents, this result seems in accordance with the recent conclusion of the FDA advisory committee which agreed that dose(s) for adolescents (>12 years) can be derived from adults data on the basis of allometric scaling with a fixed exponent of 0.75 without the need for a dedicated PK study [39]. In contrast, the estimates of the allometric exponents in FDA defined groups of infants and neonates were found to deviate from 0.75 (0.60 and 1.11 respectively), while the resulting allometric functions were also not capable of describing all individuals across these two groups (Figure 3-3 F, infants and neonates). As such it seems that extrapolation from adults to infants and neonates is not possible using either ¾ allometric scaling or allometric scaling with another exponent, while scaling to adolescents and potentially children older than toddler age (3 or 4 yrs) could be considered.
Figure 3-3 Post hoc individual clearance values (symbol) and estimated allometric function from the model (line) versus bodyweight plots for all 19 Type I and Type II models in log-log scale (with ¾ reference line).

A. Neonates: Post hoc clearances versus bodyweight from the five type I models that comprise the neonates sub-population (model 1-5, Table 3-3). Dark green filled circles are median post hoc clearances of neonates from the models 1-5; Light green filled triangle: post hoc clearances of infants from model 1; Dark blue filled square: post hoc clearances of toddlers from model 2; Light blue filled circle: post hoc clearances of children from model 3; Dark orange filled triangle: post hoc clearances of adolescents from model 4; Light orange filled square: post hoc clearances of adults from model 5; Dark green solid line: ¾ allometric scaling line that scales from the adult population; Light green dash line: the allometric scaling line with exponent value 2.01 from model 1; Dark blue solid line: the allometric scaling line with exponent value 1.64 from model 2; Light blue dash line: the allometric scaling line with exponent.
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value 1.39 from model 3; Dark orange solid line: the allometric scaling line with exponent value 1.13 from model 4; Light orange dash line: the allometric scaling line with exponent value 1.11 from model 5

B. Infants): Post hoc clearances versus bodyweight from the four type I models that comprise the infants population (model 6-9, Table 3-3). Light green filled triangles are median post hoc clearances of infants from the models 6-9; Dark blue filled square: post hoc clearances of toddlers from model 6; Light blue filled circle: post hoc clearances of children from model 7; Dark orange filled triangle: post hoc clearances of adolescents from model 8; Light orange filled square: post hoc clearances of adults from model 9; Dark green solid line: ¾ allometric scaling line that scales from the adult population; Light green dash line: the allometric scaling line with exponent value 0.20 from model 6; Dark blue solid line: the allometric scaling line with exponent value 0.46 from model 7; Light blue dash line: the allometric scaling line with exponent value 0.32 from model 8; Dark orange solid line: the allometric scaling line with exponent value 0.56 from model 9

C. Toddlers): Post hoc clearances versus bodyweight from the three type I models that comprise the toddlers population (model 10-12, Table 3-3). Dark blue filled squares are median post hoc clearances of toddlers from the models 10-12; Light blue filled circle: post hoc clearances of children from model 10; Dark orange filled triangle: post hoc clearances of adolescents from model 11; Light orange filled square: post hoc clearances of adults from model 12; Dark green solid line: ¾ allometric scaling line that scales from the adult population; Light green dash line: the allometric scaling line with exponent value 0.88 from model 10; Dark blue solid line: the allometric scaling line with exponent value 0.72 from model 11; Light blue dash line: the allometric scaling line with exponent value 0.81 from model 12

D. Children): Post hoc clearances versus bodyweight from the two type I models that comprise the children population (model 13-14, Table 3-3). Light blue filled circles are median post hoc clearances of children from the models 13 and 14; Dark orange filled triangle: post hoc clearances of adolescents from model 13; Light orange filled square: post hoc clearances of adults from model 14; Dark green solid line: ¾ allometric scaling line from the adult population; Light green dash line: the allometric scaling line with exponent value 0.55 from model 13; Dark blue solid line: the allometric scaling line with exponent value 0.69 from model 14

