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

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Chapter 5

Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations?

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Abstract

AIM: To assess the predictive value of a model-based approach for dose selection across paediatric populations in early clinical drug development.

METHODS: Abacavir was selected as a paradigm compound using data across a wide age range. Abacavir pharmacokinetics in children was analysed separately from infants and toddlers. Two independent models were obtained and systemic exposure (AUC) was then simulated across populations based on the estimates from each model. Drug exposures in infants and toddlers were predicted using pharmacokinetic parameter distributions obtained from children, and the other way around.

RESULTS: The pharmacokinetic models (a two-compartment PK model for infants and toddlers and a one-compartment PK model for children) accurately described the exposure in the population from which they were built. However, either model failed to predict exposure in a different population: in infants, the median AUC (95%CI) was estimated at 7.03 (6.72-7.48) $\mu\text{g}\cdot\text{h}/\text{ml}$, whilst it was predicted at 5.75 (4.82-6.26) $\mu\text{g}\cdot\text{h}/\text{ml}$; in children, the estimated median

AUC was 6.96 (5.85-7.91) $\mu\text{g}\cdot\text{h}/\text{ml}$, whilst the predicted one was 6.45 (5.80-7.01) $\mu\text{g}\cdot\text{h}/\text{ml}$.

CONCLUSIONS: These findings suggest that the assumption of an identical (linear or non-linear) correlation between pharmacokinetic parameters and demographic factors may not hold true across age groups. Whilst the use of modelling enables accurate characterisation of pharmacokinetic properties, extrapolations based on such parameter estimates may have limited value due to differences in developmental growth across populations.

5.1 Introduction

GIVEN THE REQUIREMENTS of the new paediatric regulation in the EU and the renewal of the paediatric equity act in the USA, a higher demand for paediatric clinical trials can be anticipated. Whilst bridging approaches should be encouraged to prevent unnecessary trials, guidance is lacking about the dosing rationale and how to optimally implement dose titration or adjustment across the paediatric population. One should note that inaccurate dose extrapolation across population groups has implications to the overall paediatric development programme in which rigid protocol designs and fixed dose levels are used. Performing a trial with a sub-optimal dose regimen may lead to wrong conclusions about the exposure-response relationship or about treatment efficacy in a particular population. On the other hand, a higher-than-required dose may inflate the side effects and toxicity. In either case, incorrect conclusions about the suitable dose in a given paediatric age range may be carried forwards when the dose is extrapolated to other groups.

To prevent such a bias, differences in PK parameter distributions across populations rather than differences in body size should be used as basis for the dose rationale. However, paediatric dose selection is still driven by empiricism [1–4]. Clinical practice assumes linear correlations between body weight (BW) and dose, which results in dosing recommendations in children often expressed as mg/kg [5–7], irrespective of the changes in physiology across age groups or differences in the pharmacokinetic properties of different drugs and biopharmaceuticals. Other methodologies use age as scaling factor: the paediatric population is divided into sub-categories (pre-term newborns, term newborns, infants, toddlers, children and adolescents) [8] and the recommended dose is selected according to a child's age [9]. Scaling the dose from adults can also be performed by normalisation based on body surface area (BSA), under the assumption that metabolic processes in humans are constant when expressed as a function of BSA [10].

The assumption of a linear relationship between body size and drug exposure or response is not always justifiable. Body size itself may not be a surrogate for the differences in physiology associated with growth during childhood and adolescence. Implicitly and most importantly the widespread use of demographic variables imposes unidirectional increase of the absolute dose with body size, which constrains the paediatric dose to be always smaller than in adults, irrespective of the relevance of various pharmaceutical, physiological and disease factors. These views also imply that pharmacokinetics can be interpolated within and extrapolated between

populations. Mounting evidence suggests, however, that non-linear relationships must be considered when correlating drug exposure to demographic covariates, and in particular to body weight [11].

Non-linearity may exist between pharmacokinetics and demographic factors due to the influence of developmental growth and organ maturation. In fact, different examples show the implications of non-linearity for dosing regimen in children [12–14] and how non-linear mixed effects and Bayesian hierarchical modelling can take into account such non-linearity. Recently, we have shown how a parametric approach can be used that incorporates the physiological factors underlying the changes in drug exposure due to developmental growth. Based on parameter distributions, it is then possible to extrapolate doses across populations. In this case, estimation of pharmacokinetic parameter distributions becomes critical to accurately describe individual differences in exposure in paediatric patients [15].

