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Does size matter? : bridging and dose selection in paediatric trials

Cella, M.

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Chapter 6

Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models

Massimo Cella, Catherijne Knibbe, Saskia de Wildt, Joop van Gerven,
Meindert Danhof and Oscar Della Pasqua

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Abstract

AIM: The objective of this investigation was to assess the performance of a model built on data from one paediatric subpopulation to predict drug exposure in another subpopulation.

METHODS: Midazolam was selected as a paradigm compound. Two non-linear mixed effects models were developed to describe midazolam pharmacokinetics in infants, toddlers and adults (*model 1*) and in children and adolescents (*model 2*). Subsequently, drug exposure in children and adolescents, expressed in terms of the area under the concentration *vs.* time curve (AUC), was predicted based on pharmacokinetic parameter distributions obtained from the model describing infants, toddlers and adults (*model 1*). Results were compared to the values obtained from modelling of the data in the corresponding population (*model 2*). **RESULTS:** The two pharmacokinetic models accurately described midazolam exposure in the population on which they were built. However, the model based on data from infants, toddlers and adults failed to predict the exposure estimated in children and adolescents. The discrepancy between estimated and predicted exposure increased proportionally with body weight.

CONCLUSIONS: The current results indicate that irrespective of whether extrapolation or interpolation methods are to be applied during paediatric drug development, model predictions beyond the range of the data used for parameter estimation may be biased. For accurate inter- or extrapolation to different populations, the assumption of identical parameter-covariate correlations across age groups may not be taken for granted.

6.1 Introduction

CONDUCTING CLINICAL STUDIES in a paediatric population is widely recognised as a difficult task. Developing drug for children faces two opposing concerns: on one hand, a child may present fundamental differences compared to adults in terms of pharmacokinetics, efficacy and safety. These differences may result from or compounded by the developmental changes that occur throughout childhood and adolescence and as such should be taken into account when designing a clinical trial. On the other hand, children are considered a vulnerable population, and every effort must be made to decrease the burden on paediatric patients, minimising the risk and discomfort which are always present in a clinical trial. The coming into effect of legislations such as the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) in the US [1] and, most recently, the 2007 Paediatric Regulation in the EU [2] has boosted clinical research activities in children and prompted the development of both regulatory and scientific guidelines for the design of paediatric clinical trials.

Despite such a favourable environment, some issues concerning technical aspects in the implementation of paediatric studies remain. Amongst the others, of particular importance is the choice of the dose to be administered to children in a trial [3]. Inaccurate dose selection will likely affect the results of a study even if all other aspects of the design are formally correct. A sub-optimal dosing regimen may lead to wrong conclusions about the exposure-response relationship or about treatment efficacy in a particular population, while a higher-than-required dose may inflate the side effects and toxicity.

Given that formal dose escalation studies similar to those carried out in adults are not appropriate in children, starting a trial at the effective dose range is of crucial importance in paediatric pharmacology [4]. Extrapolation methods are therefore often used to address this requirement, providing some initial estimation of dose to be administered to paediatric patients. This is normally done by scaling the dose from adults or from one paediatric subgroup (pre-term newborns, term newborns, infants, toddlers, children and adolescents) [5] to another. Different approaches have been proposed for the purposes of extrapolating pharmacokinetic data, which vary from the simple linearisation of the dose based on bodyweight (i.e., mg/kg) to the more complex methods like pharmacokinetic-pharmacodynamic (PKPD) modelling or physiologically-based pharmacokinetic (PBPK) modelling [6–9]. A discussion over the benefits and problems associated to each of these approaches is beyond the scope of this article. We just need to keep in mind that all of them rely

on the use of data from a reference population as the basis for inferences about potential differences in pharmacokinetics and consequently for recommendations about the dosing regimen in the target population. In addition, we will not discuss here the potential differences in pharmacodynamics in some disease conditions and hence the need to take those differences into account when scaling the dose across age groups.

Assuming that the exposure-effect relationship is independent of age, differences in PK parameter distributions across populations should be used as basis for the dose rationale. Such an approach must identify which physiological factors alter pharmacokinetics and how these (might) differ across the paediatric population(s), without relying on *a priori* assumptions about the correlation between pharmacokinetic parameters and demographic covariates. For these reasons, we strongly suggest to use a physiologically-based scaling approach, which we describe as *scaling for function* [3].

