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

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Chapter 3

Optimisation of pharmacokinetic studies in children: a non-linear mixed effects approach

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Abstract

INTRODUCTION: no specific guidelines exist about the requirements for the design of a paediatric pharmacokinetic study in terms of sampling frequency and population size. Despite practical and ethical challenges, the use of non-compartmental methods still prevails for the analysis of pharmacokinetic data in early paediatric clinical trials. Concerns exist about the reliability of population pharmacokinetic modelling as the basis for the analysis of sparsely sampled data in children. The objective of this study is to explore the feasibility of characterising pharmacokinetics in children based on an integrated analysis of data from serial blood sampling in adults and sparse sampled data in children.

METHODS: a series of simulation scenarios were developed to evaluate how sampling frequency and group sizes affect the estimation of pharmacokinetic parameter distributions in children. Simulated plasma concentration data from hypothetical compounds with different PK properties were analysed using non-linear mixed effects modelling. PK parameter point estimates in children were assumed to deviate from adults across a range that varied from 10% to 300%. For each scenario, clearance, volume of distribution and absorption rate

constant were summarised as population mean values, confidence intervals and bias. The acceptance or rejection of the models were based on statistical and graphical diagnostic criteria:

1. A minimum difference of 3.84 points in the objective function ($P = 0.05$, χ^2 distribution) was defined as the statistical level for acceptance.
2. The relative errors associated with the parameter estimates.

RESULTS: pharmacokinetic parameter distribution in children can be accurately estimated for a new population by integrated data analysis of adult and paediatric data. Depending on sampling scheme and pharmacokinetic properties, the minimum detectable difference in parameter point estimates between adult and children can vary from 10 to 100%. Overall across all scenarios, it was found that parameter estimation is more sensitive to population size than to sampling frequency.

CONCLUSIONS: Integrated analysis of sparse pharmacokinetic data in children with data from adults allows accurate assessment of the differences between the two populations. Furthermore, our results provide insight into the requirements for a paediatric PK study in terms of sampling frequency and population size.

3.1 Introduction

DESPITE THE ADVANTAGES OF MODEL-BASED APPROACHES for the characterisation of pharmacokinetics, pharmacodynamics, efficacy and safety, empirical methods still prevail as the basis for clinical drug development in adult indications. Paediatric drug development is also fraught with various practical and ethical challenges, many of which often prevent the implementation of research protocols.

In addition to these difficulties, other scientific and methodological issues need to be considered, which cannot be adequately addressed by empiricism. Among other things, one should mention:

- the lack of formal dose escalation studies. In paediatric trials, the choice of dose or dose range is always obtained using some extrapolation methods from the adult dose [1];
- the need to perform dose adjustment ensuring correct assessment of potential differences in pharmacokinetics and/or PKPD relationships associated with developmental growth.

Unfortunately, and despite the vivid debate in the paediatric pharmacology community over the past few years, no consensus has been reached regarding the best approach for dose selection taking into account the effects of developmental growth in a very diverse population, from pre-term newborns to adolescents [2, 3].

Model-based approaches can be used to address the aforementioned issues, which if overlooked, can have far reaching implications for dosing recommendations in children. In this context, population pharmacokinetic (PPK) modelling may be suitable for paediatric studies in general and particularly useful for the purposes of

pharmacokinetic bridging [4, 5]. PPK allows the use of sparse measurements without the requirement for balanced design across all subjects or stringent sampling times. In conjunction with novel bio-analytical techniques, such as dried blood spots [6], PPK may represent a unique solution to both practical and methodological issues, reducing the burden of protocol procedures for children enrolled on clinical research. Despite the endorsement of population approaches by regulatory guidelines [3, 7], the lack of expertise regarding the requirements for protocol design and subsequent data analysis continues to prevent its implementation in clinical research. Many paediatric pharmacokinetic studies still use serial sampling schemes and noncompartmental methods for the analysis of pharmacokinetic data [8–10]. Furthermore, no comprehensive evaluation has been performed regarding the implication of differences in drug properties and influential covariates on the accuracy of parameter estimates and consequently on study design requirements.

Given the aforementioned issues, a high degree of scepticism exists when PPK is used. Studies are proposed with a very limited number of children, without careful consideration of stratification for covariates, population size or sampling frequency. Even if optimality concepts have evolved over the last few years, no clear answer has been given to questions such as how many children and how many samples are needed per subject in order to obtain reliable parameter estimates, in particular during early clinical development. Many authors have tried to address these questions [11–13], to the point that today there is a branch of pharmacology focused on optimal design [14–19]. Optimal design maximises the information one can extract from the dependent variables (e.g., drug concentrations), increasing the accuracy of parameter estimates. However, it relies on one fundamental conundrum, i.e., one has to have a well-defined model and provide reasonable starting values to the parameters of interest, a dilemma ingeniously described by Cochran as follows:

“you tell me the value of θ and I promise to design the best experiment for estimating θ ” [20].

