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

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Chapter 4

A model-based approach to dose selection in early paediatric development

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Abstract

The rationale for dose and dosing regimen in children remains a challenge in drug development. In the current investigation, we explore different methodologies to support bridging studies and evaluate the best descriptor of developmental changes that can be used as covariate for dose adjustment in children. The proposed approach is illustrated for the antiviral drug abacavir. Using data from six pharmacokinetic studies in adults and one study in children, a model-based analysis was applied to characterise differences in parameter distributions and their implications for systemic exposure to abacavir. Simulations were subsequently performed to define the appropriate dosing regimen in children. Even though weight was identified as covariate for clearance and volume, dosing recommendations based on mg/kg may not be linear across all weight ranges. Our analysis shows the consequences of empirical dose adjustment and the importance of priors from historical data to support dose selection in children.

4.1 Introduction

DURING DRUG DEVELOPMENT, the dose regimen used in the very first study in children is mostly based on empirical scaling factors that tend to linearise

the relationship between dose and body weight, surface area or age. This approach is applied by default, irrespective of whether these demographic variables have been identified as covariates on pharmacokinetic parameters in adults or another reference population. Moreover, an implicit assumption is made that differences in exposure due to developmental growth (e.g., maturation) can be accounted for by correcting for differences in body size [1]. From a therapeutic perspective, a different dose is required only if changes in exposure are likely to alter clinical response (i.e., safety and efficacy). If not, dose adjustments are not recommended. In this regard another less used, but valuable approach is bridging, which consists in dose selection and adjustment based on evidence from pharmacokinetic differences relative to a reference population.

In the current investigation, we propose the selection of paediatric doses according to differences in pharmacokinetic parameter distributions rather than scaling for differences in body size. Using non-linear mixed effects modelling, a less empirical approach to dose selection can be derived, which relies on the estimation of parameter distributions in a reference population or group. These concepts also enable the implementation of sparse sampling schedules and reduction in population size, tackling an important ethical and practical limitation in paediatric research [2].

Abacavir was selected as a paradigm compound for the evaluation of the methodology, after careful consideration of the regulatory guidelines for the use of pharmacokinetic bridging [3]. Abacavir is a powerful nucleoside analogue reverse transcriptase inhibitor (NRTI) used to treat HIV infection [4]. Published data clearly show differences in pharmacokinetic parameters between adults [5] (clearance (CL/F) = 47.5 L/h, volume of distribution (V/F) = 75 L, absorption constant (Ka) = 1.8 h⁻¹) and children [6] (CL/F = 24.3 L/h, V/F = 42.9 L, Ka = 1.79 h⁻¹). In contrast to many antiviral drugs, abacavir is not metabolised by cytochrome P450. It is extensively metabolised primarily through two enzymatic pathways: UDP-glucuronyl transferase and alcohol dehydrogenase, producing a glucuronide metabolite (~36% of dose) and a carboxylate metabolite (~30% of dose), respectively, with less than 2% excreted unchanged. Faecal elimination accounts for ~16% of the administered dose. Furthermore, abacavir is only active in phosphorylated state and the catabolic metabolites do not have any antiviral activity [7].

According to the ICH E11 guidelines [8], abacavir meets the following requirements for bridging:

1. the pathophysiological processes subsequent to viral infection in adults do not differ significantly from those observed in children;
2. 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 [9];
3. given the mechanism of action of abacavir, the exposure-effect relationship can be assumed to be independent of age.

The recommended oral dose of abacavir for adults is 600 mg daily, administered either as 300 mg twice daily or 600 mg once daily, in combination with other

antiretroviral agents. In adult patients, the twice daily regimen yields an exposure of 6.02 ± 1.68 mg·h/L, $CI_{95\%} = 2.66$ - 9.38 mg·h/L [10]. Assuming the same exposure-effect relationship in the paediatric population, this value can be set as target exposure for an effective and safe treatment. Although dosing recommendation exists for the use of abacavir in children aged 3 months and older [7], in the current investigation the available paediatric data is treated as if this analysis were a prospective evaluation for a paediatric indication.

