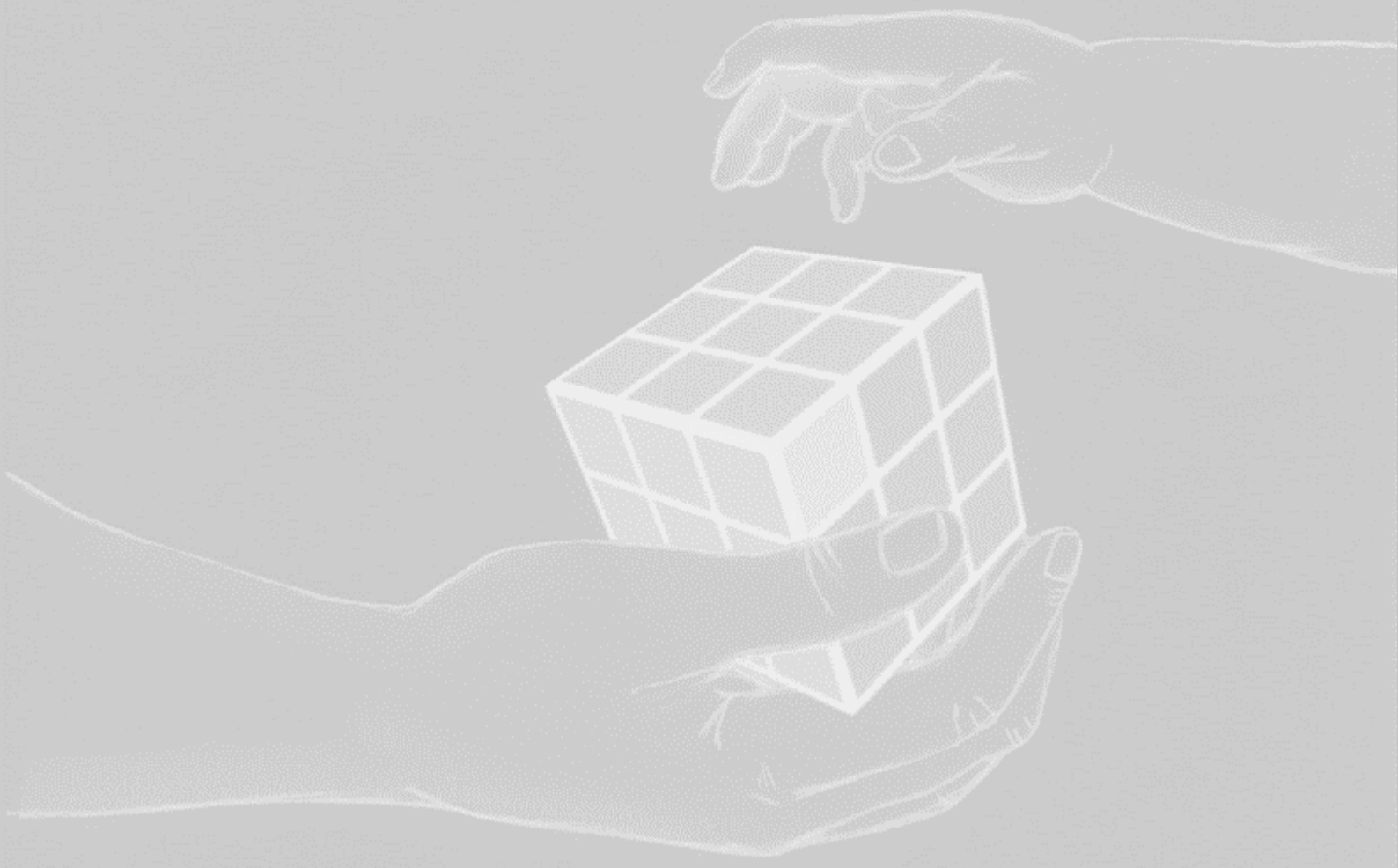
How to scale clearance from adults to children for drugs undergoing hepatic metabolism? Insights from advanced PBPK modelling and simulation

Calvier, E.A.M.

Chapter 4

Children are not small adults, but can we treat them as such?

Elke H. J. Krekels*, Elisa A. M. Calvier*, Piet H. van der Graaf, Catherijne A. J. Knibbe,
*Both authors contributed equally



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Abstract

While children cannot be considered small adults due to nonlinear processes underlying the pharmacokinetics of drugs, pediatric doses are typically still expressed per kg. We use a physiologically-based pharmacokinetic workflow to assess the accuracy of linear scaling of plasma clearance (CLp) for hypothetical drugs with range of realistic parameter values in pediatric patients of different ages. The results are compared with 0.75 fixed allometric scaling (AS0.75). Linear CLp scaling is accurate down to the age of 1 month for drugs undergoing glomerular filtration, except when these drugs are highly bound to AGP. For hepatically cleared drugs, linear scaling is reasonably accurate down the age of 2 years, except for AGP bound drugs with a low ER and mature isoenzymes. In neonates, linear scaling outperforms AS0.75 for HSA and AGP bound drugs excreted through glomerular filtration. These results suggest that pediatric patients can in many cases be treated as small adults.

Study highlights

What is the current knowledge on the topic?

Clearance is the most important determinant for drug dosing. In children, nonlinear processes underlying the pharmacokinetics of drugs result in complex maturational patterns in drug clearance.

What question did this study address?

