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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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The $3/4$ allometric scaling approach is often used for dose selection in paediatric drug development and paediatric clinical practice.

WHAT THIS STUDY ADDS

- The $3/4$ allometric scaling approach may be of value for scaling clearance from adults to adolescents and perhaps children, but it cannot be used for scaling from adults to neonates, within neonates or between two paediatric populations.

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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 cases where the neonate dataset was included. When two paediatric datasets were analyzed, 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, $3/4$ 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.

Introduction

In paediatric pharmacokinetic (PK) modelling, scaling of PK 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 $3/4$ allometric scaling approach is nowadays recommended.

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

$$CL_i = CL_{std} \times \left(\frac{BW_i}{BW_{std}} \right)^{exp_{CL}} \quad (1)$$

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 $3/4$ 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 the 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 old 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 the 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 analyzing data from clinical practice. In the 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.

Methods

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] and 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) kg, post-natal 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 who had undergone major craniofacial surgery with a median bodyweight of 8.9 (4.8–12.5) kg, aged 10 (3.8–17.3) months received 2–4 mg kg⁻¹ h⁻¹ propofol for a median of 12.5 (6.0–18.1) h.

Toddlers [19] Twelve toddlers with minor burns, who had a median bodyweight of 11.2 (8.7–18.9) kg 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) kg 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 min, followed by an infusion of $0.125 \text{ mg kg}^{-1} \text{ min}^{-1}$ until the end of the procedure.

Adolescents [21] Fourteen adolescents with a median bodyweight of 51 (36.6–82) kg and median age of 14.7 (9.8–20.1) years were anaesthetized with propofol-remifentanyl ($2\text{--}10 \text{ mg kg}^{-1} \text{ h}^{-1}$) for scoliosis surgery which lasted 6.8 (3.3–7.7) h with an intra-operative wake-up test followed by re-induction of anaesthesia.

Adults I [22] Twenty-four women undergoing gynaecological surgery, with a median bodyweight of 68.5 (55–80) kg and a median age of 45.5 (33–57) years, received 2.5 mg kg^{-1} propofol over 60 s for induction of anaesthesia.

Adults II [23] Twenty-four healthy volunteers with a median bodyweight of 79.4 (44.4–122.7) kg and median age of 53 (26–81) years were administered a bolus dose of propofol, followed 1 h later by a 60 min infusion with an infusion rate of 25, 50, 100 or $200 \text{ mg kg}^{-1} \text{ min}^{-1}$ in a study which investigated the influence of the method of administration, infusion rate, patient covariates and EDTA (ethylenediaminetetraacetic acid) on the PK of propofol.

Combined datasets that were analyzed

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 the FDA Guidance for industry of 1998 [16]:

- (1) neonate (birth to 1 month)
- (2) infant (1 month to 2 years)
- (3) children (2 to 12 years)
- (4) adolescent (12 years to 16 years)
- (5) adult (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).

Pharmacokinetic modelling

The population PK 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 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 and 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 vs. individual predicted concentrations and vs. population predicted concentrations, and conditional weighted residuals vs. time and vs. 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. Stratified observed vs. population predicted goodness-of-fit plot and *post hoc* clearance vs. bodyweight plots were considered, as in each of the 19 analyses two populations with a different human age range were analyzed [24]. According to Karlsson *et al.*, a high value for shrinkage of the inter-individual variability (η), named as η -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 η -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 was modelled with a three compartment model, which was parameterized in terms of total clearance (CL), volume of distribution of the central compartment (V_1), volume of distribution of the rapid-equilibrating peripheral compartment (V_2) and slow-equilibrating peripheral compartment (V_3), and inter-compartmental clearances between central compartment and two peripheral compartments (Q_2 , Q_3). 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 PK parameters was tested in the model assuming log-normal distributions, expressed as

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

where θ_i is the individual PK parameter value for the i th individual, θ_{TV} is the population PK parameter value or typical value, and η_i is a random variable for the i th individual from a normal distribution with mean zero and variance ω^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:

$$\log C_{ij} = \log C_{pred,ij} + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2) \quad (3)$$

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 ε is a random variable for this observation from a normal distribution with mean zero and variance σ^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 PK parameters, bodyweight was also incorporated in an allometric manner (equation 4) if this would decrease the OFV significantly ($P < 0.005$).

$$P_i = P_{TV} \times \left(\frac{BW_i}{BW_{median}} \right)^k \quad (4)$$

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 and assessment were met ($P < 0.05$).

Results

An overview of the data of the seven propofol PK 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 1 and Table 2, respectively.

Table 3 provides an overview of the results of all 19 models (15 type I models and four type II models) indexed by the model number with their estimated allometric exponent, including the relative standard error (RSE%) and corresponding 95% 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. Shrinkage values for clearance for all models were very low with values varying between 2.06% and

Table 1

Characteristics of the six study populations used in the type I models

Study population	Reference	Number of individuals	Weight (kg)	Age (years)	Samples per subject (range)
Neonates	[20]	25	2.82 (0.68–4.03)	8 (1–25)†	4–14
Infants	[21]	20	9 (4.8–12.5)	10.2 (3.8–17.3)‡	4–15
Toddlers	[22]	12	11.2 (8.74–18.9)	1.25 (1–2.6)	11–12
Children	[23]	53	23.3 (15–60.5)	7 (3–11)	5–18
Adolescents	[11]	14	51 (36.6–82)	14.5 (9.6–19.8)	6–21
Adults	[24, 25]	48	79.4 (44.4–122.7)	53 (26–81)	18–21

†Age in days; ‡Age in months.