On top of this, it is critical for paediatricians, regulators and clinical researchers to realise that non-linearity may exist between pharmacokinetics and demographic factors, due to the influence of developmental growth and organ maturation. Different examples show the implications of non-linearity for dosing regimen in children [7, 10, 11] and how non-linear mixed effects and Bayesian hierarchical modelling can take into account such non-linearity, yielding appropriate estimates of the differences in pharmacokinetics [12, 13]. Recently, we have shown how a parametric approach can be used to characterise changes in drug exposure due to developmental growth [14]. Based on the predicted differences in parameter distributions, it is possible to define doses in the paediatric population. In this case, estimation of pharmacokinetic parameter distributions becomes critical to accurately describe individual differences in exposure in paediatric patients.

In this paper we focus on the predictive value of pharmacokinetic modelling, allegedly the most used method for initial dose estimation in paediatric drug development [15]. This methodology is preferred because it enables the assessment of pharmacokinetics based on sparse sampling, taking into account the confounding effects of developmental growth common to paediatric trials. Given that historically pharmacokinetic modelling has been used to analyse existing compounds (e.g. therapeutic monitoring), it remains unclear whether the approach has comparable performance when applied prospectively in drug development. Moreover, it is important to realise that most statistical criteria and model validation procedures are based on goodness-of-fit of data representative of the population comparable to the source data.

The objective of this investigation was therefore to evaluate the ability of a pharmacokinetic model built on data from infants, toddlers and adults to predict pharmacokinetic differences in a population composed by children and adolescents. Strictly speaking, it was our endeavour to evaluate the performance of a model-based approach to interpolate rather than extrapolate. From a methodological point of view, interpolation and extrapolation are not very different, except for the fact that intuitively one may take for granted the continuity of covariate-parameter correlations when dealing with interpolations and assume the validity of

approximation by linearisation methods [16, 17]. Here we attempt to demonstrate whether parameter values estimated in a reference population can be used to make inferences about the dose requirements in a paediatric subgroup that has not been investigated yet. In this particular case, the focus is on those groups which have not contributed to the data supporting initial model fitting and validation.

As paradigm compound for the purposes of our investigation, we have selected midazolam, a short-acting water-soluble imidazobenzodiazepine, which is used for treatment of acute seizures and for inducing sedation and amnesia before medical procedures [18, 19]. The pharmacokinetics of midazolam has been previously described by many authors in adults [20–23], pre-term newborns [24, 25], neonates [26–28], infants [29], children [30, 31] and adolescents [32]. Despite the availability of numerous models describing the pharmacokinetics of midazolam, these efforts were aimed at obtaining accurate, unbiased parameter estimates and subsequently evaluate the implication of different dosing recommendations for the same population used to develop the model. Irrespective of whether data analysis was limited to a specific subgroup or whether modelling involved meta-analysis of different patient populations, validation procedures have not included the assessment of model performance on a different group or sub-populations. Whilst most paediatric drug development programs involve staggering procedures in which age groups are included in a trial in a decreasing order (i.e., from adolescents to newborns), we have selected adults, infants, toddlers as reference and children and adolescents as target population. In reality, this unusual combination may happen when deferral of trials occurs or when disease severity increases with age, making the inclusion of older children in a trial more challenging. Interpolation of pharmacokinetics to an older paediatric group is therefore plausible and desirable.

6.2 Methods

Patients

Adult data were obtained from three studies performed by the Centre for Human Drug Research (CHDR, Leiden, The Netherlands). Study 89110-pilot was a dose validation study in which six healthy volunteers received 0.15 mg/kg of midazolam intravenously. Study 89110 was a randomised, double blind, placebo controlled, four-way crossover experiment in eight healthy volunteers. Each subject received four treatments:

1. placebo;
2. midazolam 0.1 mg/kg over 15 min by intravenous infusion;
3. midazolam 5 mg for subjects weighing less than 60 kg, 7.5 mg for subjects weighing 60–80 kg or 10 mg for subjects weighing more than 80 kg, by oral administration;
4. 1-hydroxy-midazolam 0.15 mg/kg over 15 min by intravenous infusion.

Study 94113 was a randomised, double blind, five-way crossover trial in 20 healthy males, in which midazolam was used as comparator for an investigational drug. Each subject received 0.1 mg/kg over 20 min by intravenous infusion [33, 34].

Data from infants and toddlers were obtained from the Erasmus MC - Sophia’s Children Hospital (Rotterdam, the Netherlands), where infants admitted to the paediatric surgical intensive care unit (PSICU) were studied during the first 24 h after elective craniofacial surgery. Twenty-three infants and toddlers between 1 month and 2 years of age were administered with a bolus of midazolam 0.1 mg/kg followed by an infusion of 0.05 mg/kg/h. COMFORT [35] and visual analogue scale were assessed every two hours and used as basis for dose titration during the course of treatment when needed [36].

