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The accuracy of model-based predictions often reported in paediatric research has not been thoroughly characterised. The aim of this exercise is therefore to evaluate the role of covariate distributions when a pharmacokinetic model is used for simulation purposes. Of interest is the evidence that model predictions are unbiased when the covariate range is beyond the data distribution available during model-building. Such an analysis is critical for the use of nonlinear hierarchical modelling in extrapolation and bridging of findings across different populations in paediatric drug development.

Plasma concentrations of a hypothetical drug and demographic characteristics of a paediatric population were simulated using a pharmacokinetic model in which body weight was correlated to clearance and volume of distribution. Two subgroups of children were then selected from the overall population according to a typical study design, in which pre-specified body weight ranges (10-15 kg and 30-40 kg) are used as inclusion criteria. The simulated data sets were then analysed using non-linear mixed effects modelling. Model performance was assessed by comparing the accuracy of AUC predictions obtained for each subgroup, based on the model derived from the overall population and by extrapolation of the model parameters across subgroups.

Our findings show that systemic exposure as well as pharmacokinetic parameters (CL and V) cannot be accurately predicted from the pharmacokinetic model obtained from a population with a different covariate range than the one explored during model building. Predictions were accurate only when a model is used for prediction in a subgroup of the initial population. In contrast to current practice, the use of pharmacokinetic modelling in children should be limited to interpolations within the range of values observed during model building. Furthermore, the covariate point estimate must be kept in the model even when predictions refer to a subset different from the original population. These findings highlight the importance of meta-analytical procedures in paediatric bridging. It also suggests the need for more mechanistic parameterisations, which discriminate drug from system-specific parameters.
5.1. INTRODUCTION

Modelling and simulation (M&S) of clinical data represents a powerful approach for evidence synthesis and consequently for a more comprehensive interpretation of the data available at any point in time during the process of drug development. Ideally, it should also provide the basis for inferences and extrapolation of findings from a subgroup to the entire target population at any point in time during the process of drug development. At present, regulatory bodies in Europe encourage the application of the M&S approach during drug development (1), as it may circumvent some practical and ethical difficulties in the evaluation of paediatric medicines. In fact, industry and academia have been developing and applying models under the assumption that nonlinear mixed effects modelling methods are robust enough to enable the characterisation of pharmacokinetics and pharmacodynamics even when sparse sampling and unbalanced data sets are used (4–8).

More recently, M&S has been applied as a design tool for pharmacokinetic and pharmacokinetic-pharmacodynamic bridging. In this case, the main objectives of such models include the selection of dose and prediction of drug exposure and/or effects in a new population, for which no data has been generated. In this context, the identification of influential covariates such as demographic characteristics can play a major role in the accuracy of parameter estimates and subsequent predictions. The assessment of the correct correlations between covariates and parameters is crucial, given that it will have direct implication for the dose selection in a new population with different demographic characteristics. In the paediatric research, however, the identification of the correct covariates is often complex due to the presence of correlations and co-linearity between covariates. As shown by a previous investigation from Ribbing et al., competition between multiple covariates may further increase selection bias, especially when there is a moderate to high correlation between the covariates (9).

Different methods are available to select significant covariates during model building. The most used one is the stepwise covariate selection in which two processes, forward inclusion and backward elimination, are applied (10,11). Alternative methods, such as genetic algorithms for covariate selection (12) and automated covariate model building (13, 14) are also becoming more common, but have not been scrutinised to the same extent in pharmacokinetic research. In contrast to traditional data analysis, models developed by the stepwise covariate selection are also being used to predict drug exposure and consequently define the dose rationale in new patients, whose characteristics differ from the original patients in the trial.

Model-based predictions can be considered for a population with similar characteristics as the one under investigation during model building (interpolation) or for a new population beyond the covariate range explored during model building (extrapolation). Many examples are available in literature of studies in which modelling has been applied to interpolate data (15–17). Fewer examples exist however in which extrapolations are made to a population which does not share exactly the same characteristics or includes individuals beyond the range of values explored during model building. In fact, two recent publications by Cella et al. (18, 19) showed the lack of predictive performance of pharmacokinetic models when they are used for extrapolation purposes.