Given the importance of pharmacokinetic bridging in paediatric drug development, the ultimate objective of our analysis is to demonstrate the feasibility and advantages of a model-based approach for assessing dosing requirements in children, instead of relying on prior beliefs about the existence of a linear relationship between dose and demographic variables. Different scaling strategies were tested to identify the requirements for dose adjustment in children. In particular, focus was given to the characterisation and extent of overlap in pharmacokinetic parameter distribution in children, as compared to adults or another reference population. Since accurate inferences about parameter distributions cannot be made with limited data, a Bayesian method [11] that incorporates parameter estimates in adults as priors for the analysis of pharmacokinetic data in children is proposed.

4.2 Methods

Clinical studies

Four phase I (CNAA1006 [12], CNAB1007 [13], CNAA1009 [14], CNAA1010 [15]), one phase I/II (CNAA1004 [16]) and one phase II (CNAB2002 [17]) studies consisting of 111 adult subjects were retrieved from GlaxoSmithKline's clinical database and used as reference population. Data on abacavir pharmacokinetics included a wide range of doses under different conditions (i.e., single *vs.* multiple doses, oral *vs.* IV administration and food interaction). Blood sampling for pharmacokinetics ranged from 4 to 17 samples per subject. Further details of these trials can be found at GSK clinical trial register.

Paediatric data were obtained from an open label two-period crossover study conducted by Paediatric European Network for the Treatment of AIDS (PENTA-13) [18]. The study consisted of 14 African HIV-1-infected children between 2 and 13 years old who were given q12h lamivudine and/or abacavir as part of their HAART regimen. The dose of abacavir was 8 mg/kg q12h and 16 mg/kg q24h after crossover. The daily adult dose (600 mg for abacavir) was not exceeded. Abacavir was prescribed in tablets of 300 mg or oral liquid formulation containing abacavir at 20 mg/mL. Blood samples of 2 mL were drawn at time points 0 (pre-dose), 1, 2, 3, 4, 6, 8 and 12 h post-ingestion of medication for q12h regimens and at time points 0 (pre-dose), 1, 2, 3, 4, 6, 8 and 24 h for q24h regimens. A summary of the demographic variables and treatment allocation is provided in Table 4.1.

Table 4.1: Study characteristics and patient demographics. Mean values $\pm$ SD (range) are shown for age and body weight

	ADULTS	CHILDREN
N. of studies	6	1
N. of subjects	111	14
N. of blood samples	4-17	9
Sampling occasions	1-4	2
Administration route	IV or Oral (tablets)	Oral (20 mg/L solution)
Dose: q.d.	300-600	8 mg/kg
Dose: b.i.d.	100-300-600	4 mg/kg
Age (years)	37.3 $\pm$ 8.3 (21-65)	5.9 $\pm$ 3.4 (2.1-12.8)
Body weight (kg)	72.2 $\pm$ 12.0 (48.4-110)	23.8 $\pm$ 13.0 (13.7-60.5)
Male/female	91/20	8/6
Fed/fasted	93/18	14/0

b.i.d., twice daily; i.v., intravenous; q.d., once daily.

Pharmacokinetic analysis

Non-linear mixed effects modelling was used to analyse the pharmacokinetic data in adults and children. The first-order conditional estimation method in NONMEM VI (release 1.0) [19] was used to fit the data to the various pharmacokinetic models describe later in this section. Previous publications have shown that a 1-compartment [6, 20] and a 2-compartment [5] model can be used to fit abacavir data. In our analysis, abacavir kinetics was best described by a 1-compartment model using the ADVAN2 TRANS2 subroutine. The model was parameterised in terms of CL, V, Ka bioavailability (F1) and lag time (T_{lag}). Inter-occasion variability was taken into account by estimating inter-individual variability parameter on CL and Ka by differentiating the first occasion from any other subsequent assessment (single *vs.* multiple dosing). This combination seemed to enhance the model performance and has been kept in all analyses for consistency.

Fixed and random effects were introduced into the model in a stepwise fashion. Inter-individual variability in pharmacokinetic parameters was assumed to be log-normally distributed. A parameter value of an individual i (*post hoc* value) is therefore given by the following equation:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i} \quad (4.1)$$

in which θ_{TV} is the typical value of the parameter in the population and η_i is assumed to be random variable with zero mean and variance ω^2 . Residual variability, which comprises measurement and model error, was described with a proportional error model. This means for the j^{th} observed concentration of the i^{th} individual, the relation Y_{ij} :

$$Y_{ij} = F_{ij} + \epsilon_{ij} \cdot W \quad (4.2)$$

where F_{ij} is the predicted concentration and ϵ_{ij} the random variable with mean zero and variance δ^2 . W is a proportional weighing factor for ϵ .

