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Physiology-based versus allometric scaling of clearance in children; an eliminating process based comparison

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***Aim*: To scale clearance from adults to children, allometric and physiology-based approaches have been suggested. The allometric approach is common but does not account for the maturation processes of the eliminating organ and therefore may not be appropriate to scale clearance to young children. The physiology-based approach accounts for maturity but requires detailed knowledge regarding eliminating processes. This study compared the approaches and determined if their appropriate use was dependent on the clearance pathway.**

***Methods*: A data set of experimentally-obtained clearance values was used. Predicted clearances using both approaches were calculated using the mean age and weight of the studied group. The ratio of predicted to observed clearances were graphed separately for compounds with a predominant clearance pathway (> 85%, *n* = 8). Other compounds with multiple clearance pathways were graphed together (*n* = 7). The process specific age at which both approaches produced accurate clearance predictions was noted.**

***Results*: The allometric approach systematically overestimated clearance in children below a certain age, contrary to the physiology-based approach that accurately predicted clearance at all ages. The age at which clearances were not biased using the allometric equation was within the first year for compounds eliminated via CYP3A4, four years for CYP1A2 and six months for UGT2B7. Allometric scaling systematically overestimated renal clearance in children up to two years and underestimated clearance above two years.**

***Conclusions*: Physiology-based clearance scaling accurately predicted clearance in children from birth to 18 years. The allometric approach is only accurate above the age at which the major clearance pathway is fully, or near to fully, matured. A combined use of approaches is suggested.**

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Introduction

Pharmacokinetic studies in children have lagged behind those in adults such that the majority of drugs prescribed to children have not been significantly studied within the paediatric age range[1]. Since the pharmacokinetic profile is an important predictor of the probability of therapeutic or adverse effect events, the profile differences between children and adults are highly important. One of the major drivers of profile differences is the pharmacokinetic parameter of clearance.

Clearance describes the volume of reference fluid (usually plasma) that is removed of compound per unit time. Because of the importance of this parameter to determining the pharmacokinetic profile, *a priori* knowledge of its compound-specific age-related changes would advance the preparation of the paediatric clinical trial.

Predicting clearance in children based on the clearance in an adult has been the topic of recent publications[2-6]. A physiology-based approach has been found to be useful for predicting clearance across all age ranges[2,5]. This has been demonstrated for a number of the major enzymatic (e.g. CYP1A2) and physiological (e.g. glomerular filtration) eliminating processes. The drawback of the approach is that detailed knowledge about the eliminating processes in adults is required and further, the age-dependence of the ontogeny of these clearance processes is needed. Another established approach, allometric scaling, has been demonstrated to determine the age at which the maturity of the processes responsible for clearance no longer affects the clearance value[7,8]. Thus, the allometric equation can be predictive of clearance in children following a specific age. The approach is only based on the difference in body weight between the child and the adult and has the benefit of being very easy to calculate. Since the approach does not account for maturation processes, it becomes invalid when used below a certain age where the activities of the eliminating processes are not yet fully developed[5].

The objective of this study was to retrospectively compare the accuracy of the allometric clearance scaling approach with the physiology-based approach using compounds eliminated via various enzymatic and physiological processes (glomerular filtration). Furthermore, by using compounds for which the clearance process in adults is dominated (> 85%) by one clearance pathway, the pathway-specific age range of appropriate use for each scaling approach will be determined.

Methods

Age dependent clearance data set

A data set of observed clearances for children aged premature to 18 years from previous studies was used[2,9]. Age-dependent observed clearances from 15 compounds were presented. In one previous study[2], eight of the compounds, where clearance was primarily (> 85%) due to one process, were used to develop ontogeny models for the scaling of clearance via the physiology-based scaling approach. These were gentamicin and isepamicin (renal clearance due to glomerular filtration), alfentanil and midazolam (CYP3A), caffeine and ropivacaine (CYP1A2) and morphine and lorazepam (UGT2B7). The seven remaining compounds, namely fentanyl, theophylline, paracetamol, ciprofloxacin, lidocaine, levofloxacin and buprenorphine were cleared via multiple pathways (see Table III in Edginton et al[2] and levofloxacin data in Edginton et al[9]) and were used to evaluate the ontogeny models[2].

