Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4
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Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4

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Received: 16 June 2010 / Accepted: 19 October 2010 / Published online: 4 November 2010
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Abstract The aim of this work was to determine whether optimizing the study design in terms of ages and sampling times for a drug eliminated solely via cytochrome P450 3A4 (CYP3A4) would allow us to accurately estimate the pharmacokinetic parameters throughout the entire childhood timespan, while taking into

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account age- and weight-related changes. A linear monocompartmental model with first-order absorption was used successively with three different residual error models and previously published pharmacokinetic parameters ("true values"). The optimal ages were established by D-optimization using the CYP3A4 maturation function to create "optimized demographic databases." The post-dose times for each previously selected age were determined by D-optimization using the pharmacokinetic model to create "optimized sparse sampling databases." We simulated concentrations by applying the population pharmacokinetic model to the optimized sparse sampling databases to create optimized concentration databases. The latter were modeled to estimate population pharmacokinetic parameters. We then compared true and estimated parameter values. The established optimal design comprised four age ranges: 0.008 years old (i.e., around 3 days), 0.192 years old (i.e., around 2 months), 1.325 years old, and adults, with the same number of subjects per group and three or four samples per subject, in accordance with the error model. The population pharmacokinetic parameters that we estimated with this design were precise and unbiased (root mean square error [RMSE] and mean prediction error [MPE] less than 11% for clearance and distribution volume and less than 18% for kₐ), whereas the maturation parameters were unbiased but less precise (MPE < 6% and RMSE < 37%). Based on our results, taking growth and maturation into account a priori in a pediatric pharmacokinetic study is theoretically feasible. However, it requires that very early ages be included in studies, which may present an obstacle to the use of this approach. First-pass effects, alternative elimination routes, and combined elimination pathways should also be investigated.

**Keywords** Population pharmacokinetics · Protocol optimisation · Children · Maturation function

**Introduction**

To thoroughly evaluate any drug, an investigation of the dose–concentration–effect relationship is essential. This is the aim of phase I and II studies, the results of which are used to establish an optimized dosage regimen. The pharmacokinetics of drugs in children are different from those in adults, because of growth and maturation [1]. Allometry allows parameters to be adapted according to body weight, thus taking growth into account. Many studies have demonstrated that body weight and age are the major contributors to variability of clearance [2]. However, simple allometric scaling does not take into account variations in the maturation of the metabolic pathways, which are reflected by age. This was demonstrated by Bjorkman et al. who found that it was not possible to accurately predict the clearance of midazolam and alfentanil in neonates using allometric scaling alone [3]. The influence of maturation should be taken into account for each metabolic pathway through ages.

Recently, several published studies focused on scaling pharmacokinetic parameters for children from those of adults using physiologically based pharmacokinetics (PBPK) [4, 5]. Some studies have focused on equations regarding the maturation of...
metabolic function [3, 6]; for example, in 2006, Johnson et al. published equations regarding the maturation of the main cytochrome pathways [7].

As described in the European Medicine Agency (EMEA) guidelines [8], population pharmacokinetics (POP PK) methodology is an optimized approach compared to classical pharmacokinetics, because it requires fewer samples per child [9]. However, the population pharmacokinetics approach (POP PK) requires a high number of individuals, which may be a drawback, due to difficulty in recruiting children, which may account for the absence of some ages. The predictions drawn from a POP PK model should be limited to the age ranges that were included in the population of the study. However, it may be possible to use maturation patterns to identify the age ranges necessary to enable robust extrapolations throughout childhood; Thus, it might be possible to not include children of certain age intervals in which a reliable prediction can be made. Furthermore, using population pharmacokinetics, factors can be used as covariates and integrated into pharmacokinetic models. This allows the influence of bodyweight and age on pharmacokinetics parameters to be investigated [10]. Moreover, the efficiency of PK studies and the precision with which parameters are estimated are directly related to the study design. In this context, methods based on D optimization have been developed to optimize PK study designs in order to accurately estimate PK parameters using as few samples as possible. Several software packages are currently available to perform design optimization [11–13], and some of the results of the present study were obtained using one of them, PFIM3.0 [14].

The goal of the present work was to determine whether including samples from children of specific ages in a pediatric PK study would allow us to determine the PK profile throughout childhood. The methodology was developed around a theoretical drug exclusively metabolized by the hepatic cytochrome P450 3A4 (CYP3A4) pathway and was based on simulated data.