The minimal objective function value (OFV; equal to -2 log likelihood) determined by NONMEM was used as a diagnostic criterion with a decrease in OFV of 3.84 points corresponding to a statistically significant difference between hierarchical models ($P = 0.05$, χ^2 distribution with one degree of freedom). In addition, goodness-of-fit plots, including observed (OBS) *vs.* individual prediction (IPRED), OBS *vs.* population prediction (PRED), conditional weighted residuals (CWRES) [21] *vs.* time and CWRES *vs.* PRED were used for diagnostic purposes. The confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual concentration *vs.* time plots were also used as diagnostic criteria during model building.

Modelling approach 1: Pooling of adult and paediatric data

The first method is based on the concurrent analysis of individual plasma concentration data from adult and children. Model building consisted of random and arbitrary dichotomisation of the study population. The purpose of the splitting of the populations was to assess whether adults and children can be considered part of the same parameter distributions or vary from each other due to relevant covariate factors. The dichotomisation of data assumed that two populations exist which do not share the same parameter distributions, in particular CL and V.

Random dichotomisation was implemented by the MIXTURE subroutine in NONMEM [22] to describe the hypothesised mixture model, whilst two subpopulations according to age (i.e., child <18 y or adult >18 y), were defined for the arbitrary dichotomisation.

Finally, an exploration of the relationship between parameters and demographic variables was performed using a stepwise covariate analysis, with the objective of describing the difference in pharmacokinetics between the two populations using a covariate model. The following covariates were explored: body weight (BW), height (HT), age, body mass index (BMI), creatinine clearance (CR, according to Cockcroft-Gault formula), sex and fasted/fed status. Significant correlations between covariates and parameters were incorporated using an exponential relationship for continuous variables, according to the formula:

$$\theta_i = \theta \cdot \left(\frac{COV_i}{median} \right)^{EXP} \quad (4.3)$$

in which θ_i represents the individual value for the parameter, θ the population parameter 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 objective function value was used as a diagnostic criterion for covariate inclusion (Δ OFV = 3.84, $P = 0.05$, χ^2 distribution). The contribution of each

covariate was confirmed by a stepwise backward deletion (Δ OFV = 6.89, $P = 0.01$, χ^2 distribution).

Modelling approach 2: Use of priors from a reference population

The second method was aimed at integrating prior information about parameter distributions in the analysis of paediatric pharmacokinetic data. This method relies on the estimates of the posterior distribution, rather than on the assumptions about pre-existing differences. The use of priors is also expected to overcome the difficulties in parameter estimation due to limited sample size [23]. Data analysis was implemented with the PRIOR subroutine [24] using Wishart distribution for parameter priors.

Model evaluation and predictive performance

The precision of model parameters was investigated by performing a stratified nonparametric bootstrap procedure. 500 bootstrap samples were generated by re-sampling with replacement and used for the evaluation of model stability and confidence intervals of parameter estimates. Each model was fitted repeatedly to the replicate bootstrap samples using the standard options in PsN (Perl-speaks-NONMEM [25]). The mean and standard errors of the parameters obtained from bootstrapping were compared with those obtained from the original dataset. In addition to bootstrapping, the predictive performance of the models was evaluated using the visual predictive check. For this purpose, 500 datasets were simulated using model parameter estimates. From the simulated data, 90% prediction intervals (P_5 - P_{95}) for each regimen were constructed and superimposed with the observed data from the original dataset. The observed data were compared to the 5th, 50th, and 95th percentile of the simulated data. The identification of approximately 90% of data points within the prediction interval (5% above and below) was indicative of a suitable model.

Rationale for dosing regimen

The final parameter estimates were used to simulate abacavir concentration *vs.* time profiles in children over a wider cohort: the dataset used consisted of individuals of 10, 20, 30 and 40 kg who received different doses of the drug. This dataset was simulated 500 times. Based on the simulated abacavir profiles, AUC values and the percentage of time above IC_{80} were estimated for each patient. These results were subsequently summarised graphically and dosing recommendations derived according to frequency of AUC values reaching target exposure (mean adult level: 6.02 mg·h/L). In addition, we have explored the percentage of subjects showing concentrations above IC_{80} values [26]. For abacavir, intracellular concentrations of carbovir-triphosphate are believed to be associated with the pharmacodynamic effect. The exact relationship between the abacavir and carbovir-triphosphate

concentrations is not known. For the purpose of this analysis, 3 hours were deemed to be an appropriate marker of the pharmacodynamic effect.