The observed adult clearance value was the weighted mean as previously presented[2] and, for levofloxacin, was the adult clearance taken from Chien et al[10]. Only mean adult clearance values were regarded in this study.

Allometric clearance scaling

This approach to clearance scaling makes use of an allometric equation for the ratio of body weights to a specified power. The power function, for the purposes of scaling clearance is ¾[7,11]. The clearance in a child (CL_{child}) is calculated from the clearance in the adult (CL_{adult}, both given in flow units, e.g. mL/min) using the equation;

$$CL_{child} = CL_{adult} \times \left(\frac{BW_{child}}{BW_{adult}} \right)^{\frac{3}{4}} \quad (1)$$

where BW_{child} is the body weight of the child and BW_{adult} is the body weight of the adult. The mean body weight of the paediatric population from each study was used in the allometric equation. If this value was not reported in the study, the mean weight value was taken for the mean age (or middle of the age range in some cases) using information from the International Commission on Radiological Protection (ICRP)[12]. If the weight for a group of premature neonates was not reported (five of the 25 studies), the weight value was set at 2.5 kg. The adult body weight was set at 70 kg for all calculations.

Physiology-based clearance scaling

This approach uses information regarding clearance pathways in adults and scales them to children. The compound-specific proportion of total adult clearance is delineated into the compound-specific pathways of clearance. In the case of renal clearance, based on body weight and age of the child, glomerular filtration and tubular secretion are scaled to children based on a predictive equation generated retrospectively in children of different ages following administration of compounds undergoing renal elimination[13], later slightly modified to account for even younger children[2]. For hepatic enzymatic clearance, an adult intrinsic clearance (CL_{INT}) is calculated based on the well-stirred liver model;

$$CL_{INT} = CL_H \frac{Q_H}{Q_H - CL_H} \cdot \frac{1}{f_u} \quad (2)$$

where Q_H is the hepatic blood flow, CL_H is the plasma clearance, CL_{INT} is the intrinsic hepatic clearance per gram of liver weight and f_u is the fraction unbound in plasma. The generated adult intrinsic clearance value is then multiplied by an ontogeny factor that represents the activity of the specific enzyme in relation to the age of the child. This new child-scaled intrinsic clearance is used to generate an age-specific plasma clearance (CL_H) calculated from the re-arranged equation 2 using the age-specific body weight, liver weight, liver blood flow and predicted fraction unbound (scaled from adults based binding protein concentrations in plasma)[14]. The clearance pathways are summed to generate a total plasma clearance for the child. Detailed information on this approach, and the scaled clearances from the data set, is available in our previous study[2].

Approach comparison

The ratios of experimentally predicted to observed clearances (ml/min), using allometric and physiology-based scaling, were calculated and plotted against age for each compound. The compounds were grouped according to the primary process of clearance, which included the processes of renal, CYP3A4, CYP1A2 and UGT2B7 clearance. The ratio of predicted to observed clearances for the remaining multiple pathway clearance compounds were graphed together. The line of unity at which the predicted value was equal to the observed value was plotted together with the lines for where predicted clearance was either twice or half the observed clearance.

To determine the age range for which allometric scaling was appropriate, and to determine if this age range depended on the process of clearance, the clearance of the eight compounds that are cleared via one prominent pathway were calculated and compared to the observed clearance values. The ratios of predicted to observed clearances were visually examined for bias. A visual assessment was preferred over a numerical assessment of bias[15], because the latter would be unfair. It is understood *a priori* that the allometric equation overestimates clearance in the young age groups[5,11], since this approach can not account for the enzymatic ontogeny and maturation process of the eliminating organ. Thus, the bias for the allometric equation would be heavily dependent on the number of data points under the age at which it can no longer reasonably predict clearance. Thus, the age at which the data points were equally above and below the line of unity was noted. To compare the two models of scaling clearance, the seven evaluation compounds[2] were assessed. A visual assessment of the resulting graphs was focused on the bias of data points around the line of unity across the entire age range.