These requirements can be met for existing drugs, but may be a major limitation for early clinical development when a pharmacokinetic model accounting for the effects of developmental growth is not available, nor are the parameter values known with sufficient certainty.

Here we propose a different approach, directly applicable to early clinical development, which may contribute to the implementation of paediatric development plans soon after phase I and II trials in adults, i.e., when pharmacokinetic data in adults has been characterised. At this point depending on the disease or therapeutic indication, paediatric doses are proposed based on extrapolation from adults. Pharmacokinetics in children may need to be assessed for bridging purposes or to further support the evaluation of PKPD relationships, safety and efficacy. The choice or rationale for the scaling methodology is beyond the scope of this paper. Instead, we focus on the feasibility of combining information from serial pharmacokinetic sampling in adults with sparse sampled data in children, with the objective of optimising the number of patients and paediatric samples required per patient for the estimation of PK parameters in paediatric early clinical trials. The

proposed methodology relies on meta-analytical principles using non-linear mixed effects modelling. The underlying assumption is whether or not parameter distributions in children differ significantly between children and adults and whether such differences can be accurately characterised given the differences in drug disposition, limitations in sampling frequency and population size. The use of meta-analysis offers an alternative to Bayesian techniques, which are discussed elsewhere [21]. It should be noted that inclusion of priors on parameter distributions to make inferences about the differences in pharmacokinetics may not be appropriate when covariate-parameter correlations cannot be fully characterised or when parameter estimates are expected to differ considerably from the parameter distributions observed in adults.

3.2 Methods

The sensitivity analysis proposed in this paper is based on the use of non-linear mixed effects modelling and included four hypothetical compounds, each of them showing different pharmacokinetic profiles: one-compartment pharmacokinetics after intravenous administration, one- and two-compartment pharmacokinetics after oral administration and pharmacokinetics with metabolic saturation after oral administration. These profiles were chosen to explore the impact of differences in drug disposition and delivery route on the requirements for parameter estimation.

For each of these compounds, drug concentration *vs.* time profiles were simulated assuming single dose administration. The same parameter estimates for fixed and random effects in adults (i.e., inter-individual variability) were used for simulation and subsequent meta-analysis. In children, parameter point estimates were assumed to deviate from the adults across a wide range of values for the purposes of the simulation scenarios (Figure 3.1). Data simulated for the reference adult cohort was combined with paediatric data obtained according to different sampling schemes and variable group sizes. Each dataset was simulated 200 times using NONMEM VI (release 1.0 and 2.0) [22]. Dose selection took into account issues such as limit of quantification, which would require advanced modelling techniques to avoid bias and prevent computational difficulties. Details of the various scenarios are summarised in Table 3.1 and 3.2.

It should be clear that the following assumptions apply to the analysis and interpretation of the various scenarios:

- the structural model describing drug disposition is the same in adults and children. It is only the parameter values and their respective distributions that differ.
- The paediatric dose was the same used in adults for the purposes of this analysis.
- For computational time reasons, potential differences in pharmacokinetics between adults and children were not defined by a covariate model, but rather

Table 3.1: Summary of the simulated scenarios: 1-compartment with IV administration (left) and 2-compartment with oral administration (right)

1 COMP, IV			2 COMP, ORAL				
Reference population	200		200				
Reference samples	11		13				
N population	5,10,20		5,10,20				
N samples	3,4,5		5				
	CL (L/h)	V (L)	CL (L/h)	V _c (L)	V _p (L)	Q (L/h)	K _a (h ⁻¹)
Reference values	10	173	13.3	14.5	21.2	48	0.07
Test value range	1-30	-	6.66-20	7.25-21.75	/	/	0.007-0.14
IIV (%)	10-30	10-30	10-50	10-30	10-30	10	10
Estimation method	FO/FOCE		FOCE				

Table 3.2: Summary of the simulated scenarios: 1-compartment with oral administration (left) and 1-compartment with oral administration and Michaelis-Menten kinetics (right)

1 COMP, ORAL				1 COMP, ORAL, MM			
Reference population	200			200			
Reference samples	14			16			
N population	5,10,20			20,30,40			
N samples	3,4,5			10			
	CL (L/h)	V (L)	K _a (h ⁻¹)	V _{max} (μg/L)	V (L)	K _a (h ⁻¹)	K _m (μg/L)
Reference values	10	173	0.5	1300	20	0.33	450
Test value range	1-30	17.3-519	0.1-2	325-2080	/	/	/
IIV (%)	10-30	10-30	10-30	30	30	30	/
Estimation method	FO/FOCE			FOCE			

by different distributions in the parameter of interest (e.g., clearance, volume of distribution and/or absorption constant).