In the current investigation we focus on the dose rationale for *first time in children (FTIC)*, i.e. the selection of the safe and effective doses of a drug for a paediatric indication involving a group or population which has not been previously exposed to that drug. In particular, the objective of this paper is to retrospectively evaluate the predictive value of a model-based approach to establish dosing requirements in a paediatric population. Exposures in younger age groups were predicted using pharmacokinetic parameter distributions obtained from the analysis of exposure data children and adolescents, and vice-versa. This scenario reflects a typical problem during clinical development of compounds with a paediatric indication for which deferral may be granted to trials in younger patients. The proposed approach is illustrated for the antiviral drug abacavir, a nucleoside reverse transcriptase inhibitor (NRTI) used to treat HIV infection [16]. According to the ICH E11 guideline [8], abacavir meets the following requirements for bridging:

- the pathophysiological processes subsequent to viral infection in adults do not differ significantly from those observed in children;
- the endpoint for efficacy in clinical trials is the same in both populations, as indicated by the change from baseline in viral load (plasma HIV-1 RNA) and CD4+ T cells count rise [17];
- given its mechanism of action, the exposure-effect relationship can be assumed to be independent of age.

5.2 Methods

Patients

Paediatric data were obtained from two studies by the Paediatric European Network for the Treatment of AIDS (PENTA), in which abacavir was dosed firstly at 8 mg/kg b.i.d and then at 16 mg/kg q.d. The studies were approved by the ethics committees of each participating institution. Written informed consent was obtained from legal guardian, carers and children where appropriate. PENTA 13 was a two-period,

Table 5.1: Study characteristics and demographics. * indicates missing data

	PENTA 15 (mean - range)	PENTA 13 (mean - range)
N patients	23	14
Ethnicity	16 Africans 4 Caucasian 2 Other*	African
Age (years)	1.8 (0.43-2.89)	5.9 (2.14-12.84)
Weight (kg)	11.6 (7.4-15.9)	23.8 (13.7-60.5)
Height (cm)	81 (62-98)	115 (89-164)
BMI (kg/cm ²)	17.8 (15.0-24.2)	16.8 (13.8-22.4)
Creatinine Clearance (dl/h)	31.7 (16.4-50.4)	81 (59-159)
Male/Female	12/11	8/6
Fed/Fasted	8/5*	14/0
Blood samples	4-9	9
Administration route	Oral	
Dosage form	20 mg/ml solution	
Dose	8-16 mg/kg	

crossover, open-label multicenter pharmacokinetic study. 14 children were included in the study [18]. PENTA 15 had the same design, but included 23 infants and toddlers (22 of them had twice-daily PK data) [19]. For both studies plasma samples for the analysis of abacavir concentrations were collected in steady state conditions, with each patient contributing with 4 to 9 blood samples. A summary of the demographic variables and treatment regimens for both PENTA trials is shown in Table 5.1.

Adult data were obtained from six clinical studies performed by GlaxoSmithKline [20–25]. 111 adult subjects were retrieved from GlaxoSmithKline’s clinical database and used as reference population. Further details on these trials can be found at GSK clinical trial register (<http://www.gsk-clinicalstudyregister.com/>).

Pharmacokinetic analysis

Non-linear mixed effects modelling was used to analyse the pharmacokinetic data in both study populations. The first-order conditional estimation with interaction method in NONMEM VI (release 1.0) [26] was used to fit all concentration data described later in this section. To explore the predictive power of parameter distributions and get further insight into how to best select doses in a staggered paediatric development programme, two independent pharmacokinetic models were developed: one to fit children data (*Mod1*) using adult parameter distribution as prior and the other to fit infants and toddlers’ data (*Mod2*), without priors.

The effects of BW, height, age, body mass index, creatinine clearance, sex and fasted/fed status were investigated as potential covariates on clearance, volume and absorption rate constant. Significant correlations between covariates and parameters were incorporated using an exponential relationship for continuous variables, according to the formula:

$$\theta_i = \theta \cdot \left(\frac{COV_i}{median} \right)^{EXP} \quad (5.1)$$

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. Priors based on adult parameters were used to stabilise parameter estimation in children using the Wishart distribution for parameter priors [27].