Using physiologically-based pharmacokinetic modeling principles, this study investigates how accurate linear (bodyweight-based) clearance scaling, and therefore linear dose scaling, is in the pediatric population and compares this accuracy to the accuracy of allometric (bodyweight-based) scaling with a fixed exponent of 0.75.

What does this study add to our knowledge?

This study defines that linear scaling is accurate down to the age of 1 month for most drugs undergoing glomerular filtration and reasonably accurate down the age of 2 years for most hepatically cleared drugs. In neonates, linear scaling outperforms fixed allometric scaling, however both scaling methods can be highly inaccurate and systematic scaling accuracy cannot be achieved without taking drug properties and enzyme maturation into account.

How might this change drug discovery, development and/or therapeutics?

Accurate simple scaling methods allow for easy establishment of pediatric study doses or therapeutic doses.

4.1 Introduction

In pharmacokinetics, the adagio "children are not small adults" reflects the non-linear impact of changes in body size and composition, and in the maturational status of physiological systems, on the plasma clearance (CLp) of drugs in children. Given that CLp is one of the most important determinants for drug dosing, it is therefore unlikely that optimal dosing can be achieved by linearly scaling drug doses from adults to children according to equation 1:

$$\mathrm{Dose_P} = \mathrm{Dose_A} \cdot \frac{\mathrm{BW_P}}{\mathrm{BW_A}} \quad (1)$$

in which BW stands for bodyweight and subscripts P and A stand for pediatric and adult respectively, in which the bodyweight of adults is often taken to be 70 kg.

The ease of linear scaling is preferred by many, as reflected in the fact that both in pediatric clinical practice and in pediatric clinical trials, drug doses are still typically expressed per kg bodyweight, albeit with dose adjustments for different age-groups. To scale pediatric doses during the design of first-in-child studies during drug development, 0.75 fixed allometric scaling (AS0.75) is probably the most commonly used empiric scaling method. However, Fisher and Shafer have recently pointed out that absolute scaled CLp values in the pediatric bodyweight-range are practically indistinguishable when using linear scaling or AS0.75 [1]. Physiologically-based pharmacokinetics (PBPK) modeling prospectively generates pediatric CLp values by collating all known information on physiological processes underlying CLp and maturation in these physiological processes and should therefore be considered the gold standard for accurate predictions of pediatric CLp values and dose selection. As PBPK modeling is time consuming, needs to be performed by trained experts and relies on knowledge on drug-specific and system-specific properties that may not always be available, there remains a need to explore the performance of empiric scaling methods.

Surprisingly, there are hardly any scientific reports investigating the basis for linear scaling of pediatric CLp. We recently developed a PBPK-based workflow to systematically investigate the accuracy of scaling methods for pediatric CLp for more than ten thousand hypothetical drugs, with combinations of realistic drug properties covering the entire theoretical parameter space [2], that can be used for this purpose. Based on this work, we concluded that the commonly applied AS0.75 method, that uses a bodyweight-based function with an exponent of 0.75 to scale CLp from adults to children, yields accurate pediatric CLp predictions for all hypothetical drugs down to the age of five years in case isoenzymes are

mature. For certain drugs, the predictions are even accurate down to the age of 1 year and younger, depending on their properties. Interestingly, this study showed that this was not because the value of 0.75 for the exponent was accurate. On the contrary, the results showed the 'true exponents' to be highly variable and dependent both on the age of the children and the properties of the drugs. Rather, the observed accuracy of the CLp predictions was the result of the CLp predictions being insensitive to deviations between the 'true' exponent and an exponent of 0.75, thereby providing a basis to explore the performance of other exponents.

In this study we evaluated to what extent linear scaling (i.e., using a bodyweight-based exponential equation with an exponent of 1) would lead to accurate CLp scaling in children of various ages for drugs undergoing elimination through glomerular filtration or hepatic metabolism. For this we use our previously developed PBPK-based workflow that was developed to systematically assess the accuracy of CLp scaling methods in children of various ages and for a large number of hypothetical drugs with a wide yet realistic range of parameter values. The results of linear scaling are subsequently compared to those obtained with AS0.75, particularly for the situations where linear scaling does not lead to accurate scaling.

4.2 Methods

Details of the PBPK-based workflow, have been presented in detail elsewhere [2] and this methodology is only briefly repeated here. Model equations and parameter values can also be found in the Supplementary Methods.

To cover the entire hypothetical parameter space, a total of 12,620 hypothetical drugs were generated based on all possible combinations of the following realistic ranges in drug properties:

1) drugs were either fully eliminated through glomerular filtration or through hepatic metabolism.

2) drugs were either exclusively bound to alpha-1-acid glycoprotein (AGP) or to human serum albumin (HSA), yielding two different groups. Published maturation profiles were used to scale the abundance of these proteins in children.

3) affinities for the plasma proteins were selected to be such that the fraction unbound (fu) in adults ranged between 1 and 100%, with eight equidistant intermediate values, yielding 10 different values in total.

4) for drugs eliminated through hepatic metabolism, the dispersion model was used and unbound intrinsic microsomal clearance ($CL_{int,mic}$) values in adults were selected to range between $0.56 \cdot 10^{-6}$ - $0.209 \cdot 10^{-3}$ L. $min^{-1}.mg^{-1}$ microsomal protein, with 124 equidistant intermediate values, yielding 126 values in total for drugs eliminated through hepatic metabolism.