Results

Figure 1 summarises the results of both scaling approaches, divided by the process responsible (> 85%) for clearance. For each process; renal (Figures 1a and b), CYP3A4 (Figures 1c and d), CYP1A2 (Figures 1e and f) and UGT2B7 (Figures 1g and h), the clearance was scaled via the ¾ allometric power model (left side figures) and via the physiology-based approach (right side figures). These compounds were used to build the models used in the physiology-based approach[2] and thus cannot evaluate the model. Thus the figures representing the physiology-based clearance scaling are only shown here for reader interest. In the case of the allometric approach, it did not accurately predict clearance below a certain age in all cases as evidenced by the systematic accumulation of data points above the line of identity towards the younger ages.

In the case of renal elimination (Figure 1a), the allometric equation was two fold off the observed clearance value at a young age; however, the allometric equation consistently overestimated clearance until an age of approximately two years at which point allometric scaling consistently underestimated clearance.

There is evidence to suggest that for physiological processes an allometric power function of ⅔ is more appropriate. Figure 2 presents the results using the allometric approach using a power function of ⅔ in the allometric equation for gentamicin and isepamicin. In this case, the overestimation in children less than two years of age was greater than using the ¾ power function. For children over two years of age, there was consistent underestimation of clearance but with less bias than using the ¾ power function.

For the hepatic enzymes, the consistency of data above the line of identity appeared to be both age and process-dependent. The age at which the allometric equation produced little bias around the line of unity was within the first year for compounds eliminated primarily via CYP3A4 (Figure 1c), four years for CYP1A2 (Figure 1e) and six months for UGT2B7 (Figure 1g).

Figure 3 presents the results for which a comparison of the scaling approaches was made. Allometric scaling systematically overestimated clearance in the young age groups as evidenced