- For every scenario, one single parameter was evaluated at a time.
- Given the large number of simulated datasets, goodness-of-fit and model diagnostics were not primarily based on individual runs, but rather on the differences in objective function, precision in parameter estimates and total number of successful runs.
- Optimality concepts were not applied in a strict manner to mimic current practice in the design of paediatric protocols. The ranges for sampling times and group sizes were based on feasibility factors and on the expected magnitude of the differences between parameter values in adults and in children.

One-compartment, intravenous administration

For this compound, the reference values in adults were 10 L/h for clearance (CL) and 173 L for the volume of distribution (V). Drug concentration *vs.* time profiles

in adults ($n = 200$) were simulated using 11 samples per subject. The paediatric cohort included 5, 10 or 20 children, each sampled 3, 4 or 5 times. As indicated previously, the group size and sampling frequency used in all scenarios were chosen to mimic a typical paediatric protocol. Model performance was evaluated for 13 different values of CL ranging from 1 L/h (10% of the reference adult value) to 30 L/h (300%). To test the feasibility of the approach, inter-individual variability (IIV) was initially set at 10% for CL and V in both populations. Model performance was then evaluated with IIV values set at 30%, which is more representative of typical variability in real-life protocols. All simulations and model fitting were performed using the ADVAN1 TRANS2 subroutine. Differences due to estimation method were also considered: the first-order (FO) and first-order conditional estimation (FOCE) methods were used and compared. All analyses based on the FOCE method included the interaction option [23].

One-compartment, oral absorption

For this compound, the reference values in adults for CL and V were kept the same as in the previous example (10 L/h and 173 L respectively), whilst the absorption constant (K_a) was set at 0.5 h^{-1} . Drug concentration *vs.* time profiles in adults ($n=200$) were simulated using 14 samples per subject. The paediatric cohort included 5, 10 or 20 subject, each sampled 3, 4 or 5 times. Model performance was evaluated for changes in CL, V and K_a , with values ranging from 10 up to 400% of adult reference value. IIV was set at 10% for all parameters, and then the analysis was repeated with the IIV at 30% for the reasons explained above. All simulations and model fitting were performed using the ADVAN2 TRANS2 subroutine. The FO and FOCE methods were used. All analyses based on the FOCE method included the interaction option.

Two-compartment, oral absorption

This pharmacokinetic model was parameterised in terms of CL, central volume of distribution (V_c), inter-compartmental clearance (Q), peripheral volume of distribution (V_p) and K_a . For this compound, the reference values in adults were 13.3 L/h for CL, 14.5 L for V_c , 21.2 L for V_p , 48 L/h for Q and 0.07 h^{-1} for K_a . Drug concentration *vs.* time profiles in the adults ($n = 200$) were simulated using 13 samples per subject. The paediatric cohort included 5, 10 or 20 children, each sampled 5 times. Preliminary investigations showed that model minimisation was impossible when children had 3 or 4 samples. This is in line with the increased complexity and number of parameters to be estimated in a typical two-compartment model with oral absorption. Model performance was evaluated for changes in CL, V_c and K_a , with values ranging from 10 up to 200% of adult reference value. IIV was set initially at 10% for all parameters and then increased to more realistic values, namely 50% for CL and 30% for V_c and V_p . All simulations and model fitting were performed using the ADVAN4 TRANS4 subroutine and the FOCE method with interaction.

One-compartment with saturable elimination, oral absorption

For this compound, the reference values in adults were 1300 $\mu\text{g/h}$ for maximum elimination rate ($V_{\max}$), 450 $\mu\text{g/L}$ for the Michaelis-Menten constant (K_m), 20 L for V and 0.33 h^{-1} for K_a . Drug concentration *vs.* time profiles in adults ($n = 200$) were simulated using 16 samples per subject. The nature and non-linearity in this pharmacokinetic model does not allow the use of similar sparse sampling schemes, as proposed for the other hypothetical compounds. We have therefore simulated the paediatric cohort with 20, 30 or 40 children, each sampled 10 times. Given the complexity of the model, data fitting turned out to be demanding long computation time. Given that $V_{\max}$ is the parameter mostly affected by ontogeny and growth in children, only changes in $V_{\max}$ were explored to characterise pharmacokinetic differences in children, with values ranging from 325 $\mu\text{g/h}$ (25% of the adult reference value) to 2080 $\mu\text{g/h}$ (175%). All other parameters used for the simulation of PK profiles in children were kept at values comparable to adults. IIV was set at 30% for $V_{\max}$, V and K_a , whilst it was assumed to be negligible for K_m . All simulations and model fitting were performed using the ADVAN6 TRANS1 subroutine and the FOCE method with interaction.

Parameter estimation and model diagnostics

Drug concentration *vs.* time profiles in adults and children were simulated according to the aforementioned criteria 200 times for every scenario. The 200 datasets were then analysed using two nested models. The first (reduced model) assumed that pharmacokinetics in adults and children can be described by the same parameter distribution (i.e., the two groups belong to a single population) and is therefore represented by a single parameter. The second (full model) assumed that pharmacokinetics in adults was described by different parameter distributions, as compared to children (i.e., two separate populations) and required therefore different parameter estimates.

