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ARTICLE

Children Are Not Small Adults, but Can We Treat Them As Such?

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Although children cannot be considered small adults due to nonlinear processes underlying the pharmacokinetics of drugs, pediatric doses are typically still expressed per kilogram. We use a physiologically based pharmacokinetic (PBPK) workflow to assess the accuracy of linear scaling of plasma clearance (CLp) for hypothetical drugs with ranges of realistic parameter values in pediatric patients of different ages. The results are compared with 0.75 fixed allometric scaling (AS 0.75). 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 alpha-1-acid glycoprotein (AGP). For hepatically cleared drugs, linear scaling is reasonably accurate down the age of 2 years, except for AGP-bound drugs with a low extraction ratio and mature isoenzymes. In neonates, linear scaling outperforms AS 0.75 for human serum albumin (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 PBPK 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.

In pharmacokinetics, the adagio "children are not small adults" reflects the nonlinear 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 Eq. 1:

$$\text{Dose}_P = \text{Dose}_A \cdot \frac{BW_P}{BW_A} \quad (1)$$

in which BW stands for bodyweight and subscripts P and A stand for pediatric and adult, respectively.

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 kilograms of 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 (AS 0.75) is probably the most commonly used empiric scaling method. However, Fisher and Shafer[1] have recently pointed out that absolute scaled CLp values in the pediatric bodyweight range are practically indistinguishable when using linear scaling or AS 0.75[1]. Physiologically based pharmacokinetic (PBPK) modeling prospectively generates pediatric CLp values by collating all known

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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. Because 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 > 10,000 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 AS 0.75 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 5 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 with those obtained with AS 0.75, particularly for the situations in which linear scaling does not lead to accurate scaling.

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 Material S1**.

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 8 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 $0.56*10^{-6}$ and $0.209*10^{-3}$ L/min/mg 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 drugs 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, extremely low or absent enzyme activity is reported in the very young, a lower cutoff 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 linear extrapolation or AS 0.75 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 the Centers for Disease Control and Prevention growth charts for each pediatric age.

The prediction error (PE) between the scaled pediatric CLp value and the "true" PBPK-based pediatric CLp value was calculated. The PE cutoff values ± 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.

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

Table 1 Prediction error for linearly scaled CLp values for hypothetical drugs undergoing glomerular filtration binding to various extends to AGP or 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 prediction error (PE) values within ± 30%, red indicates values outside the range of ± 50%, and orange indicaties absolute PE values between 30% and 50%.
AGP, alpha-1-acid glycoprotein; CLp, plasma clearance; fu, fraction unbound in adults; HSA, human serum albumin.

binding plasma protein (i.e., AGP or HSA) at various ages. The table illustrates that for these drugs the PE is only dependent on the fu and the type of plasma protein to which the drug is bound. For these drugs binding to AGP, the range in absolute PE values is generally higher compared with 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 in children below 2 years when the fu in adults is lower than 0.34. For drugs binding to HSA, CLp of drugs cleared through glomerular filtration 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**).

Figure 1 shows the accuracy of linear CLp scaling for the hypothetical drugs eliminated by hepatic metabolism. The figure illustrates that the PE depends on the extraction ratio (ER; 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, meaning that $CL_{int,mic}$ values in the children were 100% of the adult values, as well as for the highest and lowest reported percentage for isoenzyme maturation at each age. **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, linear scaling can be used down to the age of 2 years for AGP-bound drugs, 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 ER, linear scaling is accurate or reasonably accurate 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 a few cases, PE can reach up to –60% in newborns. For drugs cleared by isoenzymes with $CL_{int,mic}$ values higher than adult values (middle row for children of 6 months and older), accuracy seems limited down to adolescents for AGP-bound drugs and down to 5 years of age for HSA-bound drugs, in which the PE can go down 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 toward considerable overprediction 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, **Table S1** and **Figures S2 and S3** show the results obtained upon AS 0.75 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.