Data from children and adolescents were obtained from a collaborative investigation between the Purdue University in Indianapolis, USA, and the Sophia Children’s Hospital in Rotterdam, the Netherlands. The cohort (3-17 years old) comprised 18 paediatric oncology patients who were administered midazolam intravenously (average dose was 0.12 mg/kg) prior to invasive procedures [37]. A summary of the demographic variables and treatment regimens for all trials is shown in Table 6.1.

Table 6.1: *Studies characteristics and demographics*

	Populations (mean - range)		
	Infants & Toddlers	Children & Adolescents	Adults
N subjects	23	18	34
Age	10.9 m (3.2 - 24.7)	7.7 y (3.2 - 16.2)	23.8 y (19.9 - 29.7)
Body Weight (kg)	9.2 (5.1 - 12)	29.0 (12.6 - 60.1)	72.3 (59 - 91)
N samples	8.8 (3 - 13)	4.6 (3 - 5)	19.3 (14 - 31)
Dose and administration route	0.1 mg/kg bolus + 0.05 mg/kg/h IV	0.12 mg/kg IV	0.1 mg/kg IV or 5 - 7.5 - 10 mg oral

Pharmacokinetic analysis

Non-linear mixed effects modelling was used to analyse the pharmacokinetics of midazolam. The first-order conditional estimation with interaction method in NONMEM VI (release 2.0) [38] was used to fit all concentration data described later in this section. Given the objective of this exercise, different model building and validation steps were involved. A PK model was built based on infants, toddlers and adult data together (*model 1*). A second PK model, built on data from children and adolescents, was used as control for validation purposes (*model 2*). In other words, pharmacokinetic parameter estimates derived from infants, toddlers and adults were used to simulate midazolam concentration profiles in children and adolescents. The predicted concentration profiles were subsequently compared with those derived from the data in children and adolescents.

Different approaches were evaluated during the development of a model describing infant, toddlers and adult data. Initially, the use of adult data as prior

information for the analysis of paediatric data in a Bayesian framework was considered [14], but it was soon discarded due the lack of convergence. This clearly suggested that parameter distributions in the younger patients were considerably different from the healthy subjects included in the analysis. Therefore, an attempt was made to integrate infant, toddler and adult data in a single dataset and analysing this population using a covariate model, in which the demographic covariates would have described the differences between the subgroups.

The effects of body weight and age (the only covariates available in the datasets) were investigated as potential covariates on pharmacokinetic parameters. Significant correlations between covariates and parameters were incorporated using an exponential relationship for continuous variables, according to the formula:

$$\theta_i = \theta \cdot \left(\frac{COV_i}{median} \right)^{EXP} \quad (6.1)$$

where θ_i represents the individual value for the parameter, θ the population estimate, COV_i the individual value of the covariate, *median* is the median value of the covariate in the population, and *EXP* the exponent. The change in the objective function (OFV; equal to -2 log likelihood) as determined by NONMEM was used as a goodness-of-fit diagnostic for covariate inclusion (Δ OFV = 3.84, $P = 0.05$, χ^2 distribution with one degree of freedom). The contribution of each covariate was confirmed by a stepwise backward deletion (Δ OFV = 6.89, $P = 0.01$, χ^2 distribution). In addition, goodness-of-fit plots, including observed (OBS) *versus* individual prediction (IPRED), OBS *versus* population prediction (PRED), conditional weighted residuals (CWRES) *versus* time and CWRES *versus* OBS were used for diagnostic purposes [39]. Given that the accuracy of model predictions also depends on the variance structure, special attention was paid to the evaluation of model misspecifications for the random effects. Mirror plots from simulated datasets were produced and results compared to the original data. In addition, the normalised prediction distribution errors (NPDE) method was applied for an in-depth diagnosis of potentially poor behaviour [40]. This method was implemented using the NPDE add-on software package [41], which was run in R [42].

In a subsequent step, the parameter estimates obtained from this model were used to predict midazolam plasma concentrations in the 18 children and adolescents available in the control group. The exposure to the drug, expressed as AUC_{0-180} , was selected as a clinically relevant endpoint for comparison purposes. Although the original idea was to directly compare the results from model-based predictions with the observed pharmacokinetic profiles in children and adolescents, estimated exposures based on a separate model (*model 2*) were used instead of actual observations. This was caused by the use of a very sparse sampling scheme in children and adolescents (4.6 samples on average), which did not allow for accurate estimation of the individual AUCs without modelling the data separately. In addition, the use of model estimation mitigates the potential impact of outliers in a small group of only 18 patients, which could lead to misinterpretation of observed AUC distributions. In short, AUCs in children and adolescents as **predicted** by *model 1* were compared with the AUCs in the same subjects as **estimated** by *model 2*.