4.3 Results

Pharmacokinetic analysis

A one-compartment model with first-order absorption and first-order elimination was found to best describe plasma concentrations of abacavir in adults and children. Inclusion of bioavailability fixed at 83% with inter-individual variability and a lag time of 0.2 hours improved the quality of the fitting. The bioavailability value was based on literature reports [27], whilst the lag time has been defined following visual inspection of the data. For consistency, these values have been kept the same in all models.

Random dichotomisation of parameter distributions

This approach was meant to explore whether parameter distributions for CL and V in adults and children could be identified as two completely different distributions. MIX 1 consisted of 104 individuals of whom 99 were adults, whilst MIX 2 consisted of 21 individuals of which 12 were adults. Interestingly all individuals with very high exposure (higher than 6 mg/L) belong to MIX 2. Population mean values differed significantly between the two populations MIX 1 and MIX 2 (31.7 *vs.* 12.1 L/h for CL; 54.2 *vs.* 27.9 L for V). This represents a difference between populations of 38% in clearance and of 51% in volume. K_a was estimated at 2.7 h^{-1} , but the very high inter-individual variability (IIV) associated with it (136%) suggests that other covariates may need to be considered to explain variation in this parameter, other than the differences in formulation and dosage form. Model diagnostics (data not shown) revealed an underestimation of the peak concentrations in children. Furthermore, the width of 95% confidence intervals indicates clear imprecision in the estimates of variance.

Arbitrary dichotomisation of parameter distributions

In this model adults and children were dichotomised *a priori*, using a group statement. Model minimisation was successful only when the dichotomisation was applied to both clearance and volume. CL was estimated to be 37.5 L/h in adults and 18.3 L/h in children. Mean population estimates of V were 64.7 L in adults and 32.6 L in children. Despite successful minimisation, VPC and other diagnostic plots showed the same underachievement observed following random dichotomisation of the populations. High concentrations are underpredicted and estimates of variance are imprecise (data not shown). In addition, 88% of the runs submitted to the bootstrapping procedure resulted in terminated minimisations.

Table 4.2: Pharmacokinetic parameter estimates for abacavir based on pooled data from both populations (left) and based on priors from parameter distributions in adults (right)

Parameters (units)	Covariate model		Prior model	
	mean	bootstrap mean (%CV)	mean	bootstrap mean (%CV)
<i>Fixed effects</i>				
CL (L/h)	37.2	37.6 (4.9)	40.6	39.6 (5.4)
V (L)	64.8	65.0 (3.4)	69.1	68.5 (4.5)
Ka (h ⁻¹)	1.91	1.93 (12)	3.58	3.57 (37)
F (%)	83	83	83	83
Exponent on CL	0.553	0.566 (13)	0.722	0.694 (11)
Exponent on V	0.537	0.516 (17)	0.810	0.798 (11)
<i>Inter-individual variability %</i>				
CL	30	30 (24)	27	27 (11)
V	11	11 (44)	11	11 (6.9)
Ka	99	99 (19)	98	93 (13)
F	63	63 (22)	37	50 (64)
<i>Residual error %</i>				
ϵ	1.8	1.6 (41)	3.6	3.6 (37)

CL, clearance; CV, coefficient of variation; F, bioavailability; Ka, absorption constant; V, volume of distribution.

Stepwise covariate model building

This model assumes that adults and children are part of the same populations and that the variability in the PK parameters can be described using demographic or physiological covariates, which allegedly describe differences in size and function. Incorporation of the covariate weight on clearance and volume using an exponential model showed the highest improvement in fitting (Δ OFV= 37.5 points). Table 4.2 summarises the results from this analysis and indicates the uncertainty of the parameter estimation, including coefficients of variation (CV%). The diagnostic plots are presented in Figure 4.1.

These estimates seem to be confirmed by the nonparametric bootstrap analysis. However, it is important to note that only 18% of the runs have minimised successfully. Most replicates show terminations and other problems with minimisation. The inspection of VPC (not reported) also confirms overprediction of abacavir concentrations, most likely due to inflated overestimates of the inter-individual variability.