The reduced model was parameterised as $P = \theta_1$, where P is the typical value of the parameter of interest and θ_1 is the parameter estimate in adults and in children. The full model was parameterised as $P = \theta_1 * \text{GRP} + \theta_2 * (1 - \text{GRP})$, where P is the typical value of the parameter of interest, θ_1 the parameter estimate in adults, θ_2 the parameter estimate in children and GRP was a flag to discriminate the two populations. The acceptance or rejection of the models was based on statistical and graphical diagnostic criteria. A minimum difference of 3.84 points in the objective function ($P = 0.05$, χ^2 distribution) was defined as the statistical level for acceptance of the full model. The full model was declared superior to the reduced model every time the difference in objective function between the two models was higher than 3.84 points in at least 80% of the runs. The minimum number of children to be included in a hypothetical trial, together with the number of samples required, was based on the relative performance of the full model. The second criterion for the goodness-of-fit was the assessment of the relative errors

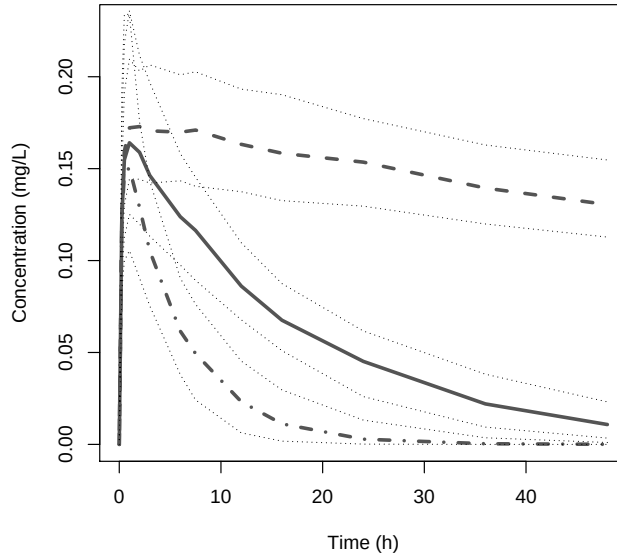


Figure 3.1: Mean concentration profiles and 90% confidence intervals generated by the 2-compartments model (solid line: adults, dashed line: children with CL= 50% of adult value, dashed and dotted line: children with CL=150% of adult value). Sampling times in children were chosen in such a way that would allow the collection of information at both extremes of the simulated CLs

associated with the parameter estimates, which can be calculated as indicated below:

$$\%Error = \left(\frac{\theta_1 - \hat{\theta}}{\hat{\theta}} \right) \quad (3.1)$$

where θ_1 is the estimated parameter value and $\hat{\theta}$ the real parameter value.

Optimisation of sampling frequency and intervals

To ensure that parameter estimation during the integrated analysis of adult and children data was not confounded by design factors in the reference population (such as poor sampling times), sampling schemes for adult subjects were generated using PkStaMp, an optimal experimental design software [24]. A detailed description of optimisation methods can be found elsewhere: briefly, optimisation of study design features with PKStaMp relies on the maximisation of the Fisher Information Matrix

(FIM) with respect to the design variables [25]. In contrast, the choice of sampling intervals in children was based on visual inspection of simulated concentration profiles and feasibility criteria (e.g., minimum interval between sampling times), taking into account the distribution of the tested parameter values. In view of the uncertainty around the paediatric parameter values, we imposed the use of a common sampling scheme for all tested scenarios. We decided to sample children in a way that would maximise the information for the so-called extreme conditions, i.e., when parameter values diverged considerably from the reference population values. To clarify this issue, Figure 3.1 illustrates the situation for a scenario in which a two-compartment drug disposition model is tested.

3.3 Results

The presentation of the results is split by pharmacokinetic model. Given the enormous amount of data generated by all the different design scenarios, only the most relevant findings are reported. Focus is given primarily to the discriminative power of this meta-analytical modelling approach to detect differences in parameter distributions (CL, V and/or Ka, depending on the hypothetical compound) between adults and children. In addition, a summary is provided regarding the key findings for different estimation methods (FO and FOCE).