Therefore, a separate pharmacokinetic model for the analysis of midazolam concentrations in children and adolescents was built in the same manner as previously described for infants, toddlers and adults. In this case, informative priors were used to stabilise the model and to minimise the variability caused by the sparse sampling and the small population [43]. This method was previously applied to abacavir and was aimed at integrating prior information about parameter distributions in the analysis of small datasets [14]. Parameter estimates are obtained based on the estimation of a posterior distribution, rather than solely based on the likelihood defined by the available data. This is an effective approach to challenge the validity of assumptions regarding the magnitude of the differences in parameter distributions. Data analysis was implemented with the PRIOR subroutine [44] using Wishart distribution for parameter priors. Prior information about midazolam parameter distribution in children and adolescents was taken from De Wildt [45].

Prediction of pharmacokinetics in children and adolescents

Based on the parameter estimates obtained from this second model, individual AUCs were simulated 200 times for each of the 18 children and adolescents in the original trial. The resulting AUC distribution for each patient was then plotted as whisker plots and used to assess the accuracy of model-based interpolations. AUCs were calculated in NONMEM by integrating the amounts in the dummy compartment, according to the equation:

$$AUC = \int_0^t C_t \cdot dt. \quad (6.2)$$

We evaluated whether drug exposure in children and adolescents can be predicted accurately under the assumption of continuity in the correlations between pharmacokinetic parameters and covariates across the age range of interest. Using the parameter estimates obtained from the model built with data on infants, toddlers and adults (*model 1*), concentration *vs.* time profiles were simulated 200 times for each patient in the group of children and adolescents ($n=18$). Predicted AUCs were summarised for each patient as mean and 95% confidence intervals and then compared with the AUCs obtained from the model built on the data from the actual children and adolescents in the trial. The discrepancy between the estimated and the predicted exposure was expressed as percentage, according to equation 6.3:

$$\Delta = \frac{AUC_{predicted} - AUC_{estimated}}{AUC_{estimated}} \cdot 100 \quad (6.3)$$

6.3 Results

PK model in infants, toddlers and adults (*model 1*)

The pharmacokinetics of midazolam in infants, toddlers and adults was described by a two-compartment model with first-order absorption and first-order elimination.

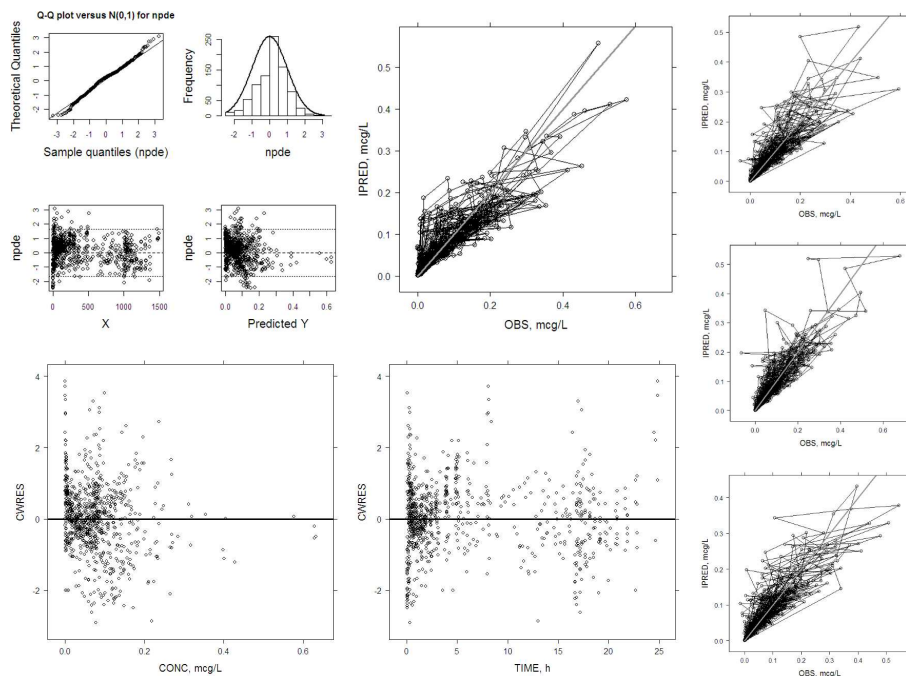


Figure 6.1: *Diagnostic plots of the model based on data from infants, toddlers and adults. (Top, left) NPDE; (top, centre) Post hoc predictions vs. observed concentrations; (bottom, left) CWRES vs. predicted concentrations; (bottom, centre) CWRES vs. time; (right-hand side) mirror plots. All diagnostic measures indicate acceptable goodness-of-fit and model performance*