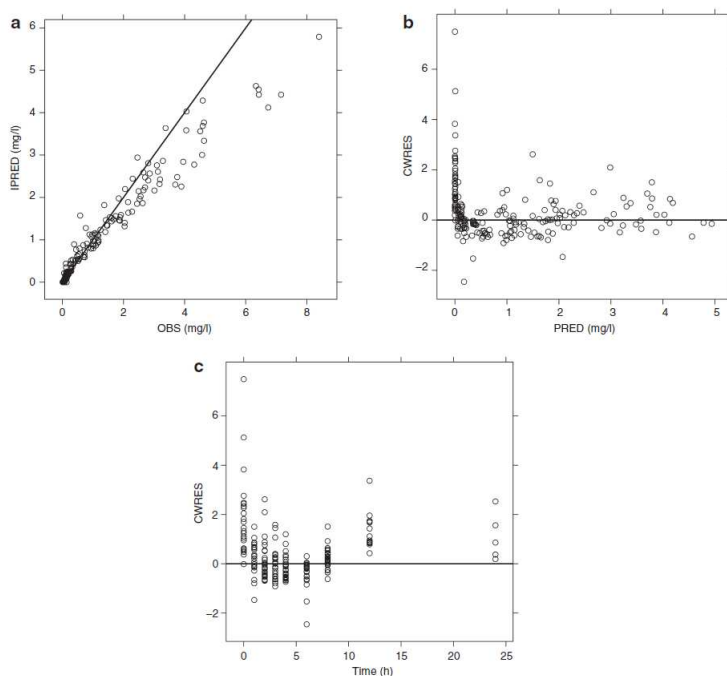


Figure 4.1: Diagnostic plots of the covariate model based on pooled data. Only paediatric data are shown for the purpose of comparison across methods. (a) Post hoc predictions vs. observed concentrations, (b) conditional weighted residuals vs. predicted concentrations, and (c) conditional weighted residuals vs. time. CWRES, conditional weighted residuals; IPRED, individual prediction; OBS, observed; PRED, population prediction

Prior distributions

This approach consisted in integrating prior information about parameter distribution in adults during model building and parameter estimation in children. First, adult data were modelled independently, yielding the following parameter estimates: $CL=37.8$ L/h, $V=65.7$ L and $K_a=1.76$ h⁻¹. The IIV associated with these parameters were respectively 32.7%, 11.3% and 96.8%. These values were subsequently used as priors in the fitting of the data from the paediatric study.

A summary of the pharmacokinetic parameters in the paediatric population is shown in Table 4.2. The final model provides an accurate description of the data. Model parameters were estimated with good precision, with the exception of bioavailability, for which the CV% is 95%. The diagnostic plots (Figure 4.2) also show a large improvement compared to the previous models.

Nevertheless, the use of priors tends to cause slight underestimation of high concentrations (above 6 mg/L). As shown in Figure 4.3, this mis-specification is

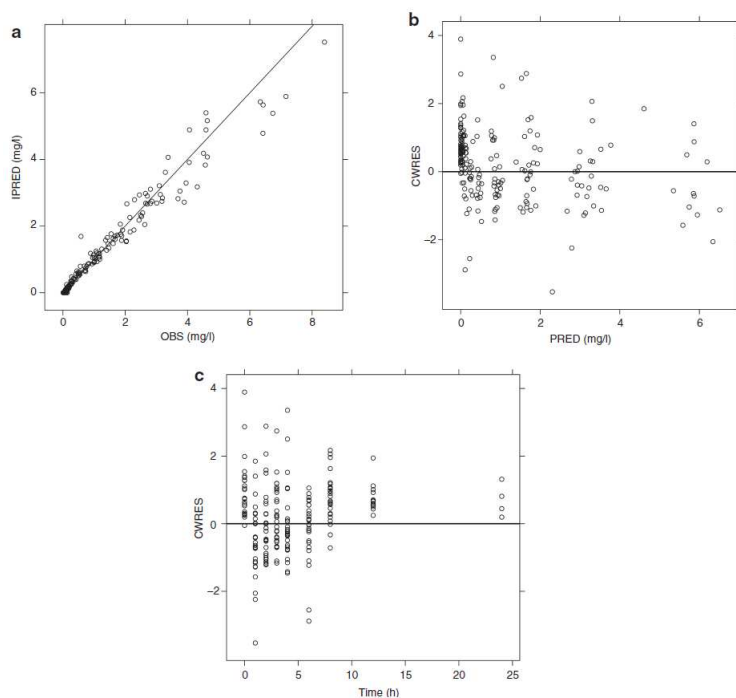


Figure 4.2: Diagnostic plots of the model based on priors from parameter distributions in adults. (a) Post hoc predictions vs. observed concentrations, (b) conditional weighted residuals vs. predicted concentrations, and (c) conditional weighted residuals vs. time. CWRES, conditional weighted residuals; IPRED, individual prediction; OBS, observed; PRED, population prediction

identified in the VPC, where data is accurately described up to 4 h after drug administration; thereafter the variance seems to be overestimated.