The change in the objective function value (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 [28]. Given that extrapolations are the primary objective of this investigation, special attention was paid to the evaluation of model misspecifications for the random effects. The normalised prediction distribution errors (NPDE) method was applied for diagnostic purposes [29]. This method was implemented using the NPDE add-on software package, which was run in R [30]. Mirror plots from datasets simulated from both models were produced and results compared to the original data.

Evaluating predictive power

The parameter estimates obtained from each model (*Mod1* and *Mod2*) were used to simulate plasma concentrations in a sub-population different from the one analysed during model building. AUC₀₋₁₂ was selected as endpoint for the purposes of this evaluation. The evidence of similar parameter distributions was the basic criterion for assessing the predictive power of each model. In adults, the reference AUC value for efficacy is 6.02 $\mu\text{g}\cdot\text{h}/\text{ml}$ [31]. No reference toxicity values were available in the published literature. Nevertheless, the use of a safety threshold was deemed unnecessary, as the main concern is the occurrence of a hypersensitivity reaction, which appears to be unrelated to abacavir concentrations [32]. We hypothesised that the AUC distribution in infants and toddlers, as extrapolated using *Mod1*, is comparable to the observed AUC values by *Mod2*. The same methodology was applied to *Mod2* with the objective of predicting AUCs in patients aged 2 to 13 years. For simulation purposes we used the b.i.d. dose, i.e. 8 mg/kg.

Enrichment procedure

Given the small group size and skewed distribution of BW in the original datasets, re-sampling was performed to obtain a uniform distribution of BW within the age ranges under evaluation. Data on BW distribution were extracted from the growth charts provided by the National Center for Health Statistics (<http://www.cdc.gov/growthcharts/>). Datasets were created which included the population in the original studies and 104 simulated patients (56 children and 48 infants and toddlers). Abacavir AUC distributions were then obtained for a total of 140 individuals (70 infants and toddlers and 70 children).

Estimation step

Drug exposure was simulated 100 times for each group of 70 patients using *Mod1* and *Mod2*. Cumulative AUCs were calculated in NONMEM by integrating the amounts in the dummy compartment, according to the equation:

$$AUC = \int_0^t C_t \cdot dt. \quad (5.2)$$

The geometric mean of each individual patient AUC was calculated and summarised as median and 95th percentile. These results were then used to assess the model's predictive power.

Extrapolation from children to infants and toddlers

We evaluated whether drug exposure in infants and toddlers can be predicted accurately under the assumption of comparable correlations between pharmacokinetic parameters and covariates across age ranges. Using *Mod1*, the concentrations in the dataset for infants and toddlers were simulated 100 times. Similarly to the procedures used in the estimation step, the geometric mean of the AUCs for each individual patient was calculated and summarised as median and 95th percentile. The AUC distributions obtained in the estimation step were then compared to the extrapolated values.

Extrapolation from infants and toddlers to children

The same methodology was applied to *Mod2* to predict drug exposures in children aged 2 to 13 years using the model developed on infants and toddlers. Although in real life this is a less common situation, extrapolating drug exposure from neonates (for whom demographic covariates represent a surrogate for both *function* and *maturation*) to children (for whom demographic covariates may only represent differences in *function* or capacity) might give some insight on the possibility of using demographic covariates as surrogates for ontogeny. In each scenario, median and 95th percentile of the estimated and extrapolated exposures were compared. A diagram of the data analysis procedures is summarised in Figure 5.1.