Inter-individual variability (IIV) was estimated for clearance (CL) and peripheral volume of distribution (V_p). Residual variability was characterised by a proportional error model. The incorporation of BW as covariate on clearance according to an exponential model showed the highest drop in objective function and improvement in goodness-of-fit. The exponent was fixed to the classic allometric value of 0.75 [46]. All attempts to estimate this parameter resulted in unsuccessful minimisations. This is explained by the narrow range of body weights in the infant and toddler population and the gap between this latter group and adults. The highest value for body weight in infants was 12 kg, whilst the lowest value for body weight in adults was 59 kg.

Bearing in mind the objective of interpolation across populations, focus was given to model validation steps, which yield information about the variance structure and variance-covariance matrix. As shown in Figure 6.1, goodness-of-fit plots reveal that the model provides an accurate description of the data. Of particular interest are the mirror plots which showed that the model was able to simulate

data with a variance structure similar to the original data. In addition, NPDE summaries indicate that the discrepancy between predicted and observed values can be assumed to be normally distributed. In spite of minor misspecification of the variance, overall these diagnostic techniques confirm the infants and adult model is suitable for simulation purposes.

PK model in children and adolescents (*model 2*)

The pharmacokinetics of midazolam in children and adolescents was also described by a two-compartment model with first-order elimination. Inter-individual variability was estimated for clearance and central volume of distribution (V_c). Residual variability was characterised by a proportional error model. In contrast to the covariate model in infants and adults, it was the normalisation of V_p by age using a linear function that caused the highest drop in objective function and improvement in goodness-of-fit. As shown in Figure 6.2, diagnostic plots show that the model accurately described the observed data. In addition, NPDE confirms that the difference between predicted and observed values is normally distributed. Final parameter estimates for both models are shown in Table 6.2.

Table 6.2: Final pharmacokinetic parameter estimates for midazolam, as estimated from data on infants and adults (Model 1, left) and on children and adolescents (Model 2, right)

	Model 1		Model 2	
Parameters (units)	mean	bootstrap mean (%CV)	mean	bootstrap mean (%CV)
<i>Fixed effects</i>				
CL/F (L·min ⁻¹)	-	-	0.19	0.12 (20.4)
CL/F (L·min ⁻¹ ·kg ^{0.75})	0.234	0.232 (9.6)	-	-
V _c /F (L)	0.312	0.310 (9.6)	1.95	2.07 (47.7)
V _p /F (L)	16.5	16.2 (8.7)	-	-
V _p /F (L· $\frac{months}{74}$)	-	-	7.14	7.38 (31.2)
Q (L/min)	1.34	1.33 (10.3)	0.105	0.107 (32.8)
Ka (h ⁻¹)	8.21	8.29 (14.7)	-	-
<i>Inter-individual variability %</i>				
CL	39.9	39.3 (28.2)	32.7	32.9 (26.0)
V _c	-	-	31.5	32.4 (22.6)
V _p	58.5	58.9 (17.0)	-	-
<i>Residual error %</i>				
ϵ	40.0	40.0 (12.4)	39.0	37.2 (21.1)