The current analysis has two main objectives. First of all, we want to define the feasibility and pre-requisites to use pharmacokinetic models as an extrapolation tool, i.e., to make predictions about a population in which the values of the covariates are beyond the covariate ranges explored during model building. Secondly, we want to investigate how the parameter-covariate correlation needs to be expressed when a model is used for simulation purposes. From a methodological perspective, there are different ways to express the correlation parameter-covariate during covariate selection. Among other options, as shown in equations 1 and 2, we evaluate the impact of “centring” on the median or the mean value of the covariate in the population. This approach is supposed to stabilise parameter estimation and facilitate the interpretation of the coefficients in the correlation.

\[ P = \theta_1 + \theta_2 \frac{\text{COV}}{\text{COV}_{\text{median}}} \]  
\[ P = \theta_1 + \theta_2 \* \text{COV} \]  

In these equations P is the parameter, COV is the covariate, COVmedian the median value of the covariate in the dataset and \( \theta_1 \) and \( \theta_2 \) are the slope and the intercept which describes the correlation between the parameter and the covariate, respectively. In both equations the intercept and the slope are estimated during model building. In the first case (equation (1)), the variation in the values of the covariate can cause instability in the estimation of slope and intercept. This contrasts with the second case (equation (2)) as the intercept is roughly centred; this means, for instance, that for adult populations 70 is commonly used as a median value of body weight.

In this study, in addition to investigating the predictive performance of a pharmacokinetic model for extrapolation purposes, we evaluate whether the covariate point estimate must be retained in the model when extrapolations refer to a population in which the median or mean value differ from the one in the population previously analysed or whether it should be adapted to reflect the covariate distribution of the new population.
5.2. METHODS

Population demographics and hypothetical protocol
A group of 43 virtual paediatric patients with a weight range between 7.43 and 61.3 kg (median weight 14.2 kg) were sampled from a pooled dataset including demographic characteristics from three pharmacokinetic studies (20–22). The sampling procedure was performed in such a way that the age and body weight distribution in the virtual population was balanced across the weight range of interest.

These patients were then treated with a hypothetical drug, given orally every 12 hours. A total of 8 plasma samples per subject were then simulated throughout the dosing interval. Using data from the overall population (group C), two subgroups were selected based on different body weight range. As shown in table 1, the first subgroup (subgroup A) comprised 20 children with weight between 10.3 and 15.4 kg (median body weight 12.5 kg), whilst the second group (subgroup B) included 8 children with weight between 30 and 43.8 kg (median body weight 35 kg).

Table 1 Summary of demographic characteristics of the hypothetical population.

<table>
<thead>
<tr>
<th>SUBGROUP A</th>
<th>SUBGROUP B</th>
<th>GROUP C (Full population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Median weight (kg)</td>
<td>12.5</td>
<td>35.05</td>
</tr>
<tr>
<td>Min weight (kg)</td>
<td>10.3</td>
<td>30.05</td>
</tr>
<tr>
<td>Max weight (kg)</td>
<td>15.4</td>
<td>43.8</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>2.18</td>
<td>8.85</td>
</tr>
<tr>
<td>Min age (years)</td>
<td>0.99</td>
<td>8.1</td>
</tr>
<tr>
<td>Max age (years)</td>
<td>3.89</td>
<td>12.67</td>
</tr>
</tbody>
</table>

Predefined covariate effects
The pharmacokinetics of the compound was assumed to be described by a one compartment pharmacokinetic model with first-order absorption and elimination. A base model previously developed by our group for lamivudine (Covariate effects and population pharmacokinetics of lamivudine in HIV-infected children - In press British Journal of Clinical Pharmacology) was used for simulations.

Various scenarios were simulated, in which body weight was linearly and/or exponentially correlated to clearance and volume of distribution. Allometric scaling concepts were also taken into account, but the exponents were explored with values higher and lower than 0.75. Four different scenarios in which one covariate was significant were simulated, based on realistic parameter-covariate correlations:

• Body weight linearly correlated with clearance (with a slope of 0.65)
• Body weight linearly correlated with clearance (with a slope of 1.5)
• Body weight exponentially correlated with clearance (with an exponent of 0.65)
• Body weight exponentially correlated with clearance (with an exponent of 1.5)

Given that usually more than one covariate is found to influence pharmacokinetic parameters, two additional scenarios were simulated in which a second covariate was incorporated into the model.