Methods

The methodology comprised five successive steps (Fig. 1): (1) Identification of optimum ages with regard to maturation parameters of the maturation function using the D-optimality criterion to create optimized demographic databases. (2) Identification of post-dose sampling times, for each age previously identified using the D-optimality criterion, to create optimized sparse sampling databases. (3) Simulation of concentrations using the “optimized sparse sampling databases” and the theoretical (“true”) PK and maturation parameters. These databases, containing the simulated concentrations, were called “optimized concentration databases.” (4) Pharmacokinetic parameter estimation performed on the optimized concentration databases. (5) Comparisons of true and estimated parameter values.

Sample selection (Fig. 2)

The first part of this work consists in establishing an optimal design by selecting the age and sample times using the maturation function.
Age optimization (first step)

Equations describing the maturation functions for different metabolic pathways were recently published [3, 6]. Johnson et al. [7] published a general hyperbolic maturation function of cytochrome activity, which described the gradual change in clearance during childhood as a fraction of the adult clearance:

\[ MAT = \frac{PNA^\theta}{PNA^\theta + PNA_{50}} \]

where MAT is the fraction of adult cytochrome P450 (CYP) abundance, PNA is the post-natal age in years, \( \theta \) is the Hill coefficient, and PNA\(_{50} \) is the PNA at which CYP abundance is 50% that of the mature value. PNA\(_{50} \) and \( \theta \) values are cytochrome-dependant variables that were determined by Johnson et al. [7]. We
fixed these parameters to the values previously described for CYP3A4; i.e., 0.31 and 0.83 for PNA50 and θ, respectively.

D-optimality was used to determine the ages allowing the best determination of maturation function. PFIM 3.0 is a software program allowing to evaluate and optimize population designs in the context of nonlinear mixed effect models (single and multiple response). The theory is based on the expression of the Fisher information matrix, whose inverse, according to the Cramer–Rao inequality, is the lower bound of the variance covariance matrix of any unbiased estimators of the parameters [15, 16]. Using a priori PK and error models and the corresponding values, PFIM 3.0 allows to optimize both the allocation of the sampling times and the whole group structure of the population design, that is to say the number of elementary designs, the number of samples per elementary designs and the
proportion of subjects in each elementary design in order to obtained the least biased estimation of PK parameters. This step can be performed using the Simplex algorithm available in the PFIM tool as performed in this work. Regarding model specification, PK models can be described by their analytical form or by using a system of differential equations. Moreover, a library of “classical” PK models has been proposed corresponding to the model described in the subroutine models proposed by NONMEM. In this part of the study, PFIM 3.0 was used to determine those ages that allowed the least biased estimation of θ and PNA50 [17].

In this part of our work, the pharmacokinetic model normally used was replaced by the CYP3A4 maturation equation defined above. This optimization is only influenced by the maturation parameters θ and PNA50, and by the associated parameters (residual error and interindividual variability).

The errors in measuring lower CYP activity at lower age will be anticipated to be proportionally higher, then a combined residual error model was used. The multiplicative component of the residual error was fixed to 30% (σ^2_{mult} = 0.09) and the additive component was fixed to 5% (σ^2_{add} = 0.0025) when compared to the 100% of the adult metabolic capacity. For interindividual variability, the same variability (σ^2) as for clearance (Cl) and distribution volume (Vd) was chosen for the maturation parameters; i.e., an exponential model with a value of 0.1 (representing 30% interindividual variability).

The optimization was performed with ten different initial age values. The ages determined by optimization were used as initial values in the following optimization step. Because the simplex algorithm was used, optimization could yield redundant ages. In this case, only one of each redundant age was used as an initial value in order to include the smallest number of different ages. Thus, a single optimized age design was established comprising several ages. The optimization was performed with 80 as the fixed total number of patients.