DISCUSSION

Here, we report on the accuracy of linear scaling of pediatric CLp values from adult CLp values using a previously

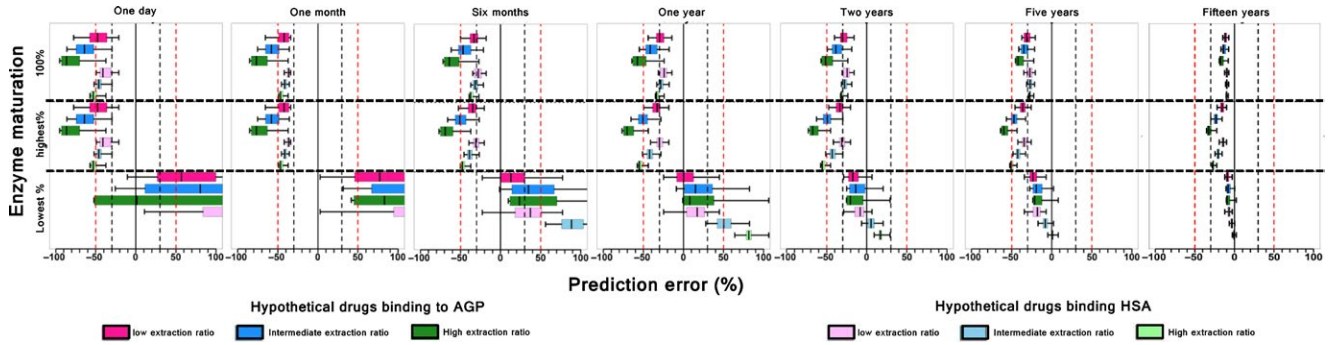

Figure 1. Prediction error for linearly scaled CLp values for hypothetical drugs undergoing hepatic metabolism, binding to various extends to alpha-1-acid glycoprotein (AGP, dark colors) or human serum albumin (HSA, light colors) and having low (pink), intermediate (blue), or high (green) extraction 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 an absolute prediction error of 30 and 50% respectively.

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 hypothetical drugs with drug-specific parameter values that cover a wide range of realistic values.

As was observed for other empiric scaling methods,[2,3] the accuracy of linear scaling of pediatric CLp is dependent on drug properties (elimination pathway, ER, 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. In addition, although Fisher and Shafer[1] have shown that absolute values of pediatric CLp may not differ greatly between linear scaling and AS 0.75 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 year (**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 underprediction 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 and Stuart-Taylor[4] who also reported trends in underprediction of drug dosing with linear scaling. In drug development, systematic underprediction may, however, be favorable, as drug doses derived from underpredicted CLp values yield more conservative pediatric starting doses. On the other hand, underdosing 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 underprediction 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 overprediction of CL in newborns (**Figure 1**).

We have previously reported that AS 0.75 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, AS 0.75 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 AS 0.75 scaling may lead to both accurate predictions or to unacceptable overprediction or underprediction 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.[5–9] In their most recent addendum on "*Clinical Investigation of Medicinal Products in the Pediatric Population – Guidance for Industry*," the Food and Drug Administration (FDA) also recommends that all existing knowledge should be used to design the pediatric drug development program and that modeling and simulation are useful approaches to integrate and leverage existing knowledge.[5] 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 the 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 kidneys 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 **Figure S2c**, the scaled values for children of the age 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 AS 0.75 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.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Supplementary Material S1. PBPK-based simulations of "true" CLp values.

Table S1. Prediction error for AS 0.75-scaled CLp values for hypothetical drugs undergoing glomerular filtration binding to various extends to AGP or HSA.

Figure S1. Enlarged scale depiction of prediction error for linearly scaled plasma clearance (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 (pink), intermediate (blue), or high (green) extraction ratio.

Figure S2. Prediction error for plasma clearance (CLp) values scaled with AS 0.75 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 (pink), intermediate (blue), or high (green) extraction ratios.

Figure S3. Enlarged scale depiction of prediction error for plasma clearance (CLp) values scaled with AS 0.75 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 (pink), intermediate (blue), or high (green) extraction ratios.

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