Table 2

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

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

†Age in days.

Table 3

Model results including estimated allometric exponent for clearance (exp_{CL}) for type I models on two study populations (models 1–15) and type II models on one paediatric FDA age group and the adult dataset (models 16–19)

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

Younger sub-population = 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; Exp_{CL} (RSE%) = estimate of the allometric exponent for clearance (equation 1) and corresponding relative standard error in percentage; 95% CI = 95% confidence interval of the estimate of the allometric exponent for clearance; η_{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.

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 PK parameters other than clearance in order to minimize the objective function and obtain optimal goodness-of-fit plots. Diagnostic plots (observed vs. population predicted plots) of the 15 type I models are shown in Figure 1, while the diagnostic plots for the four type II models are presented in Figure 2.

Of the type I models, five models (models 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). The performance of those models (models 1–5) in terms of goodness of fit were quite adequate as shown in Figure 1, although there was some bias left. In the log–log scaled *post hoc* clearances vs. bodyweight plot (Figure 3A), 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 for estimated exponents). In addition, the $3/4$ fixed allometric scaling line that was extrapolated from the adult sub-population was inserted in Figure 3 as a reference line. Figure 3A shows that for models 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 (models 1–4, 6–8, 10–11, 13, Table 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). The diagnostic plots of those 10 models were good except for some small bias when the infant population was included (Figure 1). In Figure 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 (models 6, 7, 8, 9, Figure 3B), toddlers (models 10, 11, 12, Figure 3C), children (models 13, 14, Figure 3D) and adolescents (model 15, Figure 3E). 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 $3/4$ allometric line.

In the four type II models (models 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. 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 and 0.74, respectively), while for scaling from adults to neonates a value higher than 1 was identified (i.e. 1.11) (Table 3). Figure 3F illustrates the results of these type II models 16–19 with *post hoc* clearances and scaling curves estimated in the models

Figure 1

Observed vs. population predicted concentration plots for type I models (models 1–15), each of which was based on a combined dataset comprising two out of the six study populations of Table 1 (neonates, infants, toddlers, children, adolescents and adults). Dark green open circle, younger sub-population of the combined dataset (Table 3); orange-filled triangle, older sub-population of the combined dataset (Table 3). ado, adolescents; adt, adults; chd, children; inf, infants; neo, neonates; tod, toddlers

vs. 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.

Discussion

The allometric scaling method is often propagated when scaling for size in paediatric PK modelling [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-children dose needs to be selected, this $^{3/4}$ 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 led to accept-

able 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 the absence of these age-based functions which are often not available. Therefore in this study, where relatively rich PK 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 analyzed (models 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

Figure 2

Observed vs. population predicted concentration plots for type II models (models 16–19), each of which was based on a combined dataset comprising one paediatric FDA age group (neonates: birth–1 month, infants: 1 month–2 years, children: 2–12 years, and adolescents: 12–16 years [16]) and one adult (above 16 years) age group (Table 2). Dark green open circle, younger sub-population of the combined dataset (Table 3); orange-filled triangle, older sub-population of the combined dataset (Table 3). chd, children; inf, infants; neo, neonates

2.01 was found between neonates and infants (model 1). These findings seem in accordance with previous reports stating that the fixed $3/4$ 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 aged 6 months to 7 years, where a value of 0.875 was reported [13]. It therefore seems from these findings that for scaling clearance between two paediatric populations, the allometric exponent needs to be estimated instead of 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 3B to 3E), it may seem that $3/4$ allometric scaling function may be of value in older children (>3 or 4 years).

In drug development situations, paediatric PK information is necessary if the drug is to 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-children 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 the 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 3F) at low inter-individual variability in

Figure 3

Post hoc individual clearance values (symbol) and estimated allometric function from the model (line) vs. bodyweight plots for all 19 type I and type II models in log-log scale (with $3/4$ reference line)

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 adult 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 3F, infants and neonates). As such it seems that extrapolation from adults to infants and neonates is not possible using either $3/4$ allometric scaling or allometric scaling with another exponent, while scaling to adolescents and potentially children older than toddler age (3 or 4 years) could be considered.

In the models analyzing 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 morphine in (preterm) neonates to children of 3 years of age [15]. Also, Mahmood reported that the exponent of 1.2 performs better compared with 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 whom 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 metabolized

by the UGT-1A9 iso-enzyme, the results may not be necessarily the same for other drugs which have a 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.

In 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 vs. 0.2, respectively). Our findings show that for scaling clearance, $3/4$ allometric scaling may be of value for scaling from adults to adolescents and perhaps children, while it cannot be used for scaling from adults to neonates, within neonates or between two paediatric populations.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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