One-compartment, intravenous administration

In the simplest scenario, clearance values ranging from 1 to 30 L/h were evaluated, whilst the volume of distribution was kept constant in both populations. All runs were successfully minimised. When the inter-individual variability was set to 10%, the full model outperformed the reduced model even for small differences (10%-20%) between paediatric and adult CL. The number of samples per individual did not influence the performance of the models: the same results were obtained when 3, 4 or 5 samples were available. The relative error associated with the estimation of paediatric CL was scattered around 0 and remained very low across all scenarios with a maximum of 5%. The relative error is not influenced by the number of children included in the datasets: no difference can be found in the patterns relative to 5, 10 or 20 children. When IIV was set at 30%, the minimum detectable difference between paediatric and adult CL ranged from 30% (for $n=20$) to 50% (for $n=5$). Under these circumstances higher values of IIV did not appear to influence the pattern of model performance, which was not affected by the number of samples. The relative error associated with the paediatric clearance, as estimated by the full model, remained generally lower than 6%, with a few exceptions where it reached 12% (Figure 3.2). Interestingly, with higher IIV values, the error was not scattered around 0, but always positive. This indicates that the full model tends to slightly overestimate the paediatric clearance. The reason for this small bias remains unknown.

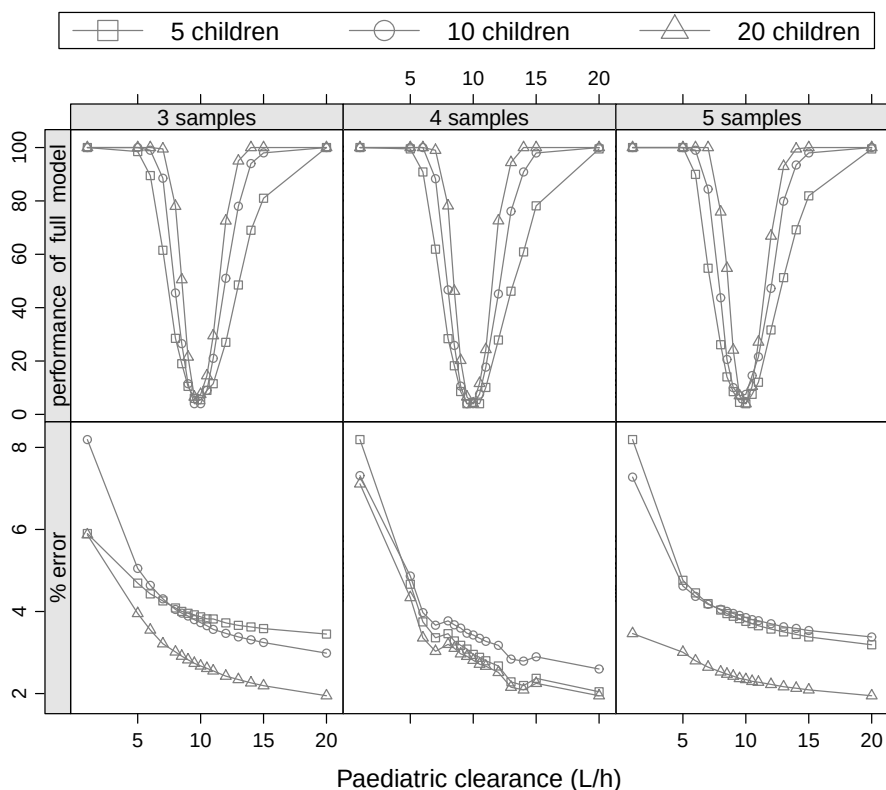


Figure 3.2: *One-compartment model with intravenous administration: relative performance of the full model. Upper panel: fraction of simulated scenarios in which the full model outperformed the reduced model. Lower panel: relative error associated to the estimation of the paediatric CL by the full model*

One-compartment, oral absorption

In this scenario, all pharmacokinetic parameters were allowed to vary across population, one at the time. CL and V values in children ranged from 10 to 300% of the adult value, whilst K_a ranged from 20 to 400% of the adult value. All runs were successfully minimised. With regard to CL, the full model outperformed the reduced model when the difference between adults and children was at least 10% ($n=20$) or 20% for smaller group sizes ($n=5$ and 10). Similar results were observed for V and K_a , with two separate parameter distributions being detected when parameters differed by at least 10% ($n=20$ and 10) or 15% for smaller group sizes ($n=5$). Also in this scenario the number of samples does not affect the relative performance of the models. For all parameters, the relative error of the