• Body weight linearly correlated with volume of distribution (with a slope of 1.8) (15) and exponentially correlated with clearance (with an exponent of 0.65)
• Body weight exponentially correlated with volume of distribution (with an exponent of 0.635) and exponentially correlated with clearance (with an exponent of 0.705) (Covariate effects and population pharmacokinetics of lamivudine in HIV-infected children - In press British Journal of Clinical Pharmacology)

The relationship between parameter and covariate was described as follows:

\[ P = \theta_1 + (\frac{WT}{WT_{median}}) \cdot \theta_2 \] \hspace{1cm} (3)
\[ P = \theta_1 \cdot (\frac{WT}{WT_{median}})^{\theta_2} \] \hspace{1cm} (4)

In these equations P is the pharmacokinetic parameter (in this case clearance or volume of distribution), WT is body weight and WT_{median} is the median of the body weight distribution in the population analysed during model building. Equation (3) represents a linear relationship between the parameter and body weight with \( \theta_1 \) and \( \theta_2 \) as the intercept and the slope of the correlation, respectively. Equation (4) represents an exponential relationship between the parameter and body weight with \( \theta_1 \) and \( \theta_2 \) as the coefficient and the exponent of the correlation, respectively.

Analysis of simulated patient data: pharmacokinetic model and covariate criteria
The simulated plasma concentration datasets (full population and subgroup A) were subsequently fitted to a pharmacokinetic model according to the standard model building criteria. Body weight and age were tested according to a stepwise covariate inclusion approach (23), i.e., the covariates were entered one by one into the population model. After all significant covariates have been entered into the model (forward selection), each covariate was removed (backward elimination), one at a time. The likelihood ratio test was used to assess whether the difference in the objective function between the base model and the full (more complex) model was significant.
Additional parameters leading to a decrease in the objective function ≥ 3.84 were considered significant (p<0.05). During the final steps of the model building, only the covariates which resulted in a difference of objective function ≥ 7.88 (p<0.005) were kept in the final model. Each model was internally validated using a visual predictive check.

**Model predictive performance: Posterior Predictive Check (PPC)**

In order to evaluate model performance, a posterior predictive check (PPC) was carried out. PPC operates under the basic assumption that, if the model provides an adequate description of the data, then the simulated data from the same model should mimic the essential features of the observed data. In this investigation, model performance was assessed by comparing the accuracy of area under the curve (AUC) estimates obtained for each subgroup, based 1) on a model derived from the overall population and 2) by extrapolations to subgroup B (n=8), based on a model derived from subgroup A (n=20). This was done for each scenario, as described previously. AUC estimation was performed by keeping the median body weight of the population analysed during model building or by adapting the parameter correlation using the body weight median of the new population. Integration of the concentration time data was performed according to the trapezoidal rule.

**5.3. RESULTS**

In this paper, we summarise the results from two out of the six simulation scenarios that were evaluated. These scenarios are representative of the whole investigation, in that they capture the key issues regarding covariate model building and the use of model-based approaches for dose selection or extrapolation of pharmacokinetics across populations. In particular, we focus on the scenario in which body weight is exponentially correlated with clearance according to an exponent higher or lower than 0.75. As shown in figure 1, each pharmacokinetic model was validated using a visual predictive check. Both the models obtained from the full population (group C) and from the subgroup of children weighting between 10 and 15 kg (subgroup A) seem to accurately predict the observations.

In figure 2 predictions of the AUC in the children from subgroup B are derived from the model built with the data from subgroup A. Clearly, the model does not accurately predict the parameter of interest when the covariate range in the new population differs from the one of the original model. Moreover, as shown on the right panel of figure 2, adjusting the median of body weight to the distribution of the new population did not result in any improvement in model performance.