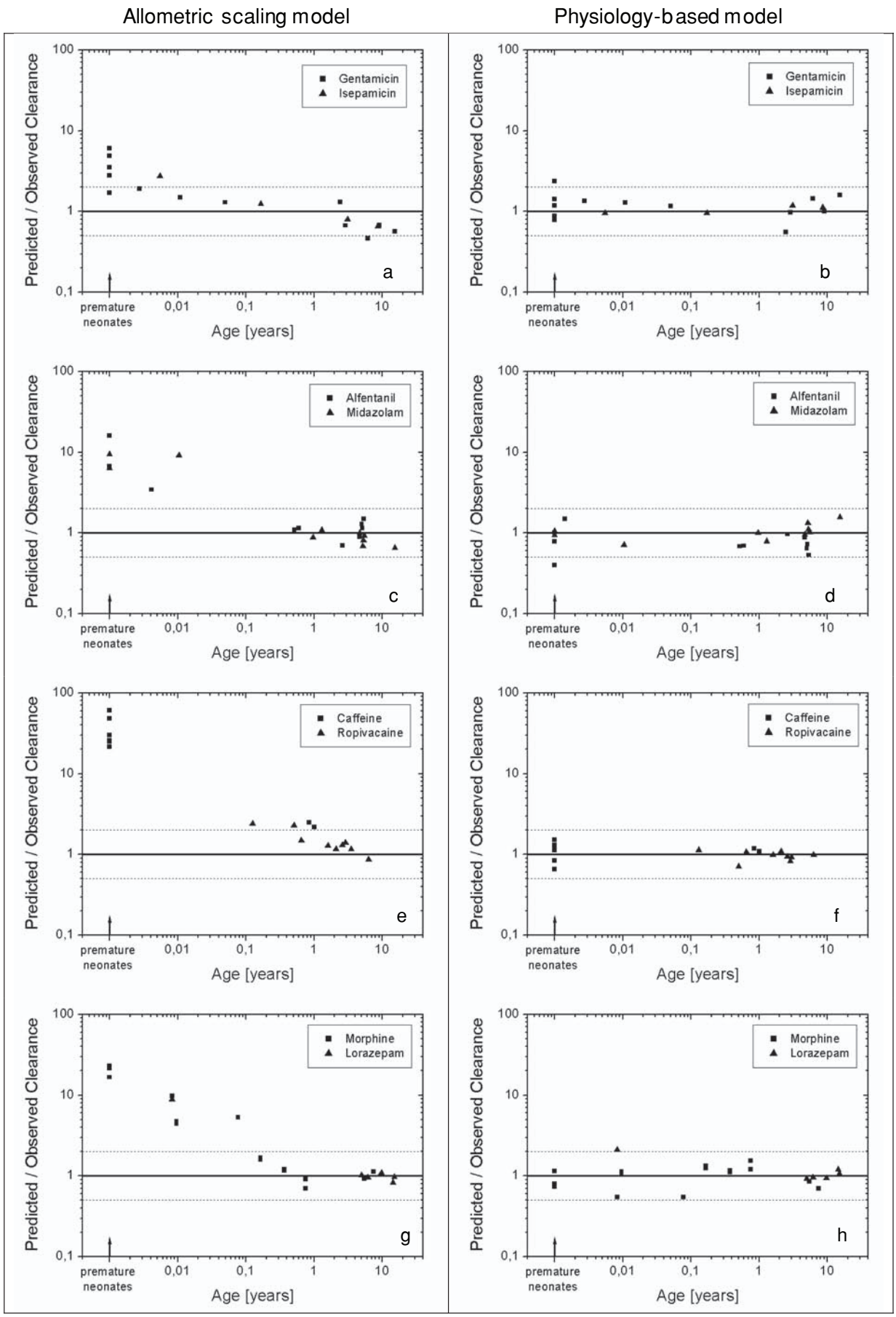

Figure 1 The predicted/observed clearance ratio plotted against age for compounds eliminated via renal clearance due to glomerular filtration (a, b), CYP3A4 (c, d), CYP1A2 (d, e) and UGT2B7 (f, g). The results using the ¾ allometric clearance scaling approach are shown on the left and the physiology-based approach results are in the right column. The solid line represents the line of identity and the dotted lines indicate where predicted clearance was twice or half the observed clearance. The arrow indicates data from premature neonates.

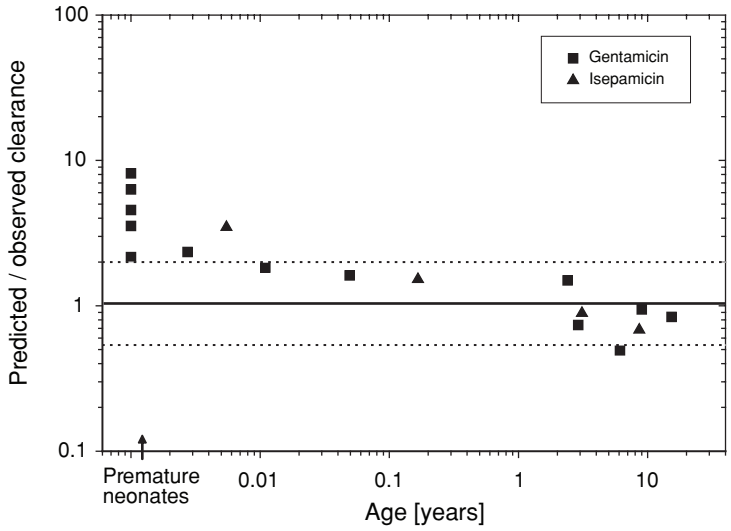

Figure 2 The predicted/observed clearance ratio plotted against age for gentamicin and isepamicin. Predicted clearances were derived using the 2/3 allometric power function. The solid line represents the line of identity and the dotted lines indicate where predicted clearance was twice or half the observed clearance. The arrow indicates data from premature neonates.