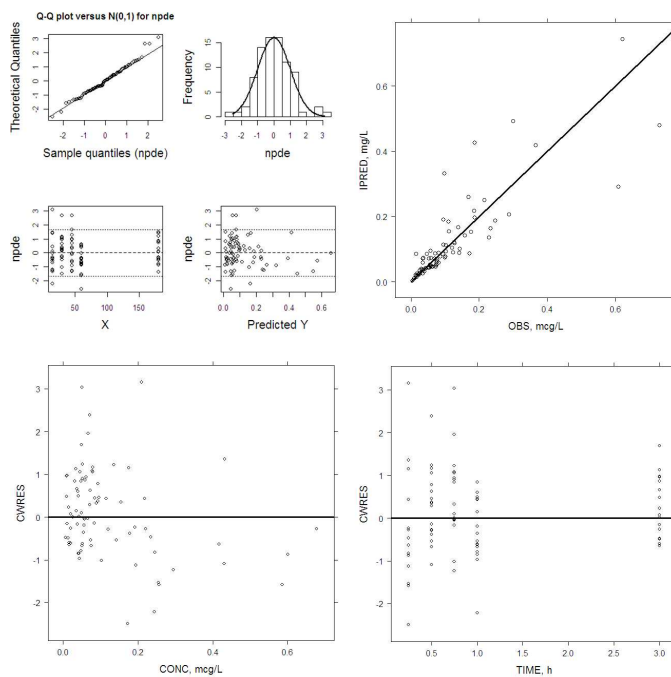


Figure 6.2: *Diagnostic plots of the model based on data from children and adolescents. (top, left) NPDE; (top, right) Post hoc predictions vs. observed concentrations; (bottom, left) CWRES vs. predicted concentrations; (bottom, right) CWRES vs. time. All diagnostic measures indicate acceptable goodness-of-fit and model performance*

Interpolation of midazolam exposure from infants, toddlers and adults to children and adolescents

To evaluate the predictive power of a model-based approach to characterise the exposure to midazolam in a different paediatric population, the parameter estimates from the model based on infants, toddlers and adults were used to predict the AUC_{0-180} in a population of 18 children and adolescents. The mean difference between the predicted and estimated AUC_{0-180} was of -17.8%, with a range of -6.8 to -38.4%. More interestingly, as it can be seen in Figure 6.3 and in Table 6.3, this discrepancy seems to increase proportionally with body weight. By splitting the study population in two subgroups across the median body weight, i.e. the first including 9 subjects up to 21.5 kg and the second including 9 patients above this threshold, the discrepancy is of 11.4% for the first subgroup and of 24.1% for the second one. A summary of individual exposures obtained by either model is shown in Table 6.3.