5) the blood-to-plasma partition coefficient (Kp) was selected to be 0, 1, 2, 3, or 4, and published maturation profiles were used to scale hematocrit in children, these 5 values are only relevant in the calculation of CLp for drug eliminated through hepatic metabolism.

This yields 20 hypothetical drugs eliminated through glomerular filtration and 12,600 eliminated through hepatic metabolism. For each of these hypothetical drugs, PBPK principles were used in combination with reported age-appropriate demographic values to calculate a point estimate of the 'true' CLp values in a typical adult and in typical children of 1 day, 1 month, 6 months, and 1, 2, 5, and 15 years of age. CLp predictions were made for scenarios in which enzyme maturation (parameterized as percentage of $CL_{int,mic}$ relative to adult values) was 100% or at the lowest or highest reported percentage for each age. For the latter, reported literature values for the maturation of various isoenzymes were collected. As for some isoenzymes in the very young extremely low or absent enzyme activity is reported, a lower cut-off of 10% was used. The lowest and highest values of enzyme maturation used at each age were: 10% and 100% at 1 day and 1 month, 25% and 122% at 6 months, 35% and 153% at 1 year, 57% and 159% at 2 years, 71% and 152% at 5 years, and 90% and 125% at 15 years. To obtain scaled CLp values for each typical child by either linear extrapolation or AS0.75 scaling from adult CLp values, the 'true' CLp value of each hypothetical drug in a typical adult of 66.5 kg was used in combination with the age-appropriate bodyweights obtained from CDC growth charts for each pediatric age [3].

The prediction error (PE) between the scaled pediatric CLp value and the 'true' PBPK-based pediatric CLp value was calculated. PE cutoff value of between ±30% were considered to indicate accurate scaling, scaled values outside the range of ±50% were considered to be inaccurate, values in between were considered to be reasonably accurate.

4.3 Results

Table 1 illustrates the results upon linear CLp scaling for drugs eliminated through glomerular filtration by showing the obtained PE values for different combinations of fu and binding plasma protein (i.e., AGP or HSA) at various ages. The table illustrates that for these drugs, the PE is dependent on the fu and the type of plasma protein the drug is binding to. For drugs binding to AGP, the range in absolute PE values is generally higher compared to those for drugs binding to HSA, but linear scaling still leads to reasonably accurate CLp values (i.e., PE within ± 50%) for children as young as 1 month, except for drugs with an fu < 0.34 for children below 2 years. For drugs binding to HSA, CLp can be accurately scaled (i.e., PE within ± 30%) using linear scaling down to the age of 1 month. For all ages included in this analysis, the absolute PE upon linear scaling for drugs excreted through glomerular filtration never exceeds 90% for any drug (Table 1).

Table 1 *Prediction error for linearly scaled CLp values for hypothetical drugs undergoing glomerular filtration binding to various extends to alpha-1-acid glycoprotein (AGP) or human serum albumin (HSA)*

fu in adults	*Binding plasma protein*	1 day	1 month	6 months	1 year	2 years	5 years	15 years
0.01	*AGP*	-86	-72	-66	-62	-57	-48	-21
0.01	*HSA*	30	-2	-27	-31	-32	-31	-12
0.12	*AGP*	-67	-62	-61	-58	-54	-46	-20
0.12	*HSA*	36	0	-26	-30	-32	-31	-12
0.23	*AGP*	-49	-52	-55	-53	-50	-43	-18
0.23	*HSA*	41	3	-25	-29	-31	-30	-11
0.34	*AGP*	-30	-41	-50	-49	-47	-41	-17
0.34	*HSA*	47	5	-24	-28	-30	-30	-11
0.45	*AGP*	-12	-31	-44	-45	-43	-39	-16
0.45	*HSA*	52	7	-23	-27	-30	-29	-11
0.56	*AGP*	7	-21	-39	-40	-40	-36	-15
0.56	*HSA*	58	10	-22	-26	-29	-29	-11
0.67	*AGP*	25	-11	-33	-36	-36	-34	-13
0.67	*HSA*	64	12	-21	-25	-28	-28	-10
0.78	*AGP*	44	-1	-28	-31	-33	-32	-12
0.78	*HSA*	69	14	-19	-24	-28	-28	-10
0.89	*AGP*	62	9	-23	-27	-30	-29	-11
0.89	*HSA*	75	17	-18	-24	-27	-27	-10
1	*AGP*	80	19	-17	-23	-26	-27	-10
1	*HSA*	80	19	-17	-23	-26	-27	-10

Green indicates PE values within ±30%, red indicates values outside the range of ±50%, and orange indicating absolute PE values between 30% and 50%. Fu, adult unbound drug fraction in plasma.

Figure 1 shows the results of linear CLp scaling for the hypothetical drugs eliminated by hepatic metabolism. The figure illustrates that the PE depends on the extraction ratio (categorized as low, intermediate, or high) and the type of plasma protein the drug is binding to (AGP or HSA) as depicted with different colors. Additionally, the maturation of the metabolizing isoenzyme is of importance for the accuracy of pediatric CLp scaling (results depicted in different rows). For the various ages included in this analysis, results are shown for 100% isoenzyme maturation (upper row), meaning that $CL_{int,mic}$ values in the children were 100% of the adult values, as well as for the highest (middle row) and lowest reported percentage for isoenzyme maturation at each age (lowest row). Supplemental Figure S1, shows the same results for children of 1 day, 1 month and 6 months, but with an enlarged scale to allow for the assessment of PE values in the younger individuals with low enzyme maturation.