by the lack of data points at or below the line of identity (Figure 3a). The physiology-based approach appeared not to be biased towards either over or under estimation of clearance across the age range of term neonates to 18 years (Figure 3b). Clearance in premature neonates was slightly overestimated (Figure 3b).

Discussion

The scaling of clearance from adults to children has been the subject of recent studies. There are two primary approaches proposed to achieve this; namely allometric scaling[4-7,11,16] and physiology-based scaling[2,5,17,18]. There is currently not enough data to suggest when the use of these scaling approaches is appropriate and/or feasible. An approach is required, or an integration of approaches, that can accurately predict the general trends associated with the age-dependence of clearance.

The ¾ power model has been used to scale metabolic and physiological processes among species based on body size, including scaling to humans (for a list of key references on the history of the ¾ power model see Anderson and Meakin[7]). This easy-to-use equation presents a significant improvement over other size models such as the surface area or per kg models[11]. As expected, when the maturity of the processes responsible for clearance were immature, the allometric equation was not appropriate for predicting clearance, despite the inter-individual variability in the clearance values that are common in paediatric populations. Allometric scaling tends to systematically overestimate clearance in young children, where the intrinsic activity of the eliminating process has not yet reached the activity in the adult. This was demonstrated elegantly in a study that compared the allometric approach to the physiology-based approach for the two CYP3A4 substrates, midazolam and alfentanil[5].

In an effort to use the allometric approach in young children, others[6] have examined the use of power functions other than ¾. As observed in our study, the ¾ function was appropriate in most cases for children over the age of five years. In younger children however, the power function that most accurately predicted clearance was age and drug dependent and no generalisations could be made as when these different power functions should be used[6]. This was likely due to the fact that the allometric approach takes into account size but not the ontogeny of the clearance pathway, which is both age (ontogeny) and drug (pathway-specific) dependent, as demonstrated in our study. The physiology-based approach, which explicitly accounts for the age dependence of enzymatic activity, predicted the trends of clearance in children.

As discussed in the Bjorkman study[5] for CYP3A4, the *in vitro* assays used to determine the age-dependence of enzyme activity can vary greatly depending on the substrate used to generate the data. In his study, using these different *in vitro* ontogeny values led to greatly varying clearance predictions for children. In our previous study[2], both literature based clearance values for midazolam and alfentanil and *in vitro* activity data were used to build the ontogeny model of CYP3A4 for children, thus not relying solely on