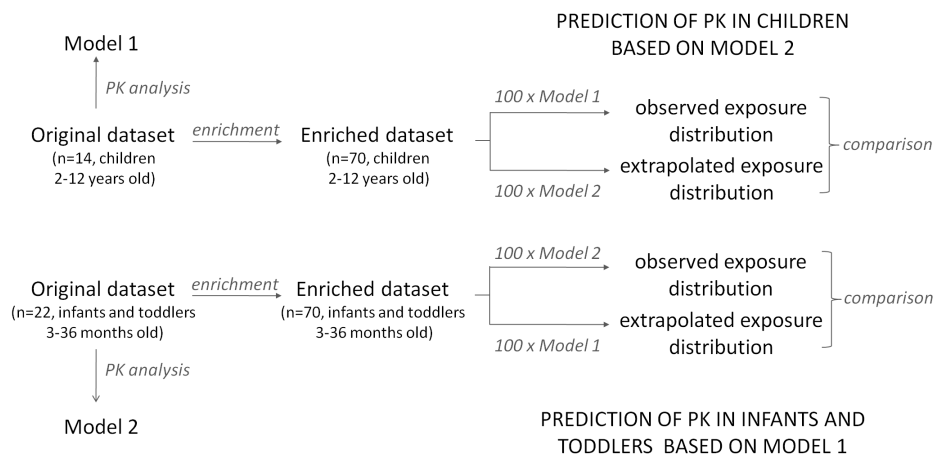


Figure 5.1: Diagram depicting model building and extrapolation procedures

5.3 Results

PK model in children (*Mod1*)

The PK of abacavir in children (2-13 years) was described by a one-compartment model with first-order absorption and first-order elimination. Inter-individual variability (IIV) was estimated for clearance (CL), volume of distribution (V), absorption constant (K_a) and bioavailability (F). Residual variability was characterised by a proportional error model. The incorporation of BW as covariate on clearance and volume according to an exponential model showed the highest improvement in fitting. Further details of the parameter estimates and their distribution can be found elsewhere [15]. Bearing in mind the objective of extrapolation across populations, focus was given to model validation steps, which yield information about the variance structure and variance-covariance matrix. As shown in Figure 5.2, goodness-of-fit plots reveal that the model provides an accurate description of the data. VPC plots indicate that the data are accurately described for up to 4 h after drug administration, after which the variance seems to be slightly overestimated.

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 *Mod1* is suitable for the purposes of data simulation (Figure 5.2).

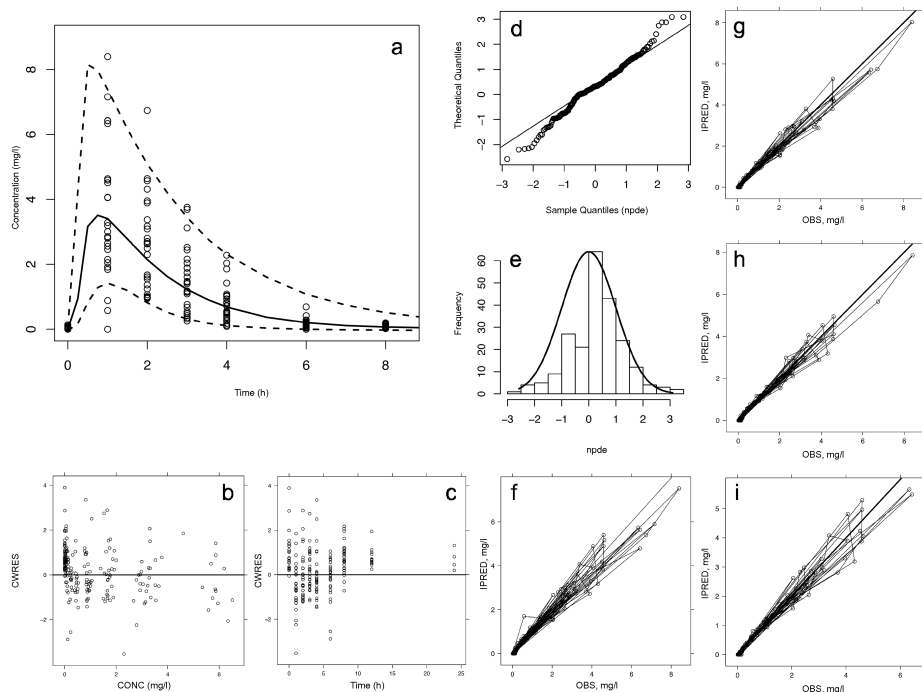


Figure 5.2: Diagnostic plots of the model based on data from children (Mod1). (a) VPC, (b) CWRES vs. predicted concentrations, (c) CWRES vs. time, (d, e) NPDE, (f) post hoc predictions vs. observed concentrations, (g, h, i) mirror plots. All diagnostic measures indicate acceptable goodness-of-fit and model performance, except for a slight skewness in the NPDE distribution and overestimation of variance after 4 h (panel a)

Bootstrapping of this model (Table 5.2) yielded mean parameter distributions similar to the values estimated during data fitting: all parameter estimates from the prior model fell within 5% of the bootstrapped mean, with the exception of IIV on F. 98% of the runs were successful.