Figure 1 shows that for drugs that are cleared through hepatic metabolism by mature isoenzymes (upper row), linear scaling can be used down to the age of 2 years for AGP bound drugs metabolized by mature isoenzymes, except for AGP bound drugs with a low ER and isoenzyme activity similar to or higher than adult values. For AGP bound drugs with a high extraction ratio, linear scaling can be used down to the age of 6 months. For HSA bound drugs linearly scaled CLp values are accurate or reasonably accurate down to the age of 1 day when isoenzymes are mature, although in some cases PE can reach up to -60%. For drugs cleared by isoenzymes with $CL_{int,mic}$ values higher than adult values (middle row), accuracy seems limited down to adolescents for AGP bound drugs and down to 5 years of age for HSA bound drugs, as the PE can go up to around -70%. When isoenzymes have the lowest reported enzyme maturation value for each age (lowest row), PE values upon linear scaling are accurate in children down to the age of 2 years, but then gradually increase towards considerable over-prediction with decreasing age, with the highest PE values reaching up to values of around 500%.

For the situations when linear scaling does not lead to accurate predictions, Supplemental Table S1 and Supplemental Figure S2 and S3 show the results obtained upon AS0.75 scaling, which were taken from or adapted from Calvier *et al*. [2]. These figures show that for newborns of 1 day and 1 month, linear scaling is more accurate, especially for renally cleared drugs and for hepatically metabolized drugs which are substrates for enzymes that are not mature, although both methods yield extreme and unacceptable values for some drugs.

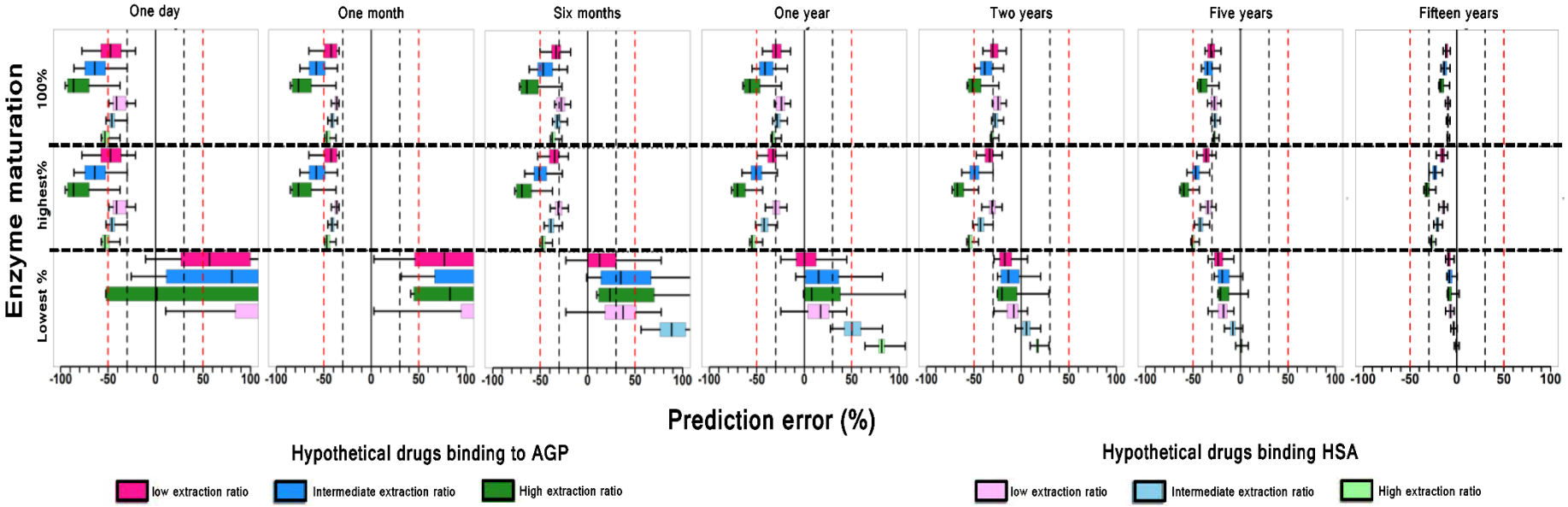

Figure 1 *Prediction error for linearly scaled CLp values for hypothetical drugs undergoing hepatic metabolism, binding to various extends to alpha-1-acid glycoprotein (AGP, dark colors) or human serum albumin (HSA, light colors) and having low (green), intermediate (blue), or high (pink) extraction ratio. At the top row, results are shown for scenarios in which enzyme maturation is 100% of adult values, the bottom and middle row show results for the lowest and highest reported enzyme maturation value for each age, respectively, which were 10% and 100% at 1 day and 1 month, 25% and 122% at 6 months, 35% and 153% at 1 year, 57% and 159% at 2 years, 71% and 152% at 5 years, and 90% and 125% at 15 years. Black and red vertical dotted lines correspond to a prediction error of 30 and 50% respectively.*

4.4 Discussion

Here we report on the accuracy of linear scaling of pediatric CLp values from adult CLp values, using a previously developed PBPK-based simulation platform [2]. This platform allows for the systematic assessment of pediatric CLp scaling methods by comparing scaled CLp values to 'true' pediatric CLp values obtained with PBPK-based simulations, for a large number of hypothetical drugs with drug-specific parameter values that cover a wide range of realistic values.