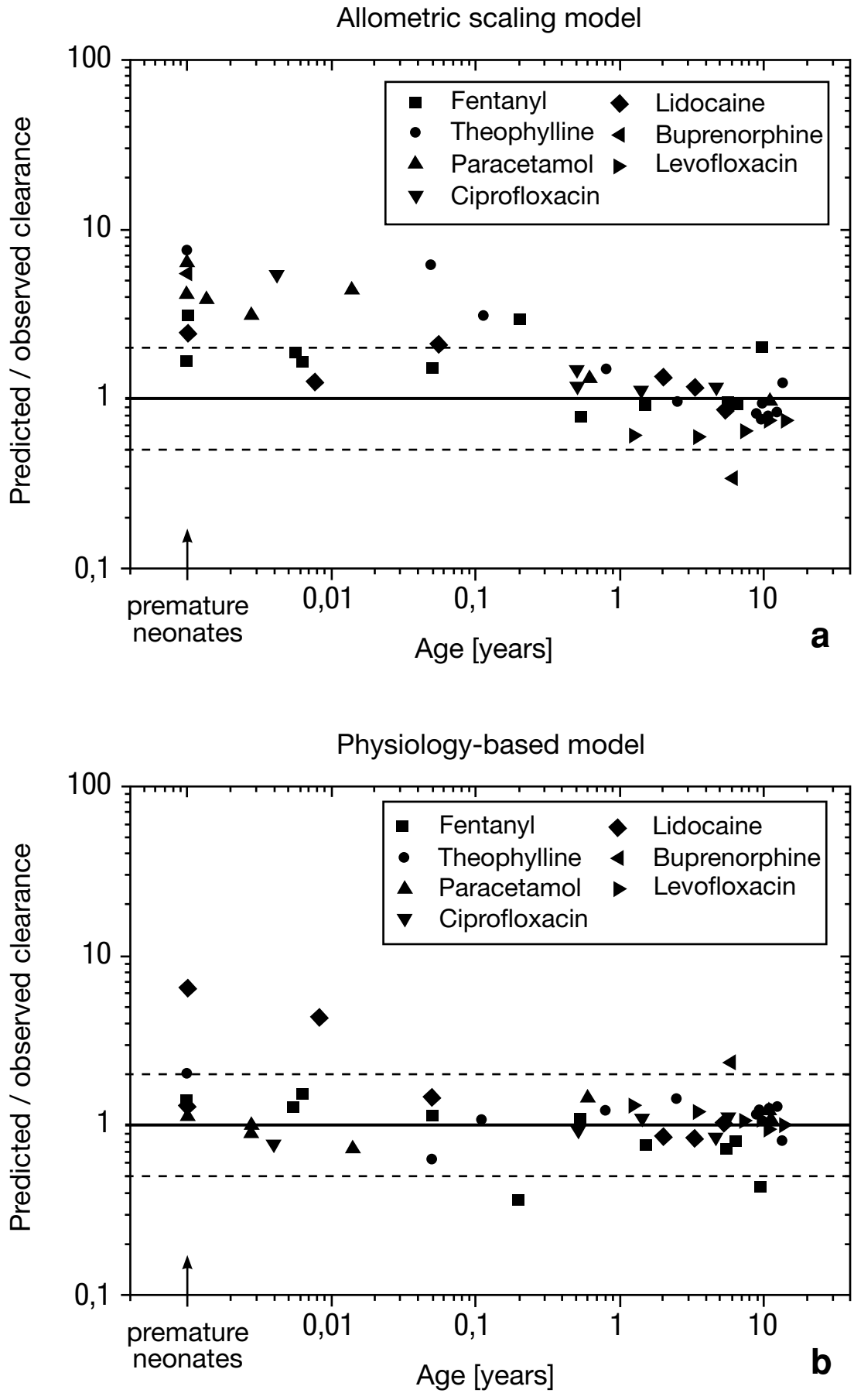

Figure 3 The predicted/observed clearance ratio plotted against age for compounds eliminated via multiple pathways. Graph a is based on clearance scaling using the ¾ power allometric approach. Graph b is based on the physiology-based clearance scaling approach. The solid line represents the line of identity and the dotted lines indicate where predicted clearance was twice or half the observed clearance. The arrow indicates data from premature neonates.

the variable *in vitro* data. This was later used to predict the hepatic clearance of other CYP3A4 substrates in children with a good agreement[2]. Using the latter approach to physiology-based clearance scaling, the accuracy of clearance predictions was independent of the age with the exception of premature neonates, which tended to be slightly overestimated.

Premature neonates represent a specific subgroup, with variable clearances dependent on weight, gestational and postnatal age. For example, to define caffeine clearance following intravenous administration in premature neonates, Lee et al[19] had to generate an empirically-based equation that included both current weight and postnatal age, with postnatal age being the more important of the two. Furthermore, premature neonates generally receive drugs for varying clinical conditions, which may alter the neonate's physiology and hence the drug's pharmacokinetics. Using the physiology-based approach, all premature experimental groups were considered equivalent such that all premature neonates in a compound group were given the same clearance value. Clearance pathway enzymatic ontogeny was considered in the physiology-based approach. Therefore, this more accurately predicted premature clearances in comparison to the allometric approach.