Post-dose time optimization (second step)

Optimized post-dose times were obtained by using PFIM 3.0 for each of the ages that were established in the first step, which established the optimized ages. Because the Cl and Vd varied with age and body weight, we calculated them for each age using the maturation function. Pharmacokinetic model The structural model was a monocompartmental model with first-order absorption and linear elimination [Subroutine ADVAN(2) TRANS (2)]. We used midazolam pharmacokinetic parameters, because midazolam is exclusively metabolized by CYP3A4 (i.e., 24 l/hour for Cl/F and 66.5 l for Vd/F) [18–20]. The doses that we used were 250 µg/kg for children and 15,000 µg for adults (corresponding to a 250 µg/kg dose for a standard adult of 60 kg, the usual dose for midazolam). The absorption constant (ka) was fixed to the value of 1.5 h⁻¹, which corresponds to four times the value of k_e, defined as:
\[ k_e = \frac{Cl}{Vd} \]

**Covariates** Clearance was established to be dependent on growth and maturation:

\[ Cl/F = TV_{(Cl/F)} \cdot MAT \cdot GRW_{Cl}, \]

where TV\(_{(Cl/F)}\) is the typical value of apparent clearance for an adult whose body weight (BW) is the adult median BW (i.e., 70 kg). Growth was integrated through a classical allometric function, as described by Anderson et al. [10]:

\[ GRW_{Cl} = \left( \frac{BW}{BW_{\text{median}}} \right)^{0.75}, \]

where BW is the bodyweight in kilograms and BW\(_{\text{median}}\) is the adult median BW (i.e., 70 kg).

Maturation was taken into account through the previously described general hyperbolic maturation equation. Here, we fixed the values of PNA\(_{50}\) and \(\theta\) to the values described by Johnson et al. for CYP3A4; i.e., 0.31 and 0.83 years, respectively [7]. Thus, the general equation for clearance was

\[ Cl/F = TV_{(Cl/F)} \cdot \frac{PNA^{0.83}}{PNA^{0.83} + 0.31} \cdot \left( \frac{BW}{70} \right)^{0.75}. \]

The distribution volume is a function of growth through the allometric function [10]:

\[ Vd/F = TV_{(Vd/F)} \cdot \left( \frac{BW}{70} \right)^{0.75}. \]

where TV\(_{(Vd/F)}\) stands for the typical value of the apparent distribution volume for an adult whose body weight is 70 kg.

**Error and covariance models** We used an exponential interindividual variability model. Interindividual variability values (\(\omega^2\)) were fixed to 0.1, 0.1, and 1, respectively, for the clearance, distribution volume, and absorption constant, corresponding to interindividual variabilities of 30% for Cl and Vd and 100% for \(k_a\), in agreement with previously published values in pediatric population pharmacokinetic studies [21, 22]. A null covariance was fixed between the pharmacokinetic parameters.

Three residual error models (i.e., additive, multiplicative, and combined) were investigated for time post-dose optimization. The values of the variance \(\sigma^2\) of the residual variability \(\varepsilon\) was fixed to 0.1 and 10, respectively, for multiplicative and additive residual error terms, when applicable, in agreement with previously published values for midazolam multiplicative residual error and limit of quantitation (LOQ) [23, 24]. Each residual error model generated an optimized sampling schedule per selected age. As previously described for age selection, the optimization was initially conducted with ten different initial sampling times. The times determined by optimization were used as initial values in the following optimization. When the optimization gave redundant times, only one was used as the initial value in order to include the smallest number of different times. Thus,
three post-dose time designs per selected age were established and then evaluated. These three optimized sampling schedules were combined with the optimized demographic databases; thus, three optimized sparse sampling databases were created according to the residual error model.

We created two other databases, the “optimized rich pharmacokinetics database,” which comprised the same optimized age design but 15 samples per patient, and the “complete rich pharmacokinetics database,” which comprised 400 patients from 2 days old to adulthood, with 15 samples per patients. These databases were used as references for the estimations.

**Simulation of concentrations and estimation of the population pharmacokinetic parameters (third and fourth steps)**

### Pharmacokinetic model and covariates
Simulations of concentrations and parameter estimations were performed using NONMEM VI [25]. We used the population pharmacokinetic model previously described (monocompartmental with first-order absorption and elimination). Age and bodyweight were used as covariates with the equations described for sampling time optimization.

### Error and covariance models
The interindividual variability used for simulation and modeling was the same as that used for the sampling time optimization. The residual error model used during one database optimization was used for the simulation and modeling of the same database. However, when an additive component was used in the residual error model, the equation used for residual error was:

\[
C(t_i) = f(P_{it}) + \theta_6 \cdot \varepsilon_1,
\]

where \(C(t_i)\) stands for the concentration measured in patient, \(f(P_{it})\) for the concentration predicted in the same patient using the population model, and \(\theta_6 \cdot \varepsilon_1\) for the additive component of the residual error. \(\varepsilon_1\) was fixed to 1 and \(\theta_6\) could vary between 0 and 20, allowing the additive residual error to take values between 0 and 20; i.e., between 0 and twice the value of the residual error used for simulations.