PK model in infants and toddlers (*Mod2*)

The PK of abacavir in infants and toddlers (3-36 months) was characterised by a two-compartment model with first-order absorption and first-order elimination. IIV was identified on clearance, peripheral volume and inter-compartmental clearance. In addition, inter-occasion variability was also identified on clearance. Residual variability was described by a proportional model. In contrast to the previous model, BW was found to be a significant covariate on CL only. As shown in Figure 5.3, goodness-of-fit plots show that the model accurately described the

Table 5.2: Final pharmacokinetic parameter estimates for abacavir, as estimated based on 2-13 years old children (Mod1, left) and on 3-36 months old infants and toddlers (Mod2, right)

	Mod1		Mod2	
Parameters (units)	mean	bootstrap mean (%CV)	mean	bootstrap mean (%CV)
<i>Fixed effects</i>				
CL (L/h)	40.6	39.6 (5.4)	-	-
CL/F (L/h)	-	-	13.4	13.2 (6.9)
V (L)	69.1	68.5 (4.5)	-	-
V _c /F (L)	-	-	4.94	4.45 (34)
V _p /F (L)	-	-	8.12	8.25 (18)
Q (L/h)	-	-	1.25	1.26 (21)
Ka (h ⁻¹)	3.58	3.57 (37)	0.76	0.75 (6.1)
F (%)	83	83	-	-
Exponent on CL	0.722	0.694 (11)	1.14	1.16 (26)
Exponent on V	0.810	0.798 (11)	-	-
<i>Inter-individual variability %</i>				
CL	27	27 (11)	29	28 (41)
V	11	11 (6.9)	-	-
Ka	98	93 (13)	-	-
F	37	50 (64)	-	-
V _p /F	-	-	40	41 (42)
Q	-	-	31	51 (169)
<i>Residual error %</i>				
ϵ	3.6	3.6 (37)	14	14 (15)

observed data. In addition, mirror plots reveal that the variance is well defined: the simulated datasets reproduce the dispersion pattern observed in the original data. NPDE confirms that the difference between predicted and observed values is normally distributed.

Bootstrapping results also confirm the precision of the parameter estimates obtained during the data fitting (Table 5.2).

Extrapolation of abacavir exposure from children to infants and toddlers

To evaluate the use of a model-based approach in prospective drug development, the pharmacokinetic parameter estimates from each model were used to predict drug exposure, in terms of area under the curve (AUC₀₋₁₂), in the other population. Pharmacokinetics in infants and toddlers was extrapolated from the model built