As was observed for other empiric scaling methods [2,4], the accuracy of linear scaling of pediatric CLp is dependent on drug properties (elimination pathway, extraction ratio and binding plasma proteins and unbound drug fraction) and on the age of children and the maturity of isoenzymes. This may lead to unacceptably biased CLp values for at least a subset of drugs in all studied ages, except in 15-year-olds. And although Fisher and Shafer have shown that absolute values of pediatric CLp may not differ greatly between linear scaling and AS0.75 [1], when expressed on a relative scale distinct differences do become apparent.

Our results show that linear CLp scaling is systematically accurate for all drugs in adolescents of 15 years (Table 1 and Figure 1) and for HSA bound drugs that are cleared through glomerular filtration in newborns down to the age of 1 month (Table 1). For hepatically cleared drugs there is some under-prediction when enzyme maturation is close to maturity, leading to PEs that are acceptable for some drugs, but that may with decreasing age lead down to almost -100% for others (Figure 1). This is in line with observations by Lack *et al.*, who also reported trends in under-prediction of drug dosing with linear scaling [5]. In drug development systematic under-prediction may however be favorable, as drug doses derived from under-predicted CLp values yield more conservative pediatric starting doses. On the other hand, under-dosing in early pediatric clinical trials may lead to a lack of therapeutic effect in the children participating in the trial which raises questions about the trial-related burden that would be ethically acceptable. In case hepatic enzymes are not mature, the systematic under-prediction of CLp upon linear scaling is reversed (Figure 1). This leads to reasonably accurate CLp values in children of 2 years and older when enzyme maturity is low, but also leads to extreme over-prediction of CL in newborns (Figure 1).

We have previously reported that AS0.75 scaling of CLp is accurate in children of 5 years and older for all drugs that are cleared through glomerular filtration and for drugs undergoing hepatic metabolism, when enzyme activity is close to adult values [2]. Comparison

of these results with the results obtained with linear scaling, suggest that in the aforementioned situations, AS0.75 scaling is on average less biased than linear scaling. In newborns of 1 month and younger for drugs cleared through glomerular filtration and for drugs that are hepatically cleared by isoenzymes that are not close to maturity, linear scaling will on average lead to less biased scaling, although in these young children both methods can lead to unacceptable bias for some drugs depending on the drug properties.

Given the wide range in PE values in all scenarios included in our current investigation, even within a specific age, it seems that simple scaling methods that do not take drug properties and isoenzyme maturation into account are not likely to systematically yield accurate pediatric CLp values. This suggests that especially in the very young only physiologically-based scaling approaches have a rational basis for CLp scaling, because linear scaling or AS0.75 scaling may lead to both accurate predictions or to unacceptable over- or under-prediction and without taking drug properties or maturational status into account, it cannot be predicted what situation will apply.

Our results are predicated on the validity of pediatric PBPK modeling principles. In our opinion PBPK models are most suitable to integrate and leverage all existing knowledge on drug clearance in children, which is supported by a number of publications assessing the accuracy of predictions by PBPK models in the pediatric population [6–9]. In their most recent addendum on "*Clinical Investigation of Medicinal Products in the Pediatric Population – Guidance for Industry*", the FDA recommends that all existing knowledge should be used to design the pediatric drug development program and that modeling and simulation is a useful approach to integrate and leverage existing knowledge [10]. Regarding the drug-specific properties of the hypothetical drugs used in this analysis, it has to be noted that although the range in each of drug-specific parameters separately is realistic, it cannot be excluded that hypothetical drugs with an unrealistic combination of parameters have been generated.

To enhance the interpretability of our results, it has to be noted that the PBPK-based 'true' CLp values in this work were generated without taking variability or uncertainty in parameter values into account. To compensate for this, a very stringent PE value of ±30% was arbitrarily chosen to indicate accurate scaling and a value of 50% for reasonably accurate scaling. Moreover, as very little is known about maturation of transporters in the kidney and liver, these were not taken into account in the generation of PBPK-based 'true' CLp values. Finally, for enzyme maturation a lower limit of 10% was chosen, because in case an isoenzyme is inactive in the very young, generally other elimination routes take over, at least partially. As

a result, in Supplemental Figure 2, the scaled values for children of 1 day and 1 month, do not reflect scaling for the least mature metabolic route, but they may reflect the CLp that is observed for a drug in real life for which other elimination routes take over.

In summary, even though children are not small adults due to the known complex physiological changes across the pediatric age range, linear CLp scaling is (reasonably) accurate down to the age of 1 month for drugs undergoing glomerular filtration, except for drugs highly bound to AGP. For hepatically cleared drugs, linear scaling is reasonably accurate down the age of 2 years, except for AGP bound drugs with a low ER and mature isoenzymes. In neonates of 1 day and 1 month, linear scaling outperforms AS0.75 for drugs excreted through glomerular filtration and for hepatically metabolized drugs which are substrates for enzymes that are not mature, however at very young ages simple scaling approaches that do not take drug properties and enzyme maturation into account can generally not reach systematic accuracy. Altogether these results suggest however that in many cases pediatric patients can be treated as small adults.

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Supplementary Methods

PBPK-based simulations of 'true' CLp values

System-specific parameters

PBPK simulations were performed for a typical adult of 35 years and in typical children of 1 day (term neonate), 1 month, 6 months, and 1, 2, 5, and 15 years of age. Demographic values (average for males and females) were taken from the CDC growth charts [1] for the typical pediatric individuals. For a typical adult, these values as well as cardiac output value were taken from the ICRP annals [2]. Body surface area (BSA) was estimated using the equations of Dubois and Dubois [3] for children weighing > 15kg, and of Haycock *et al.* [4] for those weighing ≤ 15kg.