In the case of passive renal elimination via glomerular filtration, it appeared that the allometric equation did not accurately scale clearance. Since the ¾ power model has primarily been used to scale active physiological and metabolic processes, the inability to accurately scale the passive process of glomerular filtration may have been expected. For passive processes, an allometric power function of ⅔ may be more appropriate as this is directly related to body surface area. While the underestimation in children over two years of age was less than using the ¾ power function, the overestimation in children under two years of age was greater. For renal clearance, other means of scaling should be used[2,13].

Interestingly, it appeared that at the age below which the allometric equation was no longer accurate, closely matched the age at which the enzymes responsible reached intrinsic adult activities. For example, the allometric equation seems appropriate for scaling the clearance of the UGT2B7 and CYP3A4 compounds in children over the age of at least six months. This corresponds to the age at which *in vitro* enzyme activity reaches adult activity for UGT2B7[3] and CYP3A4[3]. CYP1A2 is the last major enzyme to develop reaching adult activity levels well beyond one year of age[20], up to potentially 15 years of age[3]. The age at which the allometric equation correctly predicted clearance of the compounds primarily eliminated via this enzyme was approximately four years. More confidence could be gained in determining the youngest age at which the allometric approach is appropriate for scaling clearance with an increase in the quite sparse data for neonates between birth and one year of age. Unfortunately, a complete range of ages was not available for all compounds potentially skewing these results. Regardless, it appears from this study that the age at which the allometric equation becomes a useful means of scaling clearance is following the age at which the maturity of the process is complete or near to complete and, is thus, process specific.

These studies represent those of normal weight for age children, based on a comparison of the reported average weights to standard weights in children from the ICRP publication[12]. We did not have enough data to support the assertion that the allometric equation could be used to predict clearance in overweight and underweight children. Holford[11] suggests that in cases of unusual body composition, a good place to start is using size based on the normal weight for age. Only with individual clearance data from children with unusual body composition can we begin to test the sensitivity of clearance scaling to altered body composition.

This study has shown that the appropriate use of the allometric equation depends on two factors; the age of the child and the primary process responsible for clearance. While this study only focused on four primary processes of clearance, renal, CYP3A4, CYP1A2 and UGT2B7, the age-dependent predictivity of the allometric equation varied greatly. As has been demonstrated previously[2], a physiology-based approach is predictive of these processes from birth (term) to 18 years, however; the physiology-based approach requires more input and is mathematically more challenging. Because of the ease of use of the allometric equation, it is suggested to have an integrative approach that uses the allometric approach when appropriate and switches to the physiology-based approach in the younger age range. An advantage of the physiology-based approach is that clearance in a child due to a medical condition, such as a reduced eliminating organ blood flow, can be assessed with greater confidence than using a body weight scaling approach.

Clearance scaling is a first step towards the scaling of pharmacokinetic profiles from adults to children. The next step is a determination of the age-dependence of distribution volumes using either an allometric approach[7] or a physiological approach[9]. Together, these two parameters

can lead to a reasonable prediction of a child's pharmacokinetic profile and decisions regarding dosing and potential therapeutic and/or adverse effect events can be informed.

Competing interests

None declared

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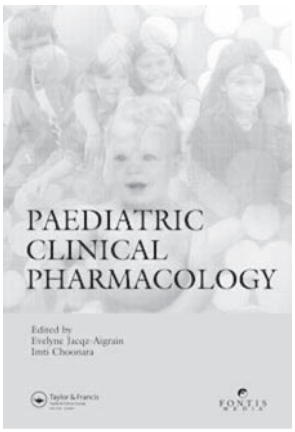

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