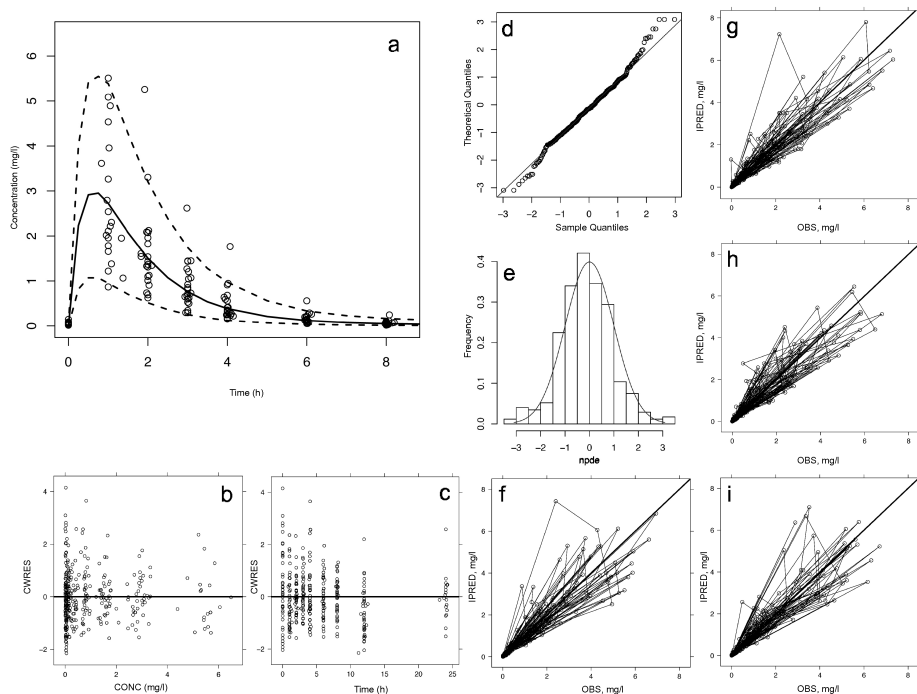


Figure 5.3: Diagnostic plots of the model based on data from infants and toddlers (*Mod2*). (a) VPC, (b) CWRES vs. predicted concentrations, (c) CWRES vs. time, (d, e) NPDE, (f) post hoc predictions vs. observed concentrations, (g, h, i) mirror plots. All diagnostic measures indicate acceptable goodness-of-fit and model performance

on children data and vice-versa. The population selected for the purposes of simulation and extrapolation was defined in such a way that covariate factors could be accounted for in a balanced manner.

The AUC distribution was expressed as median and 95th percentile. AUC values in infants and toddlers, as estimated by *Mod2*, were 7.03 (6.72 - 7.48) $\mu\text{g}\cdot\text{h}/\text{ml}$ with all values above the target AUC observed in adults (6.02 $\mu\text{g}\cdot\text{h}/\text{ml}$). In contrast, predictions by *Mod1* were generally lower: the median AUC was 5.75 (4.82 - 6.26) $\mu\text{g}\cdot\text{h}/\text{ml}$. This difference was statistically significant (Wilcoxon-Mann-Whitney test, $p < 0.001$), with only 17% of the values reaching the proposed efficacy threshold. Figure 5.4 shows the discrepancies between predicted and observed AUCs in infants and toddlers, as extrapolated from the model based on children (*Mod1*).

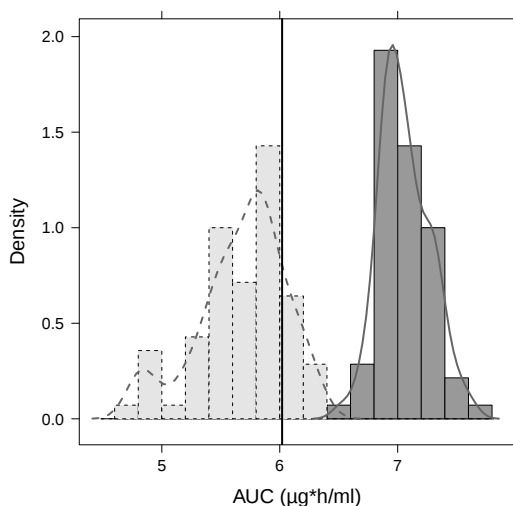


Figure 5.4: Exposure distribution in infants and toddlers (3-36 months) as estimated by *Mod2* (dark gray, solid line), and as predicted by *Mod1* (light gray, dashed line). The black vertical line represents the target exposure (6.02 $\mu\text{g}\cdot\text{h}/\text{ml}$)

Extrapolation of abacavir exposure from infants and toddlers to children

The AUC distribution in children aged 2-13 years, as estimated by *Mod1*, yielded a median of 6.96 (5.85 - 7.91) $\mu\text{g}\cdot\text{h}/\text{ml}$, whilst predictions from *Mod2* resulted in 6.45 (5.80 - 7.01) $\mu\text{g}\cdot\text{h}/\text{ml}$. This difference was also statistically significant (Wilcoxon-Mann-Whitney test, $p < 0.001$), with all values above the efficacy threshold defined in adults. Similarly, predictions by *Mod2* show that target exposure is reached in 88% of the cases. Figure 5.5 presents the observed AUC distributions in children and the corresponding predictions by the model developed from data in infants and toddlers (*Mod2*).