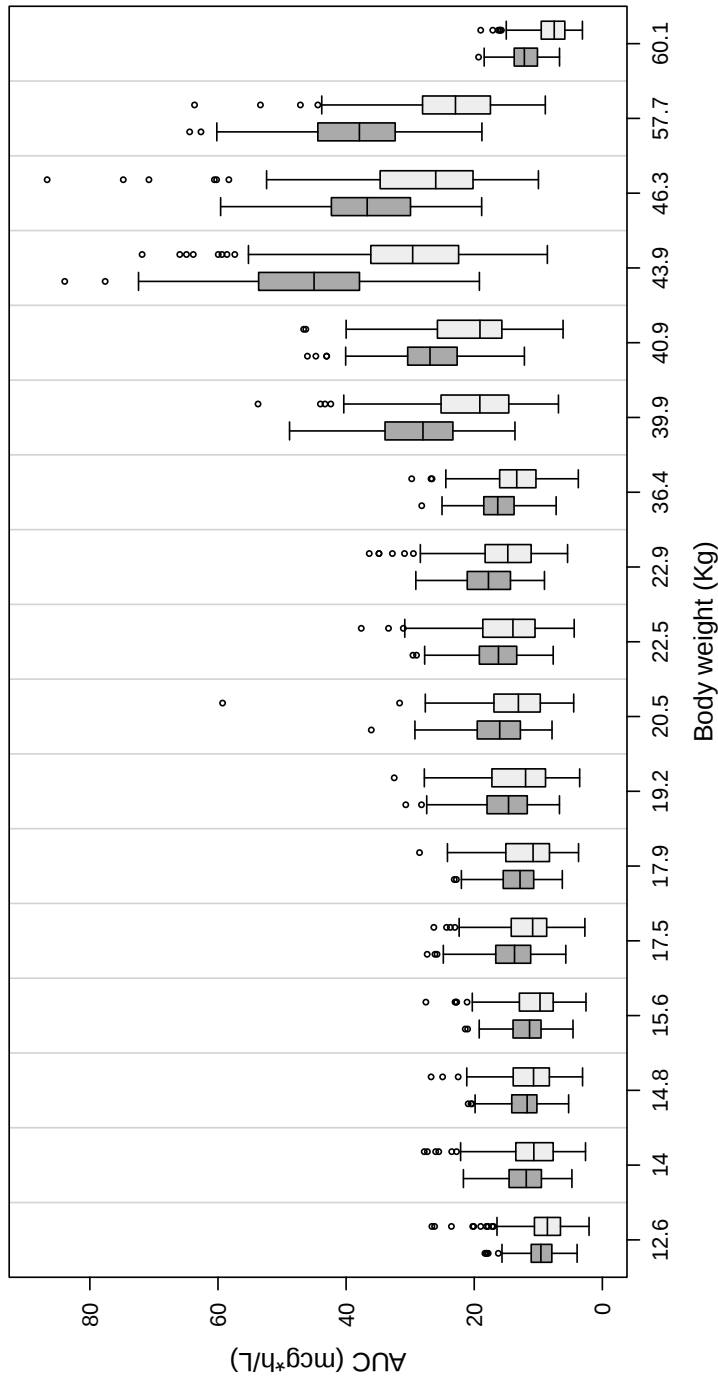


Figure 6.3: Whisker plots of the exposure to midazolam in children and adolescents, as estimated by modelling of the original data (dark grey) and as predicted by the model based on data from infants and adults (light grey). Subject 7 has been excluded from the plot because of the extreme values (see Table 6.3 for details)

Table 6.3: Individual exposure to midazolam in children and adolescents ranked by body weight. The presented values indicate the AUC_{0-180} vs. time curve obtained by the original model (i.e., estimated exposure) and as interpolated from the model built on data from infants, toddlers and adults. The relative difference between estimated and interpolated values appear to become larger with increasing body weight

Subject, bodyweight (kg)	Estimated AUC (mg·min/L)	Predicted AUC (mg·min/L)	Relative difference (%)
1 - 12.6	9.78	9.12	-6.75
2 - 14.0	12.29	11.12	-9.52
3 - 14.8	12.25	11.27	-8.00
4 - 15.6	11.80	10.58	-10.34
5 - 17.5	14.15	11.45	-19.08
6 - 17.9	13.17	11.74	-10.86
7 - 18.8	78.18	70.10	-10.34
8 - 19.2	15.24	13.20	-13.39
9 - 20.5	16.19	13.83	-14.58
10 - 22.5	16.40	15.23	-7.13
11 - 22.9	17.81	15.23	-14.49
12 - 36.4	16.25	13.62	-16.18
13 - 39.9	29.14	20.54	-29.51
14 - 40.9	27.24	20.89	-23.31
15 - 43.9	45.65	31.03	-32.03
16 - 46.3	36.53	28.30	-22.53
17 - 57.7	38.80	23.89	-38.43
18 - 60.1	12.00	7.95	-33.75

6.4 Discussion

The rationale for dose selection in paediatric indications, including the mechanisms for dose adjustment across the wide range of ages from pre-term neonates to adolescents remains a challenge in drug development. Historically, dosing recommendations and dose adjustment have been based on empirical methods, most of which attempt to identify a demographic or physiological factor(s) (i.e., covariates) that best describe(s) the changes occurring during developmental growth.

From a methodological perspective, there are two issues that require further attention to ensure accurate decisions are made with regard to the dose rationale. First is the recognition that parametric approaches, in particular, non-linear mixed effects modelling is required to ensure unbiased pharmacokinetic parameter estimates. Nonparametric methods do not warrant effective characterisation of the physiological factors underlying the changes in pharmacokinetics induced by developmental growth [47, 48]. Second is the need to differentiate validation requirements when assessing modelling results, with distinct metrics for estimation performance, as opposed to the subsequent use of parameter estimates in simulations,

extrapolation and/or interpolation of results, i.e., prediction of drug behaviour in new subjects or patients yet to be investigated [49, 50].

The aforementioned methodological aspects are very pertinent to research protocols in early clinical development, which often stipulate staggering of the target population according to age groups and disease prevalence. In these circumstances, the use of interpolation or extrapolation assumes the existence of a continuous function for the parameter-covariate correlation. The approximation is mostly based on linearisation principles, even for highly non-linear models. This implies that identification of covariates and selection of a covariate model during data fitting is performed under the assumption that the correlation between parameter and covariate holds true for the overall population.

Irrespective of the importance of non-linear mixed effects modelling to ensure unbiased parameter estimation, very few authors have tried to distinguish the different components of a model-based approach to address the pertinent questions in a systematic manner. It should be noted that the issues regarding the predictive power of a model are correlated, but are not necessarily dependent on the choice of the scaling factor. Thus far, most of the ongoing debate in paediatric pharmacology has been focused on the choice of the scaling factor, but the issues regarding extrapolation and interpolation have been left aside [51]. Therefore, the main point we wanted to delve into is the validity of approximation methods to describe the population of interest when data on the dependent variable and corresponding covariates are not available. In the current investigation, we have shown how a population approach can be used to characterise the pharmacokinetics of midazolam by combining infant, toddlers and adult data and analysing them in an integrated manner. A two-compartment model was identified, with body weight affecting the clearance according to an exponential function. These findings are in agreement with most of the literature about midazolam. The use of a fixed allometric correlation between clearance and bodyweight turned out to be a necessity. We defend the view that fixing model parameters is only justifiable if evidence is irrefutable about the validity and implications of their use, in particular if the model is subsequently used for making predictions related to data which has not been used to support fitting and parameter estimation.