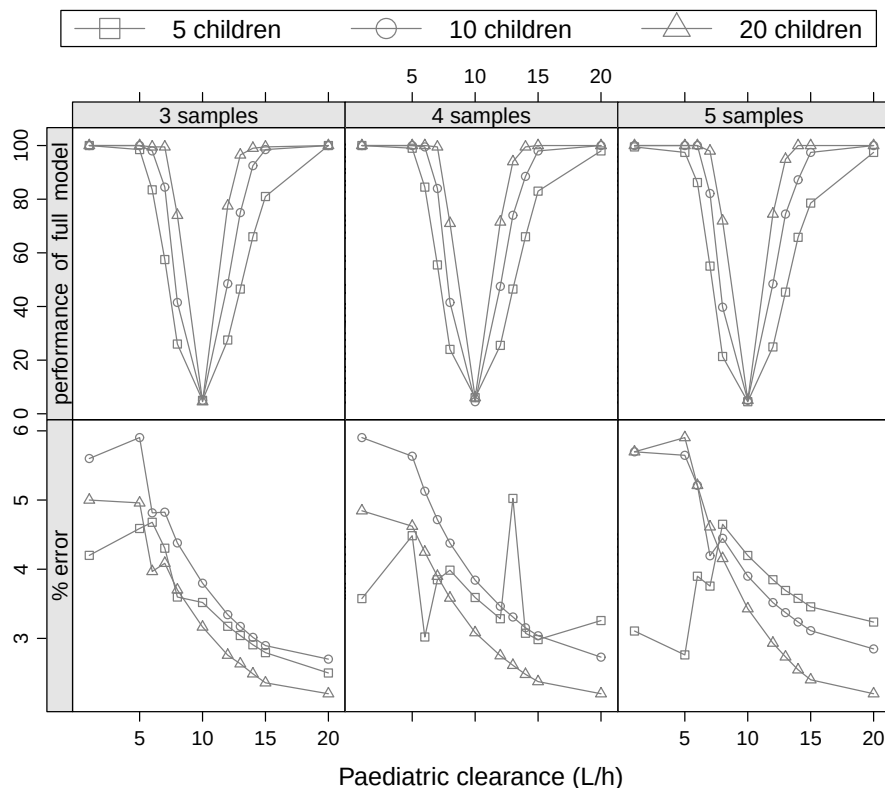


Figure 3.3: *One-compartment model with oral administration: relative performance of the full model. Upper panel: fraction of simulated scenarios in which the full model outperformed the reduced model. Lower panel: relative error associated to the estimation of the paediatric CL by the full model*

estimates remained below 7%. With the IIV set to 30%, the results reflect the findings previously observed for the one-compartment model following intravenous administration. The minimum detectable difference between paediatric and adult CL ranges from 30% ($n = 20$) to 50% ($n = 5$). Again, the number of samples does not appear to affect the performance of the models. The relative error for CL remained lower than 5% (Figure 3.3), but also showed a small bias towards overprediction.

Two-compartment, oral absorption

In this scenario, CL and V_c values in children ranged from 50 to 150% of the adult value (13.3 L/h and 14.5 L respectively), whilst K_a varied from 10 to 200% of the reference value (0.07 h^{-1}). 95.5% of the runs were successfully minimised.

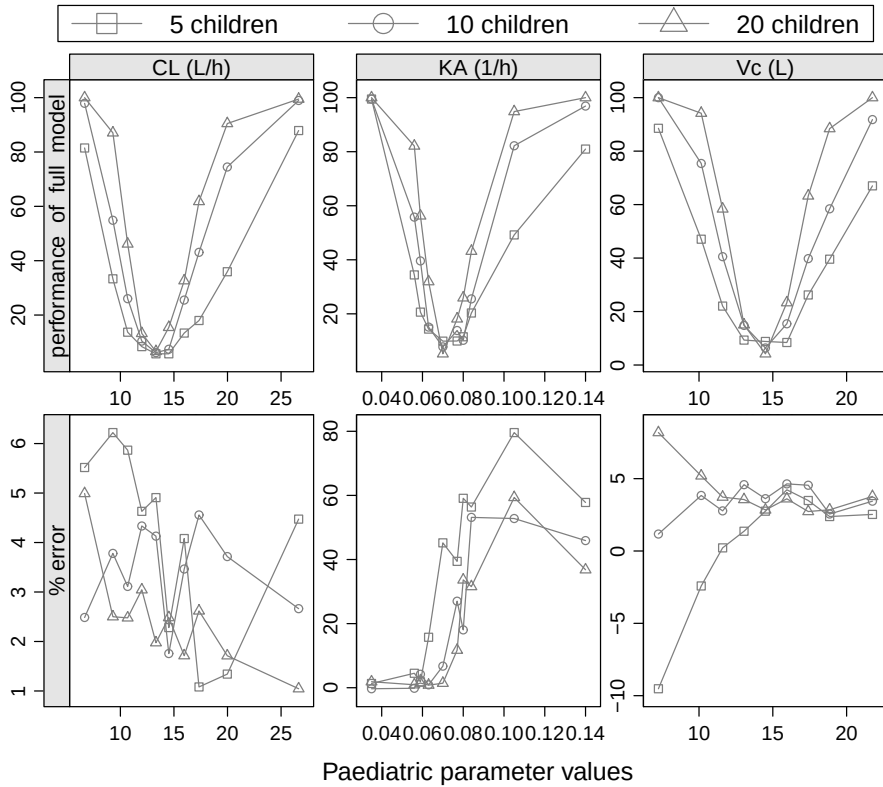


Figure 3.4: Two-compartment model with oral administration: relative performance of the full model. Upper panel: fraction of simulated scenarios in which the full model outperformed the reduced model. Lower panel: relative error associated to the estimation of the paediatric parameter by the full model

With regard to CL, the full model outperformed the reduced model when the difference between adults and children was at least 10% ($n = 20$) or 20% for smaller group sizes ($n = 5$ and 10). Similar results were observed for V_c and K_a . For all parameters, the relative error of the estimates remains below 3%, with a small bias towards overprediction. With the IIV set to 50% for CL and to 30% for V_c and V_p , the minimum detectable difference between paediatric and adult CL ranged from 30% (for $n = 20$) to 100% (for $n = 5$ and 10). Similar results were observed for V_c , whilst for K_a the minimum detectable difference ranged from 20% ($n = 20$) to 100% ($n = 5$). For CL and V_c , the relative error of the estimates remained below 6%. Instead, for K_a reached values as high as 80% (Figure 3.4).