Bootstrapping of this model 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 which deviated by 35%. 98% of the runs were successful.

Clinical relevance

Simulations

The use of priors to estimate pharmacokinetic parameter distribution in a small paediatric data set proved to be the best approach to describe the differences in systemic exposure in children. Based on these modelling results, simulations of the concentration time course in children were performed in a larger patient cohort,

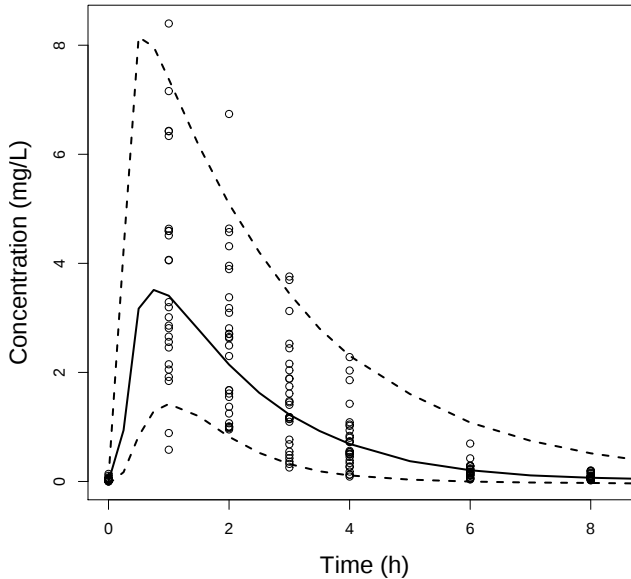


Figure 4.3: Visual predictive check of the final model using priors from adult parameter distributions. Observed data (open circles) are compared with the 5th, 50th, and 95th percentile obtained from simulations of 500 data sets. The predicted concentrations are shown up to the time of the final sampling (8 h)

including a wider range of covariates. Dosing recommendations in children were then proposed taking into account the number of simulated scenarios in which target exposure was met. Figures 4.4 and 4.5 show the dose range required to achieve exposure comparable to adults (i.e., AUC of 6.02 mg · h/L) and plasma concentrations >IC₈₀ (0.35 mg/L) for at least 3 hours for different weight ranges.

In addition, the doses recommended for different weight ranges were compared with the currently approved doses of abacavir (Table 4.3). Given the lack of consensus about the meaning of abacavir IC₈₀ estimates based on total plasma concentrations, we have considered AUC to be the best descriptor of drug exposure for the purposes of bridging. These results reveal that total doses yielding appropriate exposure to abacavir are not linearly related to weight range, suggesting that infants might benefit of a slight increase of the dose (120 mg instead of 80 mg for the 10 kg group).