In contrast to the aforementioned results, accurate predictions of the pharmacokinetic parameter of interest are obtained in each of the subgroups when using the model obtained by fitting the full population data set (figure 2 and figure 3). In addition, the model seems to perform well if the covariate point estimate is kept in the model (left panels). These results also show that predictions are accurate only when a model is used for interpolation purposes, i.e., when predictions encompass the range of covariate values included in the model building. Interestingly, the model does not perform accurately anymore when the relation between clearance and body weight is adapted to reflect the covariate distribution in the new population. This happens irrespective of the magnitude of the exponent which correlates body weight to clearance.
Influence of covariate distribution on model predictive performance

Figure 2 Predicted AUC distribution in subgroup B based on model parameter estimates obtained from data fitting of subgroup A. Upper panels show prediction distributions for an exponential correlation between clearance and body weight with an exponent of 0.65, whilst lower panels show prediction distributions for an exponent of 1.5. The line represents the true point estimate of AUC in the population. In the left panels the difference in the covariate distribution between subgroups A and B is not taken into account, with the median of the weight distribution in subgroup A being used in the simulations. In the right panels a shift is observed in the predictions when the covariate range of subgroup B is used in the simulations.

Figure 3 Predicted AUC distribution in subgroup A based on model parameter estimates obtained from data fitting of the full population (group C). Upper panels show prediction distributions for an exponential correlation between clearance and body weight with an exponent of 0.65, whilst the lower panels show prediction distributions for an exponent of 1.5. The line represents the true value of AUC in the population. In the left panels the difference in the covariate distribution between group C and subgroup A is not taken into account, with the median of the weight distribution of subgroup C being used in the simulations. In the right panels a shift is observed in the predictions when the covariate range of subgroup A is used in the simulations.
Influence of covariate distribution on model predictive performance

Figure 4 Predicted AUC distribution in subgroup B based on model parameter estimates obtained from data fitting of the full population (group C). Upper panels show prediction distributions for an exponential correlation between clearance and body weight with an exponent of 0.65, whilst the lower panels show prediction distributions for an exponent of 1.5. The line represents the true value of AUC in the population. In the left panel the difference in the covariate distribution between group C and subgroup B is not taken into account, with the median of the weight distribution of subgroup C being used in the simulations. In the right panels a shift is observed in the predictions when the covariate range of subgroup B is used in the simulations.

Figure 5 Predicted AUC distribution in subgroup B based on the model parameter estimates obtained from data fitting of subgroup A. The histograms show AUC predictions for a linear relation between clearance and body weight with a slope of 1.5. The line represents the true value of AUC in the population. In the left panel the difference in the covariate distribution between subgroups A and B is not taken into account, with the median of the weight distribution of subgroup A being used in the simulations. In the right panels a shift is observed in the predictions when the covariate range of subgroup B is used in the simulations.
5.4. Discussions

The main focus of our study was to investigate the role of demographic covariates during bridging and extrapolation of pharmacokinetic data across paediatric populations. Clearly, the identification of influential covariate effects on pharmacokinetic parameters is crucial to ensure accurate dose selection or dose adjustment in a new population. This is particularly important during the planning phase of a bridging exercise, when pharmacokinetic models are used for simulation purposes. Ideally, the predictive performance of population models should be warranted before its application in paediatric therapeutic research and drug development. Here we have shown the potential for bias in model predictions when extrapolating data beyond the covariate range explored during model building, a common practice in industry and academic research, which relies in small sample sizes for the characterisation of pharmacokinetic properties of a compound. These findings emphasise the importance of meta-analysis and other techniques for evidence synthesis as the basis for any quantitative evaluation of pharmacokinetics and pharmacodynamics in children. From a methodological point of view we have also shown the relevance of “centring” on the point estimate of the covariate distribution, which must be retained in the model when extrapolations are performed, irrespectively of the differences in the covariate distribution in the population or subgroup of interest.

Model-based extrapolation and interpolation

The current findings show that extrapolation to a new population beyond the covariate range explored during model building is not possible for exponential parameter-covariate correlations. These results appear to be in agreement with a previous publication which showed that, irrespective of whether extrapolation methods are to be applied during paediatric drug development, model predictions beyond the range of the data used for parameter estimation may be biased (18, 19). Adaptations or adjustments of parameter-covariate correlations to account for the covariate range of the new population does not improve model predictive performance. In fact, it appears that the farther the median of the covariate of the new population deviates from the covariate range explored during model building, a common practice in industry and academic research, which relies in small sample sizes for the characterisation of pharmacokinetic properties of a compound. These findings emphasise the importance of meta-analysis and other techniques for evidence synthesis as the basis for any quantitative evaluation of pharmacokinetics and pharmacodynamics in children. From a methodological point of view we have also shown the relevance of “centring” on the point estimate of the covariate distribution, which must be retained in the model when extrapolations are performed, irrespectively of the differences in the covariate distribution in the population or subgroup of interest.