One-compartment with metabolic saturation, oral absorption

Even with larger population sizes, as compared to the other pharmacokinetic models, the percentage of successful minimisations using the full model remained very low: on average only 57.1% of runs minimised. Despite the minimisation issues, the number of children included in the simulations did not seem to influence the stability of the runs. On the contrary, the reduced model minimised in 89.6% of the cases. IIV was set at 30% for $V_{\max}$, V and K_a , whilst it was assumed to be negligible for K_m . The difficulties in minimisation are clearly reflected in the (in)ability of the full model to discriminate between the two populations. The full model outperformed the reduced model only in ~50% of the cases, irrespective of the difference in $V_{\max}$ between adults and children. The relative error associated with the estimation of $V_{\max}$ in children was erratic and independent on the number of children simulated, as can be observed in Figure 3.5.

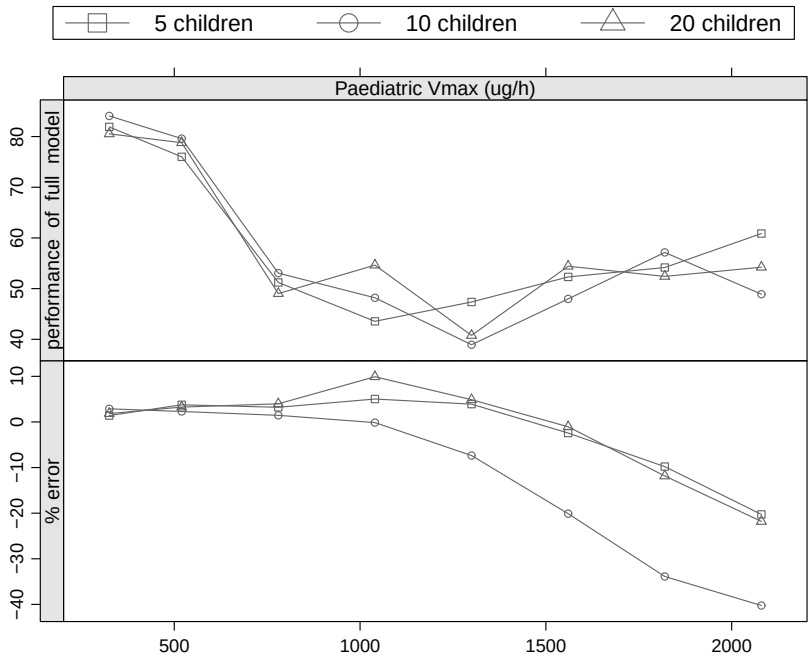


Figure 3.5: One-compartment model with intravenous administration and Michaelis-Menten kinetics: relative performance of the full model. Upper panel: fraction of simulated scenarios in which the full model outperformed the reduced model. Lower panel: relative error associated to the estimation of the paediatric $V_{\max}$ by the full model

Difference between FO and FOCE methods

In parallel to the sensitivity analysis for differences in parameter distributions, we have also evaluated the implications of different estimation methods (i.e., FO or FOCE with interaction). Based on the results from one-compartment pharmacokinetic models following intravenous and oral administration, the conditional method appears to very slightly decrease the discriminatory power of the model. This is evident especially when 5 children are tested. On the other hand, there is a decrease in the number of false positives (type I errors) when using FOCE with interaction. False positives were considered those cases in which the full model performs better than the reduced model, but the populations share the same parameter distribution (data not reported).

3.4 Conclusions

The recent changes in the EU legislation, enforcing the development of drugs for paediatric indications, will have major implications for paediatric research. The use of empiricism as basis for evidence of efficacy and safety has to be replaced by model-based approaches. In particular, it is paramount that pharmacokinetic bridging concepts are applied more systematically, so that the appropriate dose and dosing regimen are selected and accurate inferences can be made about treatment effect [26, 27]. Non-linear mixed effects modelling and meta-analytical methods can play an important role in this context and overcome many of the practical and technical hurdles imposed by empirical protocol designs.