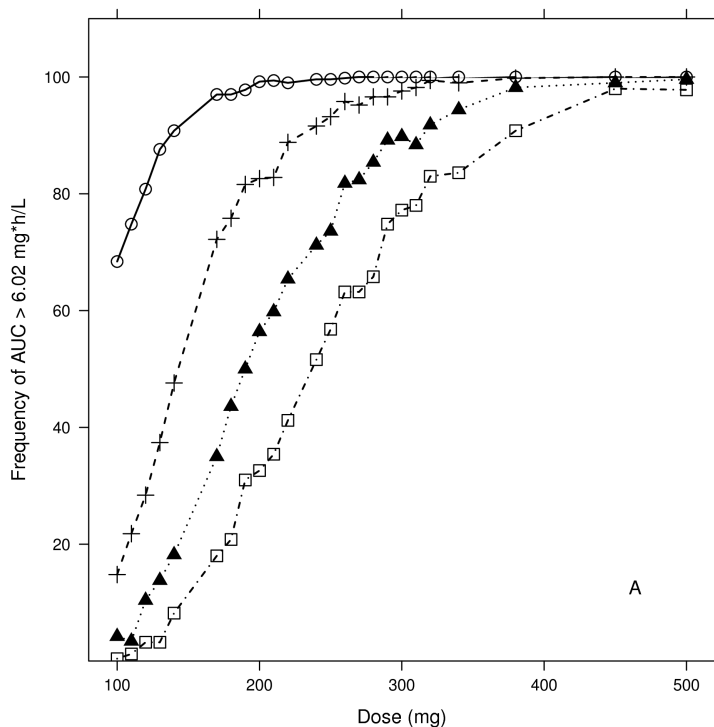


Figure 4.4: Model-based approach to paediatric dose selection. The fraction of patients, categorised by body weight, who reached the target exposure (6.02 mg·h/L) after various doses of abacavir. ○, 10 kg; +, 20 kg; ▲, 30 kg; □, 40 kg

4.4 Discussion

Paediatric prescription must ensure effective and safe treatments are provided to children. However, the rationale for dose selection in paediatric protocols is often based on empirical extrapolations from the recommended dose in adults.

In this article we have scrutinised how modelling and simulation can be optimally used to support dose selection in early clinical development for paediatric indications. Our evaluation highlights two important methodological aspects underlying current guidelines for pharmacokinetic bridging, namely, the role of parameter distributions and the inclusion of prior information from adults or another reference population. Instead of predefined assumptions about the relevance of covariates and type of relationship underlying interindividual differences, the use of parameter distributions is explored as the unit of analysis of confounders and covariates on drug exposure. Historically, pharmacokinetic data from pae-

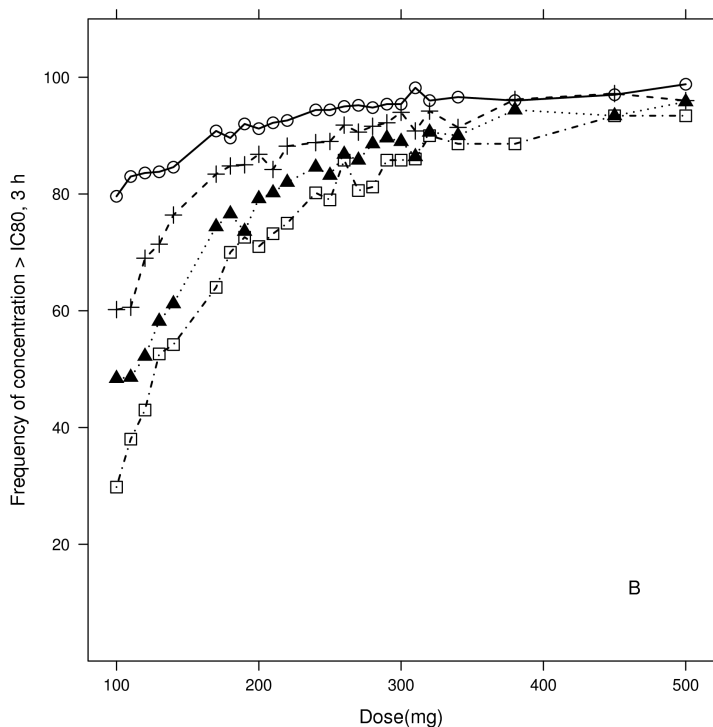


Figure 4.5: Model-based approach to paediatric dose selection. The fraction of patients, categorised by body weight, who reached the target plasma concentrations (IC_{80} for >3 h) after various doses of abacavir. $\circ$, 10 kg; $+$, 20 kg; $\blacktriangle$, 30 kg; $\square$, 40 kg

diatric trials has been analysed by non-compartmental methods, which ignore inter-individual variability in drug exposure, treating data from each patient independently.

Another important feature of paediatric trials is the limited population size and often the sparse number of blood samples available for the assessment of pharmacokinetics in children. Hence, a model-based approach is not only desirable but also necessary to address such practical and ethical limitations. Thus far, most of the published literature on pharmacokinetic modelling in children has been retrospective, from observational, non-controlled trials in hospital or ambulatory settings. Little attention has been paid to the implications of the new regulations on paediatric drug development vis-à-vis the methodological requirements for data analysis in early clinical trials. We have envisaged therefore the need to incorporate information about parameter distributions in adults to support the evaluation of differences in pharmacokinetics in children when a reduced number of patients and

Table 4.3: *Model-based dosing recommendations. The current clinical dosage has been derived empirically (8 mg/kg twice daily with a maximum of 300 mg); simulated doses are based on target adult exposure, defined for the purposes of bridging as area under the plasma concentration-time curve (AUC) = 6.02 mg · h/L, or plasma concentrations >IC₈₀ for ≥3 h*

Weight (kg)	Clinical dose (mg)	Recommended dose based on AUC (mg)	Recommended dose based on IC ₈₀ (mg)
10	80	120	110
20	160	190	170
30	240	260	210
40	300	320	240

only sparse samples are available.