E. Adolescents): Post hoc clearances versus bodyweight from the type I model that comprises the adolescent population (model 15). Dark orange filled triangle: post hoc clearances of adolescents from model 15; Light orange filled square: post hoc clearances of adults from model 15; Dark green solid line: ¾ allometric scaling line that scales from the adults population; Light green dash line: the allometric scaling line with exponent value 0.84 from model 15

F. Model 16-19): Post hoc clearances versus bodyweight from the type II models, each of which was based on a combined datasets comprising one paediatric FDA age group (neonates: birth-1 month, infants: 1 month- 2 years, children: 2 years-12 years, and adolescent: 12 years-16 years) and one adult (above 16 years) age group (model 16-19, Table 3-3). Dark orange filled triangles are median post hoc clearances of adults from four models; Dark green filled circle: post hoc clearances of neonates from model 16; Light green filled triangle: post hoc clearances of infants from model 17; Dark blue filled square: post hoc clearances of children from model 18; Light blue filled circle: post hoc clearances of adolescents from model 19; Dark green solid line: ¾ allometric scaling line that scales from the adults population; Light green dash line: the allometric scaling line with exponent value 1.11 from model 16; Dark blue solid line: the allometric scaling line with exponent value 0.60 from model 17; Light blue dash line: the allometric scaling line with exponent value 0.70 from model 18; Dark orange solid line: the allometric scaling line with exponent value 0.74 from model 19

In the models analysing neonates as one of the two groups, we found in our study that estimates for the allometric exponent for clearance were larger than 1, and were larger than the estimates for the exponent in other paediatric groups. Beside propofol, an exponent larger than 1 has been reported before for
morpine in (preterm) neonates to children of 3 years of age [15]. Also, Mahmood reported that the exponent of 1.2 performs better compared to an exponent of 1.0 when predicting drug clearance in children < 3 months, while an exponent of 1.0 was superior over an exponent of 1.2 for children ≥3 months to 1 year [40]. In addition, Paci et al. found two different allometric exponents for busulfan clearance, with an exponent larger than 1 for children < 9 kg [37]. This finding that in neonates the value for the allometric exponent for clearance is high, while lower values are identified at higher age and bodyweight ranges, are captured in our recently developed bodyweight dependent exponent (BDE) model [8]. In this BDE model, changes in propofol clearance across the entire human life-span were very well described using an allometric function in which the exponent was allowed to vary with bodyweight (range 1.34 for neonates to 0.55 for adults), without the need for an additional age-base function [8]. Considering the results of the current study in relation to the full analysis of all datasets [8], it seems that fairly similar exponents are identified, i.e. values between 1 and 1.5 for neonates to values between 0.5 and 1 for older children and adults. More recently, this BDE function in a simplified manner was also applied with success to busulfan for children from 1 month to adults in which the exponent was found to vary from 1.21 to 0.54 [9]. Given the similarities in these exponents, it seems that this BDE model should be studied across different drugs for which data are available over the entire human age range including neonates, as it may capture in a continuous function changes in clearance from neonates to adults despite the fact that maturation rates may vary at different ages.

In this study, we investigated the allometric scaling approach for clearance of propofol. As propofol is a high hepatic extraction ratio drug and it is mainly metabolised by the UGT-1A9 iso-enzyme, the results may not be necessarily the same for other drugs which have medium or low extraction ratio or have different metabolism pathway. We also recognize the allometric scaling approach is not physiologically based and it cannot explain the physiological mechanisms, such as the maturation of enzyme capacity etc. Furthermore, it should be considered that the estimated allometric exponents for clearance in this study may be influenced by the inclusion of covariates for other parameters such as volume of distribution. Given such limitations, we can only assure our findings for propofol and the feasibility and boundary of the allometric scaling approach for other drugs remains to be investigated.
3.5. Conclusion

Different allometric exponents for propofol clearance were identified depending on the included age-range, with the largest difference in allometric exponent between neonates and infants and between infants and toddlers (2.01 versus 0.2, respectively). Our findings show that for scaling clearance, ¾ allometric scaling may be of value for scaling from adults to adolescents and perhaps children, while it can not be used for scaling from adults to neonates, within neonates or between two paediatric populations.