The implications of data driven methods are evident by the differences in the covariate model structure observed when fitting the data from children and adolescents. Age was identified as the most significant covariate on the peripheral volume, instead of body weight on clearance. Even if age and body weight are highly correlated during developmental growth (co-linearity), it must be recognised that the diagnostic criteria for goodness-of-fit used with maximum likelihood methods may overrule the evidence of another plausible or even mechanistic correlation, if the data does not support such a correlation.

The degree of accuracy required from model predictions, irrespective of whether they relate to interpolations or extrapolations, depends on the purposes of the model in the first place. In our case, predictions are aimed at defining dosing recommendations in a new population, under the assumption that target exposure is known and should be reached to guarantee efficacy and safety in those patients.

Our results show that the model built on infants, toddlers and adults constantly underpredicts midazolam exposure in children and adolescents across the whole range of bodyweights, these underpredictions becoming larger with increasing body weight. This means that the differences between estimated *vs.* predicted exposures are small when the body weight is low, but differ considerably for heavier subjects. For midazolam, discrepancies observed for smaller children may have limited clinical impact and therefore the model could be considered useful, although not accurate. On the other hand, in heavier subjects these discrepancies can be as large as 38% and cannot be overlooked in the context of the dose rationale for a paediatric protocol.

The discrepancies observed between the parameter-covariate correlations across the two groups raise two important questions. The first one refers to the distinction between *mechanistic*, *descriptive* and *predictive* models, i.e. models whose parameters correspond to physical or conceptual entities, models applicable only to a restricted set of circumstances and models that explicitly incorporate variables quantifying design features so to be able to predict outcomes, respectively [52]. It is clear that the use of more physiological parameters do not circumvent the limitations imposed by current model building criteria, which rely among other things on parsimony (*Occam's razor*). Hence, no matter how plausible it may be, the notion of a common, continuous correlation between parameter and covariate across populations does not survive the criteria used by maximum likelihood estimation methods. In this sense, mechanistic and mechanism-based models remain primarily descriptive of the data used to develop them. Given the accuracy of the deterministic and stochastic components of a hierarchical model, it can also be said that simulations can be predictive of new individuals or patients under the assumption that they come from the same parameter distributions (i.e., same population) and that study design factors do not have a significant effect on these distributions. These requirements underpin the concept of Bayesian forecasting and other similar approaches used for therapeutic drug monitoring [53].

The second question regards both the approximation and inference methods which are required to make predictions about a new population or group. Subjects in the new population may not share the same parameter distributions or the parameter distributions may be comparable, but influenced by design factors or experimental conditions. Given the criteria for maximum likelihood methods, it is evident that these questions cannot be addressed by typical modelling algorithms. In this sense, model building and validation techniques are required which account for model uncertainty and permit parameter estimation irrespective of parsimony. This requirement is critical for the evaluation of a common, continuous correlation between parameter and covariate across populations, an assumption which may be plausible and defensible from a mechanistic point-of-view [54]. There are two possible alternatives to solve this conundrum: an adaptation procedure to ensure updates of previously estimated parameter distribution, so that inaccuracies or model misspecification are mitigated as new data is acquired, or alternatively to obtain parameter estimates which reflect not a single model, but all plausible ones. The ability to evaluate multiple models is quite appealing from a statistical

point-of-view. In addition, it offers advantages as compared to adaptive protocols, which cannot always be implemented. In contrast to maximum likelihood methods, a more comprehensive approach to addressing model uncertainty is Bayesian model averaging (BMA), which allows to assess the robustness of results to alternative specifications by calculating posterior distributions over coefficients and models [55]. It should be clear that in the presence of model uncertainty, model averaging procedures provide better predictive performance than any single model which might reasonably have been selected [56].

In summary, our findings show that the accuracy of model-based predictions depends not only on the characterisation of surrogate measures of function which reflect the changes induced by developmental growth, but also on the choice of diagnostics and validation procedures. Whilst the use of model-based approaches is vital for the implementation and analysis of paediatric clinical trials, the current results also indicate that model predictions based on maximum likelihood methods are valid as long as the same parameter distributions can be warranted across the population. Bayesian averaging methods should be further evaluated for the development of truly inter- and extrapolative models. The development of predictive models imposes not only novel parameterisations but also new statistical concepts.

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