Physiological parameters and ontogeny patterns in the hepatic blood flow (Qh), plasma protein concentrations for human serum albumin (HSA) and alpha-1 acid glycoprotein (AGP), liver size, milligram protein per gram of liver (MPPGL) were taken from Johnson *et al.* [5] and ontogeny pattern in hematocrit was taken from Hinderling *et al.* [5]. Isoenzymes maturations were taken from published values [6–10]. The table below provides an overview of the system-specific parameters used in the PBPK-based simulations for each typical individual.

Type of parameter	Parameter	Parameter values for the typical individuals							
	Age	***1 day***	***1 month***	***6 months***	***1 year***	***2 years***	***5 years***	***15 years***	***35 years***
Demographic parameters	Bodyweight (kg)	3.45	4.30	7.55	9.90	12.35	18.25	54.25	66.50
	Height (cm)	49.75	54.25	66.00	74.75	86.00	108.25	166.00	169.5
System-specific parameters	Liver density ($g.L^{-1}$)	1080							
	MPPGL ($mg.g^{-1}$)	33							
	Liver weight (g)	133	159	249	313	385	544	1351	1523
	Cardiac output ($L.min^{-1}$)	0.52	0.61	0.92	1.15	1.46	2.33	5.59	6.2
	Hepatic blood flow ($L.min^{-1}$)	0.14	0.17	0.25	0.32	0.40	0.64	1.54	1.70
	Glomerular filtration rate ($mL.min^{-1}$)	3.97	7.49	18.9	26.6	34.7	51.9	85.8	138
	Albumin concentration ($g.L^{-1}$)	27	31	33	34	35	36	37	38
	alpha-1 acid glycoprotein ($g.L^{-1}$)	0.04	0.13	0.22	0.27	0.32	0.40	0.49	0.56
	Hematocrit (%)	56	44	36	36	36.5	37	42	44

MPPGL, milligram microsomal protein per gram of liver.

Drug-specific parameters of hypothetical drugs

Hypothetical drugs were generated to serve as model and test drugs in the PBPK-based simulation workflow. For each individual drug-specific property, a realistic range of values was selected.

The model parameters to calculate hepatic plasma clearance (CLp) in this workflow which are based on a combination of drug-specific and system-specific parameters are: the unbound drug fraction in plasma (fu), the blood to plasma ratio (B:P), and the whole liver unbound intrinsic clearance (CLint). These parameters therefore reflect drug properties in a population of a specific age. fu values in adults were used as surrogates of their contributing drug-specific parameters (i.e., affinity to plasma proteins), since fu is most often reported.

To derive the affinity to plasma proteins from the unbound drug fraction in plasma (fu) and the concentration of the binding plasma protein in adults, equations by Rodgers and

Rowland [6,11] were used. The hypothetical drugs were assumed to be exclusively bound to either HSA or AGP. The fu in adults ranged from 1% to 100%, with 8 equidistant intermediate values. Values for the blood to plasma partitioning coefficient (Kp) of 0, 1, 2, 3, and 4 were selected, reflecting different extents of drug diffusion into the red blood cells. $CL_{int,mic}$ in adults ranged between $0.56 \cdot 10^{-6}$ and $0.209.10^{-3}$ $L.min^{-1}.mg^{-1}$ microsomal protein [12], with 124 equidistant intermediate values. These different values reflect difference in both affinities for and abundances of isoenzymes in adults.

Prediction of 'true' CLp values for drug eliminated through glomerular filtration

Analogous to Johnson *et al.* [6], equation 1 was used to compute 'true' CLp for drugs eliminated through glomerular filtration, in which GFR represents an age-specific value for the glomerular filtration rate.

$$CLp = GFR \times fu \quad (1)$$

Prediction of 'true' CLp values for drug eliminated through hepatic metabolism

'True' total hepatic plasma clearance (CLp) values were computed using the dispersion model (Equations 2 to 7). The dispersion model was selected as it has been reported to more accurately predict hepatic CLp than the well-stirred model for highly cleared drugs, while both models lead to equivalent clearance predictions for other drugs [13].

$$CLp = CL_B \times B{:}P \quad (2)$$

$$CL_B = Qh \times ER \quad (3)$$

$$ER = 1 - F_H \quad (4)$$

$$F_H = \frac{4a}{(1+a)^2 \exp\{(a-1)/2D_N\} - (1-a)^2 \exp\{-(a+1)/2D_N\}} \quad (5)$$

$$a = (1 + 4R_N \times D_N)^{1/2} \quad (6)$$

$$R_N = (fu/B{:}P) \times CLint/Qh \quad (7)$$

In these equations, CLp is the total hepatic plasma clearance, CL_B is the total whole blood clearance, B:P is the blood to plasma ratio, Qh is the hepatic blood flow, ER is the hepatic extraction ratio, fu is the unbound drug fraction in plasma, CLint is the whole liver unbound

intrinsic clearance, R_N is the efficiency number and D_N is the axial dispersion number. For the axial dispersion number (D_N) a value of 0.17 was used [14].

For each hypothetical drugs, CLint in adults was computed as the product of $CL_{int,mic}$, the MPPGL, and the liver weight. B:P in adults was derived from the adult haematocrit, from the Kp value, and the value of fu in adults [15]. Values of adult $CL_{int,mic}$, Kp, and adult fu were taken from the values defined to generate the hypothetical drugs. Qh, CLint, fu, and B:P in pediatric patients were scaled using the ontogeny functions of the relevant system-specific parameters.