5.4 Discussion

Bridging strategies and model-based dose selection

One of the challenges in paediatric research protocols is to identify the dose or dose range to be used for the first time in a new population. In drug development, bridging opportunities exist for paediatric indications when no relevant differences can be anticipated in disease, disease processes, or PKPD relationships. In these circumstances, bridging should ensure appropriate drug exposure in the target

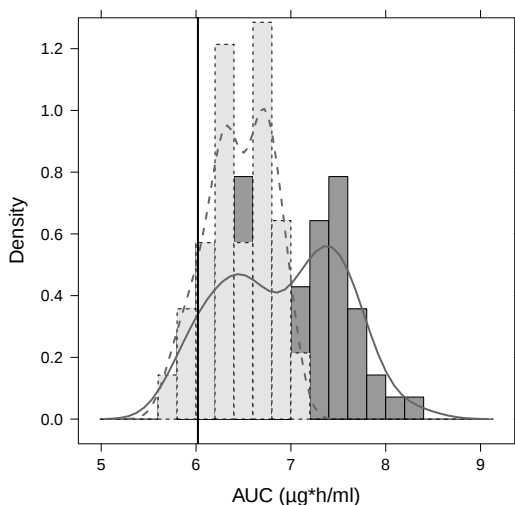


Figure 5.5: Exposure distribution in children (2-13 years old) as estimated by Mod1 (dark gray, solid line), and as predicted by Mod2 (light gray, dashed line). The black vertical line represents the target exposure ($6.02 \mu\text{g}\cdot\text{h}/\text{ml}$)

population without the need for dose finding studies. Even though some initial estimation of the paediatric dose should be obtained via extrapolation approaches, empiricism must be avoided [4]. This is particularly important as the implementation of suitable bridging studies may eliminate the need for formal efficacy trials.

In defining paediatric dosing recommendations, one must identify which demographic or physiological factor(s) (i.e., covariates) best describe the changes occurring during developmental growth, which can easily be used for the purposes of dose adjustment in a new population. This requirement may prove challenging if staggering of the target population according to age groups and disease prevalence is stipulated by protocol. This implies that any covariate analysis must be performed under the assumption that the correlation between parameter and covariate holds true for the overall population or that assumptions can be made about changes in these correlations beyond the age range from which they have been derived.

Our results support the current dosage in children and adults (8 mg/kg with a maximum of 300 mg for children and 300 mg for adults b.i.d.): when estimated by *Mod1*, 100% of derived exposures are above the reference threshold ($6.02 \mu\text{g}\cdot\text{h}/\text{ml}$). The same consideration can be applied to the age group regarding infants and toddlers, for which the current dosing regimen yields exposure levels comparable to adults as well.

In a recent publication we have indicated some of the advantages of a model-

based approach to design bridging studies, analyse pharmacokinetic data and derive dosing recommendations for the paediatric population [15]. Furthermore, the use of PKPD relationship as basis for bridging also explains a wide range of scenarios in which body size and developmental growth alone are not sufficient to define dosing requirements. Although the current investigation is limited to a single paradigm compound, the findings clearly illustrate the implications and challenges for drug developers in early clinical trials. Estimation of the effect of covariates reflecting developmental growth and subsequent use of simulations based on estimated parameter distributions is critical, but not sufficient for characterising potential differences across a population.

The dosing rationale for paediatric populations must be defined on a case by case basis, taking into account pharmacokinetic and pharmacodynamic factors. On the other hand, from a methodological perspective the use of parameter distributions from a reference population to extrapolate drug exposure and dosing requirements in a new population should be independent of the group used as reference population, i.e., model-based extrapolations should be bidirectional.

Unfortunately, this requirement has not been fully met for abacavir and it is likely to reflect the difficulties with dose selection for other drugs as well. Extrapolation from children to infants and toddlers yielded predicted AUCs ($5.75 \mu\text{g}\cdot\text{h}/\text{ml}$) which were smaller than the estimated population values ($7.03 \mu\text{g}\cdot\text{h}/\text{ml}$). At a first glance, this small difference could be considered clinically irrelevant. However, from a clinical pharmacology perspective, the objective of a bridging exercise is to define a dosing regimen that warrants an exposure range or distribution comparable to what has been observed in the reference population. With this in mind, the lower exposure in infants and toddlers would suggest the need for an adjustment of the dosing regimen: using a model built on children data the target exposure would be met only in 17% of the younger patients. According to model parameter predictions, a drastic increase of the dose would be required to ensure exposure are comparable to adults in most of the toddlers and infants. This contrasts with the data observed in the clinical studies, which show that no dose adjustment is required. A similar problem occurs when model parameter distributions from infants and toddlers are used to extrapolate exposures in older children: target exposure is achieved in 88% of the patients. Again, one could decide to increase the dose to guarantee the target exposure in all patients, whilst the appropriate exposure is obtained with the current dosing recommendation.