### Concentration simulation and parameter estimations
The pharmacokinetic model was applied to the three established optimized sparse sampling databases, the optimized rich PK database, and the complete rich PK database to simulate plasma concentrations, leading to three optimized concentration databases, an optimized rich PK concentration database, and a complete rich PK database. Standard population pharmacokinetic modeling was performed on these concentration databases to obtain estimations of the pharmacokinetic and maturation parameters. The estimation method used was FOCE (METHOD = 1). The initial values were the true PK parameters. This entire two-step process was performed 200 times to obtain 200 simulations of concentrations and 200 estimations of population pharmacokinetic parameters.

### Concordance of estimation and true values (fifth step)
Values of the 100 first successful estimations of pharmacokinetic and maturation parameters were recorded for each estimation, along with their variability and the
residual errors. An estimation was considered to be successful when a normal flag (MINIMIZATION SUCCESSFUL) was obtained, combined with a successful covariance step. When <100 successful estimations had been obtained, the number of successful estimations used in the study was specified. To check the agreement between the estimated values and the values used for simulations (“true values”), the mean of the estimation and the mean prediction error (MPE) and root mean square error (RMSE) standing for bias and precision were calculated using the following formulas [26, 27]:

$$RMSE\% = \frac{1}{P_{obs}} \cdot \sqrt{\frac{\sum_{n} (P_{obs} - P_{calc})^2}{n}} \times 100$$
$$MPE\% = \frac{1}{P_{obs}} \cdot \frac{\sum_{n} P_{obs} - P_{calc}}{n} \times 100$$

where $P_{obs}$ is the value of the parameter used for simulation, $P_{calc}$ the estimated value of the parameter, and $n$ the number of patients. Estimations were considered to be unbiased and precise if MPE and RMSE were <15%.

Results

Selection of samples

Age optimization (first step)

Table 1 describes the optimized design in terms of age, which was established according to different residual errors. Four separate ages were identified: a very early age (0.008 years old, around 3 days old), two early ages (0.192 years old, around 2 months old, and 1.325 years old), and an adult age range. Around one fourth of the population was proposed for each age range, i.e., 22 patients for the 0.008-year-old range, 20 patients for the 0.192-year-old range, 17 patients for the 1.325-year-old range, and 21 patients for the adult population, with a total of 80 patients. Pfim predicted the standard errors for the $\theta$ and PNA$_{50}$ estimates to be 17 and 41%, respectively.

Post-dose time optimization (second step)

Post-dose time optimization established that three or four samples were needed, according to the residual error model applied, for a total of 240 or 320 samples, respectively; the sampling times are described in Table 1.

Estimation of parameters

Figure 3 shows the results of the PK parameter estimates, depending on the residual error model used (different designs according to the residual error model used); the
three previously described concentration databases (i.e., optimized sparse sampling database, optimized rich PK database, and complete rich PK database) were used, and yielded different results. One hundred estimations of the pharmacokinetic parameters were obtained for all but two cases: with the complete rich PK database, less than 100 successful estimations were obtained when the residual error model was additive (89 estimations) or multiplicative (67 estimations).

When the optimized sparse sampling design was considered, regardless of the residual error model applied, the estimations of clearance and distribution volume were unbiased (MPE < 8%) and precise (RMSE < 11%). The estimation of the absorption rate was also unbiased, but less precise (MPE < 11% and RMSE increased to 18%). This design allowed a slightly biased and less precise estimation of maturation parameters: MPE remained <6% (ranging from −1.04% for the Hill coefficient with an additive error model to 5.7% for PNA50 with an additive error model), but the RMSE could exceed 36% for PNA50 (ranging from 6.63% for the Hill coefficient with an additive model to 36.72% for PNA50 with a multiplicative error model).

The use of an optimized rich PK design slightly improved the precision of the parameter estimates. The use of complete rich PK databases induced a further decrease in the RMSE of the parameter estimates, particularly for the PNA50, which registered a more than 2-fold drop. Indeed, the RMSE of PNA50 for additive, combined, and multiplicative error models decreased from 30, 31, and 29%, respectively, with the optimized rich PK design, to 15, 16, and 12%, respectively, with the rich PK database.