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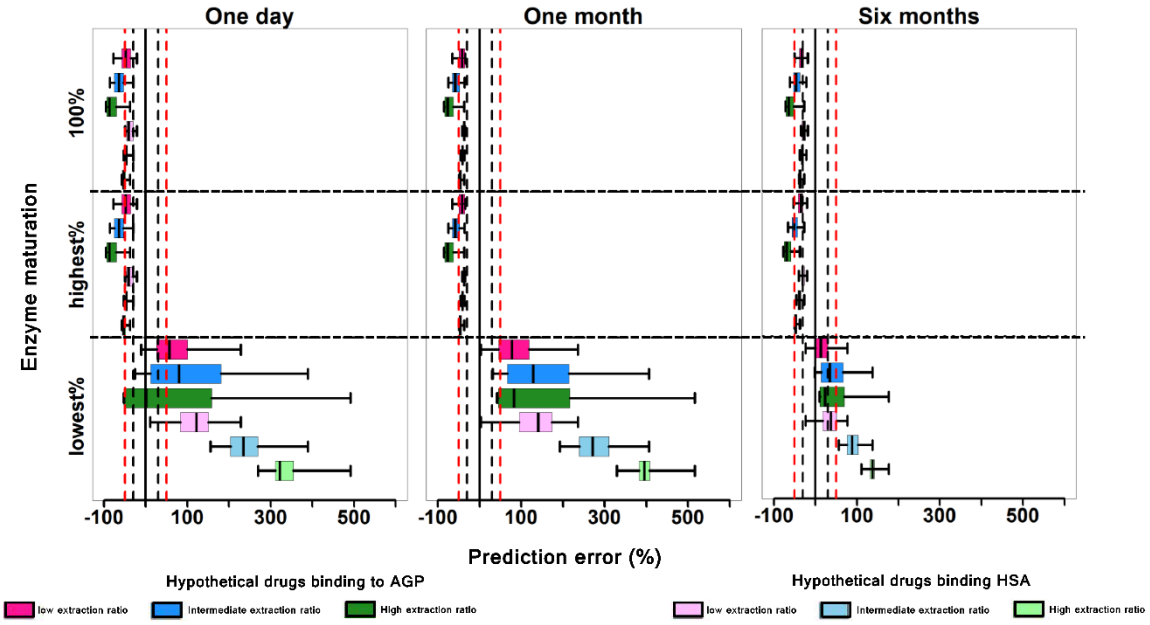
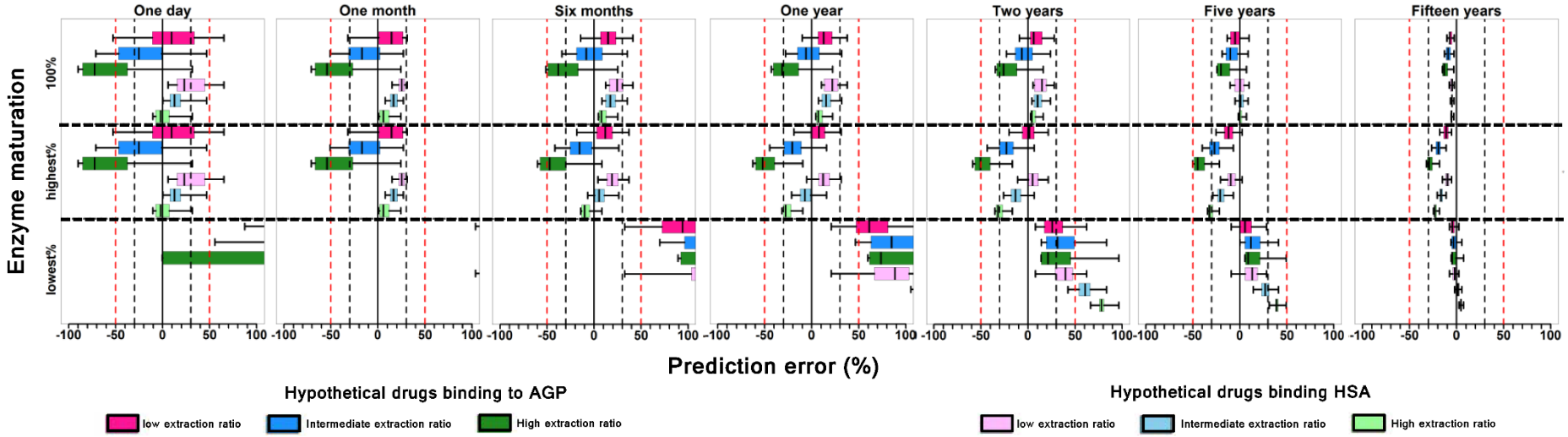
Supplemental Table S1 *Prediction error for AS0.75-scaled CLp values for hypothetical drugs undergoing glomerular filtration binding to various extends to alpha-1-acid glycoprotein (AGP) or human serum albumin (HSA)*