In summary, both models accurately described the pharmacokinetics in the population upon which they were built. However, either model failed to predict exposure (AUC) distribution in the other population, preventing straightforward extrapolations and recommendations across populations. Whilst extrapolation of children exposure from model parameters in infant and toddlers results in trivial differences, the same cannot be said about extrapolations in the opposite direction. The predicted exposure in infants and toddlers from model parameters in children results in large differences between the predicted and observed AUC, indicating

that the covariate-parameter correlation observed in children does not appear to describe the influence of developmental factors which occur during growth in the younger group of infants and toddlers.

Differences in parameter-covariate correlations

Our results also illustrate that extrapolation of exposure across different populations or groups cannot rely on the assumption that covariate-parameter interactions remain constant beyond the range of observations. Re-parameterisation of the drug disposition process may be required to mechanistically describe changes in exposure associated with ontogeny and growth. Information on the maturation profiles of the metabolic pathways that drive the elimination of the drug may be required. Thus far, parameters associated with organ function or reflecting physiological status remain formally time invariant. These findings call for caution when applying modelling and simulation techniques for the purposes of extrapolation. All standard diagnostic criteria (*post hoc* predictions *versus* observed concentrations, conditional weighted residuals *versus* predicted concentrations, visual predictive check, mirror plots and NPDE) concurred in the validation of the models, but they were not sensitive to differences in parameter-covariate correlations. This also highlights why size cannot be taken for granted as a surrogate measure of function and as such used linearly across populations. The simulation of a new population assumes that not only the pharmacokinetic model (the structural model), but also the correlations between parameters and covariates (the covariate model) are applicable. This may be appropriate as long as the new population can be considered as part of same parameter distributions (i.e., part of the reference population). When this requirement cannot be warranted, additional considerations may be necessary to enable accurate dose selection and adjustment during clinical development. Without such prerequisite, one cannot exclude the risk of sub-optimal dosing or toxicity due to the effect of ontogeny of metabolic pathways, as for example in neonates and toddlers.

Clearly, limitations exist even when modelling and simulation are used to support clinical drug development. Parametric modelling approaches, which provide accurate estimates for the parameters of interest may not be sufficient for simulation purposes [33]. Deeper understanding of the factors affecting pharmacokinetics is required for accurate model building. Physiologically-based pharmacokinetic modelling may be useful as much as parameterisation of the ontogeny of enzymatic systems associated with drug metabolism. In other words, trying to simulate individuals beyond the range of current observations requires a more mechanistic approach compared to what is currently possible using compartmental modelling. Demographic covariates may not be suitable surrogates for describing the maturation process and changes in physiological function which take place during developmental growth. An analogy can be made to dose adjustment requirements in special populations (e.g., renal failure): the dose is adapted irrespective of any demographic covariate. Instead, the decision to adjust the dose relies primarily on organ *function* rather than on *size* [34, 35]. Often, in these cases, information from

metabolic probes is used as the basis for the potential adaptation of the dose [36]. A similar approach would be desirable in paediatric research.

In conclusion, model-based approaches should represent best practice for the analysis and design of paediatric clinical trials. Decisions regarding dosing rationale should be based on parameter estimates and their distributions, rather than on empirical extrapolations. However, we show that despite statistical validation, the use of a population pharmacokinetic model may not suffice to predict parameter distribution and drug exposure in a new population, with clear implications for the selection of dosing regimen beyond the observed population. Current methods for covariate model building do not provide the means to incorporate variation in covariate-parameter correlations across populations. Models for simulation are not necessarily the same as models for estimation. Bayesian Model Averaging concepts could be considered as an alternative approach to deal with the current limitations of paediatric data analysis [37], improving extrapolation and predictive performance [38, 39]. Dose adjustment in new populations cannot therefore rely on model predictions only. A more complex bridging strategy is required, in which the population approach represents the first step.

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