<table>
<thead>
<tr>
<th>Age</th>
<th>Post-dose time depending on RE (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additive RE (10)</td>
</tr>
<tr>
<td>0.008 years old (n = 22)</td>
<td>0.594</td>
</tr>
<tr>
<td></td>
<td>0.967</td>
</tr>
<tr>
<td></td>
<td>23.997</td>
</tr>
<tr>
<td>0.192 years old (n = 20)</td>
<td>0.277</td>
</tr>
<tr>
<td></td>
<td>1.479</td>
</tr>
<tr>
<td></td>
<td>2.745</td>
</tr>
<tr>
<td>1.325 years old (n = 17)</td>
<td>0.273</td>
</tr>
<tr>
<td></td>
<td>1.468</td>
</tr>
<tr>
<td></td>
<td>2.974</td>
</tr>
<tr>
<td>adults (n = 21)</td>
<td>1.279</td>
</tr>
<tr>
<td></td>
<td>2.347</td>
</tr>
<tr>
<td></td>
<td>4.937</td>
</tr>
</tbody>
</table>

Table 1 Description of optimized design in terms of age and post-dose time according to the residual error model applied

RE residual error applied on pharmacokinetic model during post-dose time optimization
Discussion

D-optimality was used by Green et al. in an adult population [28], and by Van Rossum et al. and Turner et al. in a pediatric population for retrospective studies [29, 30]. These studies demonstrated the superiority of optimized sampling design compared to empirical sampling design. Furthermore, optimization allows for a reduction in the number of samples, which is invaluable in clinical investigations involving children. Many studies have also explored ways to scale adult clearance for a child population: as explained by Anderson et al. size and age must be taken into account in the clearance adjustment [10]. Classical allometric scaling was found to be useful for size adjustment, and the use of a variable slope sigmoidal model (Hill equation) was recommended for maturation scaling [10]. This type of function can describe maturation from birth until adulthood, and was successfully used in several studies to establish pediatric population pharmacokinetic models [31, 32]. In our work we used two different equations describing, respectively, the

![Fig. 3](image-url) Evolution of MPE (bias) and RMSE (precision) associated with estimated pharmacokinetic parameters when a an additive residual error model, b a combined residual error model, and c a multiplicative residual error model is applied. Optimised sparse sampling, Optimised rich PK, Complete rich PK RE residual error model. The black line stands for the 15% limit.
growth (standard allometric function) and the maturation (Hill equation) consequences on pharmacokinetics as described by Anderson and Holford [6].

The aim of the present work was to establish whether this theoretical maturation could be taken into account when designing a pediatric PK study and, consequently, to evaluate the feasibility of building a PK model that could be used to define dosing recommendations from birth to adulthood by including specific ages in the study.

We decided to base our investigation on a virtual drug that would be eliminated exclusively via hepatic CYP3A4 metabolism, one of the main elimination pathways for xenobiotics. In this first analysis, intestinal metabolism was assumed to be negligible and the bioavailability was considered to be total. Midazolam pharmacokinetic parameters were used, because this drug is a commonly acknowledged probe of hepatic CYP 3A4 activity [33]. The consequences of CYP3A4 polymorphism was not investigated in the study since the absence of clinical consequences of this polymorphism was reported [34, 35]. The interindividual and residual variabilities were fixed according to previously published studies in children. CYP3A4 maturation is known to have a high inter-subject variability. Nevertheless, we decided to study the CYP3A4 maturation in the present work since it is the main cytochrome for drug metabolism, although its inter-individual variability is greater than other’s. The consequence of different interindividual variabilities of PK parameters on maturation parameters should be investigated in a further work.

D-optimization was performed with PFIM software (version 3.0), dedicated to population design evaluation and optimisation, and was used to determine the essential ages and optimal post-dose times. Recently, a new version, PFIM 3.2, was proposed as an extension of PFIM version 3.0. In this version, discrete covariate integration is possible for the evaluation and optimization of protocols. This new version is, available freely since January 2010 at http://www.pfim.biostat.fr, with several new features in term of model specification and of the fisher information matrix expression.

This methodology established a design that allowed us to accurately estimate pharmacokinetics parameters (RMSE and MPE $<11\%$ for Cl and Vd, and $<18\%$ for $k_a$). Moreover, the relative standard errors (RSE) of PK parameters predicted by Pfim during sampling time optimization were consistent with the RSE reported for the Nonmem evaluation (Table 2), as previously found by Chenel et al. [36]. Estimations of maturation parameters were less precise, particularly when the combined residual error model was applied (PNA 50 RMSE of 36.7% in this case). Because the optimization that we performed was based on nonlinear regression, the differences that we found in terms of design optimization according to the residual error model were expected. However, the overall estimation of both PK and maturation parameters was satisfactory.