Historically, the use of meta-analysis as basis for the evaluation of pharmacokinetics has been applied to special patient groups, such as renally and hepatically impaired patients [28–30]. Integrated modelling of data from different clinical trials has also been applied to identify the role of demographic covariates and quantify the effect of other influential factors on drug disposition, such as co-medication and co-morbidities [31–33]. Given that these analyses are often performed at late stages of drug development, population size has always compensated for the potential limitations of sparse sampling or imbalance in the design of individual study protocols. In these circumstances, the absence of covariate effects does not immediately imply bias in parameter estimation or results in inaccurate dose selection for subsequent studies. As indicated previously, scepticism still prevails with regard to the use of a similar approach to characterise pharmacokinetics, and in particular the effect of covariates in early drug development. In contrast to the evaluation of covariate effect in adults, the use of non-linear mixed effects modelling in paediatric studies must cope with limited population, sparse sampling and imbalance in study design.

In this paper, we performed a rather comprehensive evaluation of the aforementioned design factors taking into account not only the magnitude of the difference in parameter distribution, but also the potential effect of differences in drug disposition. Our starting premise is that pharmacokinetics in children may differ from adults due to the (potential) effect of developmental growth on the underlying parameter

distributions. Such an effect is primarily described in paediatric pharmacokinetic research by a covariate model. Here we have attempted to prevent unnecessary debate about the nature and structure of covariate-parameter correlations and have therefore not used a covariate model [34, 35]. Instead, given a pharmacokinetic model, we have assessed the sensitivity of the method to detect differences in parameter distribution originating from two distinct populations.

Our results show that PPK modelling can be used to analyse rich adult data and sparse paediatric data in an integrated manner to obtain accurate estimates of parameter distributions in children, without the burden of paediatric protocols in which serial sampling from a single study is analysed by non-compartmental methods. The direct implications of such an integrate approach for early clinical development is the ability to accurately select the doses to be used in paediatric protocols. We demonstrate that a limited number of paediatric patients is enough to accurately estimate parameter distributions even when they present small differences from the reference population. We also gathered further evidence supporting the need for more patients, rather than more samples per patient. Increasing the sampling frequency from 3 to 5 samples had little influence on the ability of the model to estimate the pharmacokinetic parameters in children.

Our findings also reveal how increase in model complexity increases the demand for additional sampling and population size to maintain the same degree of accuracy. As consequence, paediatric protocols cannot be designed with small sample and group size without taking into account the complexity in model parameterisation. As observed for the scenario in which metabolic saturation occurs, differences in parameter distribution cannot be accurately identified without considerable increase in sampling and population size. These conclusions also raise an important question regarding current practice in paediatric pharmacology, which often presents results from pharmacokinetic modelling in children using sparse sampling and very small cohorts, without a reference group [36–39]. Unfortunately, the bias in parameter estimates and model misspecification in such studies cannot be easily detected by typical goodness-of-fit plots. The so-called “perfect-fit” in these circumstances results from the lack of useful information. Since the degrees of freedom are limited, alternative models cannot be explored [40, 41]. Hence, caution is required when using the results from such models for the purposes of simulations.

Limitations

This computing intensive and time consuming analysis was an informal assessment of the sensitivity of non-linear mixed effects modelling to discriminate parameter distribution when known differences exist between two distinct populations. We have therefore decided not to explore issues associated with model building, such as the identification of parameter-covariate correlations. Although the focus of the work is on the differences in CL, V and K_a , comparable results can be expected if different distributions are introduced on other parameters, such as bioavailability. Albeit somewhat intuitive, the notion that model complexity imposes a higher degree of freedom to ensure accurate estimation of parameter distributions needs to

be considered carefully when analysing paediatric data separately. The availability of pharmacokinetic studies in adults can be taken for granted in early clinical development but such information has so far remained untapped. We are aware of the fact that imbalance in the data can lead to bias in model building and in the identification of the correct covariate model. The implications of such an imbalance seem negligible for the purposes of parameter estimation, given the results obtained by data fitting and the low estimates for the relative error in the parameter estimates.

Due to computational time constraints, we have not explored more complex scenarios in which differences in parameter distribution are observed concurrently for multiple parameters and larger IIV values are considered for the paediatric population. In addition, we have also skipped scenarios in which time-variant changes occur (e.g., induction). All these conditions represent an increase in the complexity of the underlying pharmacokinetic models. Consequently, limitations similar to the example shown for metabolic saturation are likely to apply.

In conclusion, meta-analysis of rich adult data and sparse paediatric data using non-linear mixed effects modelling offers the possibility to detect differences in parameter distributions, yielding accurate parameter estimation of relevant pharmacokinetic parameters in children. Comparable accuracy and precision may not be achieved by separate analysis of paediatric data alone. Yet, accurate parameter estimation is critical for the purposes of bridging and consequently for dose selection in subsequent clinical trials. Given the impact of model complexity on protocol design requirements, we recommended the use of a similar sensitivity analysis in prospective trial design to address basic questions, such as “how many children does one need for bridging purposes? How many blood samples are required?”

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