fu in adults	*Binding plasma protein*	1 day	1 month	6 months	1 year	2 years	5 years	15 years
0.01	*AGP*	-70	-44	-42	-39	-35	-28	-17
0.01	*HSA*	172	94	25	11	3	-5	-7
0.12	*AGP*	-31	-24	-33	-32	-29	-25	-15
0.12	*HSA*	184	99	27	13	4	-4	-7
0.23	*AGP*	7	-4	-23	-25	-24	-22	-14
0.23	*HSA*	196	103	29	14	5	-4	-7
0.34	*AGP*	46	16	-14	-18	-19	-18	-13
0.34	*HSA*	207	108	31	16	6	-3	-7
0.45	*AGP*	85	36	-4	-11	-14	-15	-11
0.45	*HSA*	219	113	33	17	7	-2	-6
0.56	*AGP*	123	56	5	-4	-8	-12	-10
0.56	*HSA*	231	117	35	19	8	-2	-6
0.67	*AGP*	162	76	15	3	-3	-9	-9
0.67	*HSA*	243	122	37	20	9	-1	-6
0.78	*AGP*	201	96	24	10	2	-6	-8
0.78	*HSA*	255	127	39	22	10	0	-5
0.89	*AGP*	239	116	33	18	7	-2	-6
0.89	*HSA*	266	131	41	23	11	0	-5
1	*AGP*	278	136	43	25	13	1	-5
1	*HSA*	278	136	43	25	13	1	-5

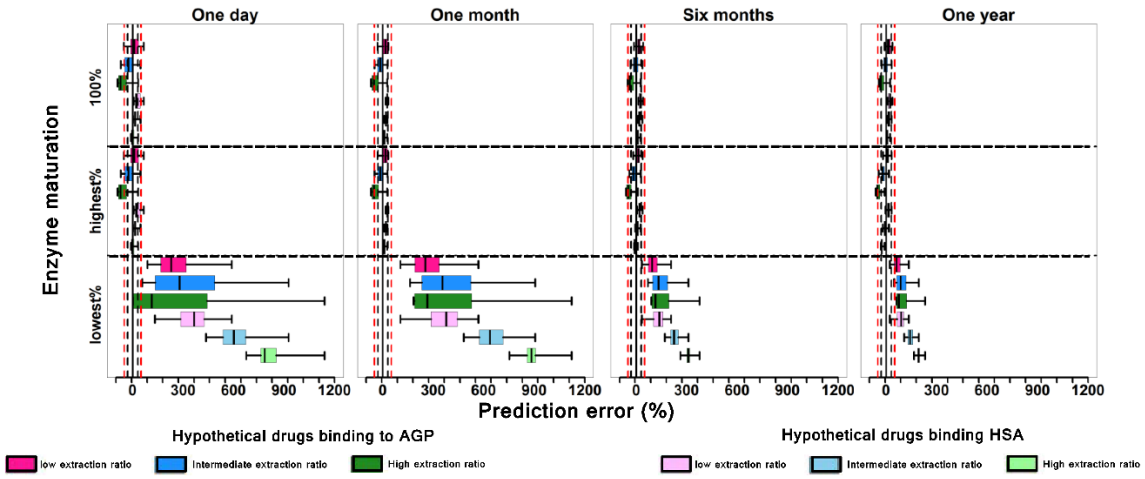
Green indicates PE values within ±30%, red indicates values outside the range of ±50%, and orange indicates absolute PE values between 30% and 50%. Fu, adult unbound drug fraction in plasma.



Supplemental Figure S1 *Enlarged scale depiction of prediction error for linearly scaled CLp values for hypothetical drugs undergoing hepatic metabolism, binding to various extends to alpha-1-acid glycoprotein (AGP, dark colors) or human serum albumin (HSA, light colors) and having low (green), intermediate (blue), or high (pink) extraction ratio. At the top row, results are shown for scenarios in which enzyme maturation is 100% of adult values, the bottom and middle row show results for the lowest and highest reported enzyme maturation value for each age, respectively, which were 10% and 100% at 1 day and 1 month, 25% and 122% at 6 months. Black and red vertical dotted lines correspond to a prediction error of 30 and 50% respectively.*



Supplemental Figure S2 *Prediction error for CLp values scaled with AS0.75 for hypothetical drugs undergoing hepatic metabolism, binding to various extends to alpha-1-acid glycoprotein (AGP, dark colors) or human serum albumin (HSA, light colors) and having low (green), intermediate (blue), or high (pink) extraction ratios. Results are shown for scenarios in which enzyme maturation is 100% of adult values (top), the bottom and middle row show results for the lowest and highest reported enzyme maturation value for each age, respectively, which were 10% and 100% at 1 day and 1 month, 25% and 122% at 6 months, 35% and 153% at 1 year, 57% and 159% at 2 years, 71% and 152% at 5 years, and 90% and 125% at 15 years. Black and red vertical dotted lines correspond to a prediction error of 30 and 50% respectively.*



Supplemental Figure S3 *Enlarged scale depiction of prediction error for CLp values scaled with AS0.75 for hypothetical drugs undergoing hepatic metabolism, binding to various extends to alpha-1-acid glycoprotein (AGP, dark colors) or human serum albumin (HSA, light colors) and having low (green), intermediate (blue), or high (pink) extraction ratios. Results are shown for scenarios in which enzyme maturation is 100% of adult values (top), the bottom and middle row show results for the lowest and highest reported enzyme maturation value for each age, respectively, which were 10% and 100% at 1 day and 1 month, 25% and 122% at 6 months, 35% and 153% at 1 year. Black and red vertical dotted lines correspond to a prediction error of 30 and 50% respectively.*

Section III

Scaling methods accounting for isoenzyme maturation for prediction of clearance in children