The (often physiologically-driven) exponential correlation between pharmacokinetic parameter and covariate is linked to nonlinearities that cannot be predicted without a semi- or fully mechanistic approach to bridging or extrapolations beyond the evidence derived from the available data. From a statistical perspective, this issue could be handled by defining uncertainty in parameter estimation. However this would lead to wide parameter distributions, with little value for dosing recommendations. It should also be noted that this bias cannot be eliminated by the identification of additional covariates. Extrapolation to a different population requires accurate estimation of the underlying parameter-covariate correlations, which in turn imposes the availability of data (likelihood) or alternatively, the use of priors that support inferences about the parameter distribution in a different population, including the magnitude and nature of the covariate effects in those conditions. At present, our findings suggest that only interpolation is feasible when making use of nonlinear hierarchical models to describe pharmacokinetics in children. Interpolations will be accurate independently of the nature of the parameter-covariate correlations.

Influence of sample size on predictive performance

In addition to the hurdles for the use of bridging and extrapolation across populations, another issue in the covariate analysis presented here was the limited sample size of the data available for model building, which may clearly lead to wrong covariates selection and inclusion bias. In our study, the correct covariate (body weight) was identified when the full dataset was analysed, whilst a confounding factor (age) or no covariate effects (results not shown) were identified when evaluating the small, imbalanced subgroup of children (n=20). This problem, previously highlighted by Ribbing in his simulation study (9), emphasises the importance to perform a stepwise covariate selection only when large paediatric datasets are available. If this is not the case, meta-analysis or different methods, such as the use of a genetic algorithm in covariate selection (12) or automated covariate model building (13), should be considered.

Recommendations on the use of models for simulation purposes

M&S represents a powerful tool to avoid unnecessary studies in the target population as well as facilitate the interpretation of the limited evidence available (24). However, our findings underscore the importance of a careful and cautious use of models. Awareness about model assumptions and formal evaluation of the predictive performance of a model is required to avoid biased predictions, which in turn, could lead to wrong dosing adjustments in clinical practice.

The main recommendations from this investigation are listed below:

• Unless a mechanism-based model can be warranted, the use of a stepwise approach for covariate analysis is not recommended when small datasets are available. Instead, alternative approaches should be considered for paediatric bridging and extrapolation.
• Extrapolation of the covariate effects beyond the parameter distributions explored during model building cannot be performed without bias, and consequently erroneous dosing recommendations.
• Pharmacokinetic models can be used for simulation purposes only when the population of interest can be considered a subgroup of the initial population.
• The covariate point estimate must be retained in the model when predictions refer to a population in which median or mean values differ from the population used during model building.

Limitations
Two main limitations need to be acknowledged in our study. First, we have restricted the analysis to a fixed number of virtual patients. This choice was based on the need to assess whether the dataset size may influence the final results. Therefore the same bioavailability was assumed in the whole population of children. We also acknowledge that from a methodological perspective, other algorithms could have been tested to confirm that these findings are not an artefact of the maximum likelihood, as implemented in NONMEM. The use of a different method, such as the stochastic approximation of the standard expectation maximization (SAEM) might have yielded different results in terms of the magnitude of the bias seen with the first-order conditional estimation method with interaction (FOCEI) (25).

Conclusions
In summary, model performance appears to be independent of the nature of the parameter-covariate correlations if predictions are restricted to interpolations. Biased results may be observed when predictions are aimed at extrapolations, i.e. covariate distribution lies outside the range observed during model building. The use of meta-analysis, mechanistic models and other alternative methods in which prior or historical data are used for inferential purposes is therefore recommended for bridging and extrapolation of pharmacokinetic data across paediatric populations. In addition, parameterisation of covariate effects based on the point estimate of the covariate distribution imposes the use of the same point estimate even when the population to be simulated differs from the original population.

These findings emphasise the need to discriminate between models for estimation and models for simulation, which are required when performing bridging and extrapolations. The discrepancies observed in the predicted distributions are not detectable with standard diagnostic tools currently used during model validation procedures.

References