During the estimation phase, the use of the boundaries on the additive component of the residual error avoided negative values for the residual variability, and thus, prevented from generating any negative simulated concentrations. Indeed, in the absence of this boundary, Nonmem runs quite often did not terminate successfully. The design that we established comprised only neonates, young infants (0.008 years old, 0.192 years old; i.e., around 3 days old and 2 months old and
1.325 years old, respectively), and adults. We used the maturation function as reported by Johnson et al. [7] that is to say without any exponent on the PNA$_{50}$ which value was established by the authors at 0.31. However, this equation could be expressed as a typical Hill function in which the $h$ exponent is applied to the PNA$_{50}$ and would become:

$$MAT = \frac{PNA^{0.83}}{PNA^{0.83} + 0.24^{0.83}}.$$  

This modified expression would not have any mathematical consequences. Nevertheless, the PNA$_{50}$ would take the value of 0.244.

In contrast to what one might expect, our results suggest that recruiting children older than 1.325 years old likely would not improve the evaluation of this type of drug when the established optimised design is applied. In spite of this, the estimations of PNA$_{50}$ values were accurate. It is commonly accepted that clinical investigations with children are difficult, in particular because of recruitment difficulties. Infants are all the more difficult to recruit; therefore, our design would probably face substantial recruitment difficulties. Thus, we plan to investigate in a future study the consequences on parameter estimates, in terms of bias and precision, of replacing the optimal ages determined by this study with more advanced ages. However, it should be emphasized that, innovative modeling approaches (such as the one described here) can not be a substitute for actual study but rather, are an extremely useful adjunct to the effective design of studies in neonates and young infants.

This work was limited to the evaluation of a drug with a unique elimination pathway, which is extremely rare. Midazolam has recently been shown to undergo

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**Table 2** Comparison of relative standard error (%) of the PK parameters predicted by PFIM during sampling-time optimization and estimated from NONMEM

<table>
<thead>
<tr>
<th>Post-dose time depending on RE (h)</th>
<th>NONMEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 0.08 yo</td>
<td></td>
</tr>
<tr>
<td>Children 0.192 yo</td>
<td></td>
</tr>
<tr>
<td>Children 1.325 yo</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Additive RE Cl/F</td>
<td>7.00</td>
</tr>
<tr>
<td>Vd/F</td>
<td>8.20</td>
</tr>
<tr>
<td>ka</td>
<td>25.9</td>
</tr>
<tr>
<td>Multiplicative RE Cl/F</td>
<td>8.40</td>
</tr>
<tr>
<td>Vd/F</td>
<td>15.6</td>
</tr>
<tr>
<td>ka</td>
<td>55.1</td>
</tr>
<tr>
<td>Combined RE Cl/F</td>
<td>8.40</td>
</tr>
<tr>
<td>Vd/F</td>
<td>15.9</td>
</tr>
<tr>
<td>ka</td>
<td>56.4</td>
</tr>
</tbody>
</table>

RSE relative standard error, defined as standard error of estimated parameters divided by mean of parameters multiplied by 100; RE residual error; Yo years old

The sampling time optimization was performed separately for each age, and each optimization predicted the RSE for the PK parameters.
direct N-glucuronidation (around 2%), which remains a minor elimination pathway [37] and that we did not take into account in our study. However, combined elimination pathways, first pass effects and alternative elimination routes should be investigated. To that end, a possible solution would be to use a PBPK model on adult data to generate PK data in children. These data would be used to generate a function describing maturation and/or growth consequences on PK. That function could be used for the optimisation approach described here to design a paediatric PK study.

Another aspect of this work that should be examined in more detail, because of practical considerations, is the post-dose times used for estimation, which were the exact optimized post-dose times. However, Turner et al. compared the biases and accuracies of parameter estimations obtained with exact post-dose times via Monte Carlo simulations and approximate post-dose times using real data [30] and did not find any significant differences in terms of biases and accuracies, which remained <15%. Therefore, our results seem relevant in a “real world” context.

Conclusion

The results of the present work suggest that including only specific ages in a pediatric PK study could provide enough information to develop a model that is predictive for the entire span of childhood. However, this work focused on a theoretical elimination solely involving hepatic CYP3A4. First-pass effects, alternative elimination routes, and complex combined elimination pathways should also be investigated.

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