Finally, we illustrate how simulations can be used at early drug development as an integrative tool for the evaluation of the initial dosing rationale. Based on population parameter distributions, pharmacokinetic profiles and systemic exposure can be generated which enable optimal dose selection and refinement of dosing recommendations in subsequent trials.

Pharmacokinetic analysis

Abacavir pharmacokinetics was best described by a one-compartment model with 1st order absorption and 1st order elimination, which is consistent with the findings of Jullien [6] and Weller [20]. For abacavir, we have shown that joint analysis of adult and paediatric data (plasma concentrations) is not appropriate. Neither random (mixture model) nor arbitrary (grouping) dichotomisation reflect the pharmacokinetic differences observed in children.

Conceptually, the findings from random dichotomisation of the population would imply that drug disposition in children and in adults may be indistinguishable from age or body weight, as indicated by the individuals assigned to each subgroup (mixture populations). However, it was found that the mixture models were sensitive to peak plasma concentrations rather than to parameter estimates. These properties prevent the use of the approach for bridging purposes. Similarly, when adult and children data were arbitrarily dichotomised, paediatric parameters such as clearance and volume of distribution were estimated with poor precision.

The inability of the aforementioned models to identify distinct parameter distributions in adults and children strongly suggests that paediatric data can be handled as part of a single population with covariates as influential factors on pharmacokinetic disposition. Unfortunately, the covariate analysis was restricted by the available demographic and physiological factors, which included only body

weight, age and height. The possibility of a comprehensive exploration of how demographic factors affect drug exposure is further compounded by the degree of correlation between them. Despite these limitations, significant correlations were found between body weight and CL and V.

The last approach was based on the use of priors instead of concurrent fitting of paediatric and adult data. This method prevented model misspecification, yielding successful minimisations with higher precision in parameter estimates. The estimates of CL and V in adults and children were comparable to literature findings (respectively 40.6 L/h and 69.1 L *vs.* 47.5 L/h and 75 L). In contrast, K_a was two-fold higher than the reported value (3.58 h⁻¹ *vs.* 1.79 h⁻¹). Overall, this Bayesian approach proved to be very effective in a situation that reflects early clinical development for paediatric indications: only a few individuals with just a few samples each across a large span of ages. We anticipate that this approach can be generalised to drugs showing different metabolic routes, including those with polymorphisms and multiple metabolic pathways.

Clinical relevance

Simulations were used to demonstrate how dosing recommendations can be optimised using body weight as covariate. Two criteria were identified as measure of target exposure. A range of doses was evaluated which resulted in individual systemic exposure of at least 6.02 mg · h/L or yielded plasma levels higher than the IC₈₀ for more than 3 hours. In both cases, doses were selected which met the aforementioned criteria in at least 80% of the population, under the assumption of comparable safety profile. A comparative assessment of paediatric dosing regimens is out of the scope of this publication. However, our results suggest the need for a slight increase in the dose administered to the youngest children (around 10 kg). From 20 - 70 kg, the proposed method yields recommendations similar to those currently approved for paediatric use. This mismatch reflects the non-linear correlation between body size and changes in physiological function (e.g. metabolic maturation) associated with developmental growth. Undoubtedly, in many cases such non-linearity may have implications for paediatric drug prescribing and labelling.

In conclusion, our assessment of the available methodologies to describe the pharmacokinetics of abacavir in children illustrates how a model-based approach can support the rationale for dose selection in early clinical development. The evaluation of covariate effect on parameter distributions, rather than on observed exposure, and the inclusion of priors from pharmacokinetics in adults allow for inferences about the clinical relevance of pharmacokinetic differences across populations. Furthermore, this case example shows how simulations can be used to make the most of pharmacokinetic bridging strategy, providing accurate dosing recommendations for children. Most importantly, the use of a model-based approach

prevents the empiricism which prevails in paediatric pharmacology, ensuring that safety and efficacy are derived from oncoming evidence rather than preconceived beliefs.

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