3.6. Acknowledgements

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Reference

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Appendix: NONMEM code of the model

Example model with 3 compartments

$SUBROUTINE ADVAN11 TRANS4
$PK
TVCL = THETA(1)*(BW/68)**THETA(7)
CL = TVCL*EXP(ETA(1))
Q2 = THETA(2)*EXP(ETA(2))
TVQ3 = THETA(3)*(BW/68)
Q3 = TVQ3 *EXP(ETA(3))
TVV1 = THETA(4)*(BW/68)
V1 = TVV1*EXP(ETA(4))
TVV2 = THETA(5)*(BW/68)
V2 = TVV2*EXP(ETA(5))
TVV3 = THETA(6)*(BW/68)
V3 = TVV3*EXP(ETA(6))
S1 = V1
ETCL = ETA(1)
ETQ2 = ETA(2)
ETQ3 = ETA(3)
ETV1 = ETA(4)
ETV2 = ETA(5)
ETV3 = ETA(6)

$ERROR
IPRE = LOG(.000001)
IF (F.GT.0) IPRE=LOG(F)
IRES=DV-IPRE
W = 1
IWRES=IRES/W
Y=IPRE+W*ERR(1)

$THETA
( 0, 1.6, ) ; TH1 CL
( 0, 1.7, ) ; TH2 Q2
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\[(0, 1.5, ) ; TH3 \text{ Q3} \]
\[(0, 4, ) ; TH4 \text{ V1} \]
\[(0, 5, ) ; TH5 \text{ V2} \]
\[(0, 100, ) ; TH6 \text{ V3} \]
\[(0, 1.3, ) ; TH7 \text{ EXP of BW on clearance} \]

\$\text{OMEGA} 0.2 \ ; \text{OMEGA1 CL}
\text{0 FIX} \ ; \text{OMEGA2 Q2}
0.2 \ ; \text{OMEGA3 Q3}
0.2 \ ; \text{OMEGA4 V1}
\text{0 FIX} \ ; \text{OMEGA5 V2}
0.3 \ ; \text{OMEGA6 V3}

\$\text{SIGMA} 0.1 \ ; \text{SIGMA1} \]

\$\text{EST NOABORT PRINT=15 MAXEVALS=9999 METHOD=1 INTERACTION COV COMP PRINT=E} \]

Example model with 2 compartments

\$\text{SUBROUTINE ADVAN3 TRANS4} \]
\$PK
\text{TVCL} = \text{THETA(1)}*(\text{BW/63.5})^{\text{THETA(5)}}
\text{CL} = \text{TVCL*EXP(ETA(1))}
\text{TVQ} = \text{THETA(2)}*(\text{BW/63.5})
\text{Q} = \text{TVQ*EXP(ETA(2))}
\text{TVV1} = \text{THETA(3)}*(\text{BW/63.5})
\text{V1} = \text{TVV1*EXP(ETA(3))}
\text{TVV2} = \text{THETA(4)}*(\text{BW/63.5})
\text{V2} = \text{TVV2*EXP(ETA(4))}
\text{S1} = \text{V1}
\text{ETCL} = \text{ETA(1)}
\text{ETQ} = \text{ETA(2)}
\begin{verbatim}
ETV1 = ETA(3)
ETV2 = ETA(4)

$ERROR
W = 1
IPRE = LOG(.000001)
IF (F.GT.0) IPRE = LOG(F)
IRES = DV-IPRE
IWRES = IRES / W
Y = IPRE + W * ERR(1)

$THETA
(0, 1.2, ) ; TH1 CL
(0, 0.8, ) ; TH2 Q
(0, 5, ) ; TH3 V1
(0, 20, ) ; TH4 V2
(0, 0.5, ) ; TH5 EXP of BW on CL

$OMEGA
0.15 ; OMEGA1 CL
0 FIX ; OMEGA2 Q
0 FIX ; OMEGA3 V1
0.1 ; OMEGA4 V2

$SIGMA
0.1 ; SIGMA1

$EST NOABORT PRINT=15 MAXEVALS=9999 METHOD=1 INTERACTION
$COV COMP PRINT=E
\end{verbatim}