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

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Introduction

Population pharmacokinetic modelling (POPPK) has enabled the design and analysis of paediatric studies. The approach is also suitable for a bridging strategy in which differences in pharmacokinetic parameter distributions are evaluated across populations. However, little attention has been paid to the feasibility of combining prior information from serial pharmacokinetic sampling in adults with data sparse data in paediatric studies. The objective of the current study is to demonstrate the value of an integrated analysis which allows for inferences about the clinical relevance of observed differences across populations and offers a robust rationale for dose selection in early paediatric development. We illustrate this concept using data on abacavir (ABC).

Scaling for Function

Dose adjustment across populations has been based on empirical use of demographic variables as proxy for function irrespective of whether or not pharmacokinetic properties are dose-dependent. This can lead to inaccurate estimation of the correlation between the demographic covariate and the variable of interest. Furthermore, demographic variables may not reflect physiological status or changes due to developmental growth (clearance, metabolic capacity, phenotype, etc). In the proposed approach, drug elimination is parameterised relative to the reference group, providing easier interpretation of differences across populations, as compared to separate analysis of the data.

Methodology

Using simulations, we have performed a sensitivity analysis to evaluated the impact of sampling frequency and group size on parameter estimation. Hypothetical drugs with different pharmacokinetic properties were included in the analysis. Data were simulated, sampled according to current clinical protocols and re-fit to a population pharmacokinetic model. Using pharmacokinetic data in adults as prior, the following scenarios were developed to explore how sampling frequencies and group sizes impact on the estimation of pharmacokinetic parameters in children.

PK model	Parameter estimate	Variance	Group Size	Sample Size
1 COMP – ORAL linear kinetics 1 COMP – ORAL saturation kinetics (Michaelis-Menten) 2 COMP - ORAL linear kinetics 2 COMP – ORAL saturation kinetics (M-M)	From -100% (adult value) To +200%	From -50% (adult value) To +50%	5 10 20	3 4 5

Table 1. Summary of the scenarios evaluated in the sensitivity analysis.

The simulations data fitting were performed using FOCE methods in NONMEM v5.0. The likelihood ratio test was performed to assess statistical differences in parameter distribution with the significance level set at p=0.05, which corresponds to a decrease of the OF ≥ 3.84 points, under the assumption that the difference in MVOF between two nested models is χ^2 distributed.

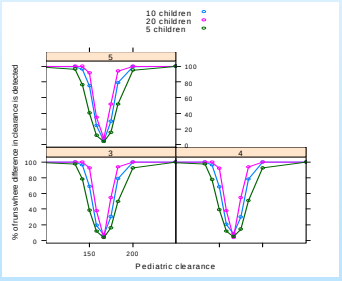

Figure 1. One-compartment PK model: % of runs in which the paediatric parameter distribution was statistically different from the reference group (MVOF=3.84, p=0.05).

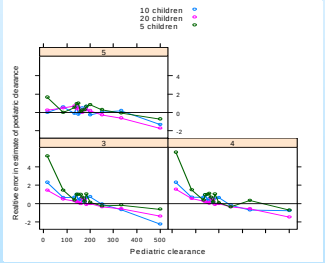

Figure 2. One-compartment PK model : relative errors associated with clearance estimated for the paediatric population

$$\%E = \frac{estimateX - realX}{realX} \times 100$$

Based on the results of the sensitivity analysis, adult data from Phase I clinical trials with abacavir were combined with sparse data from children enrolled in an efficacy trial. A summary of the population included in the analysis of the integrated dataset is shown in Table 2.

	ADULTS (n=111)	sd	CHILDREN (n=14)	sd
AGE (years)	37.3	8.3	5.9	3.4
WEIGHT (Kg)	72.2	11.7	23.8	13.1
HEIGHT (cm)	174	7.4	115	22.6
BODY MASS INDEX (BMI)	23.7	3.5	16.8	2.1

	ADMINISTRATION	number
ADULTS	oral, 300 mg	93
	oral, 600 mg	74
	intravenous, 150 mg	6
CHILDREN	oral, 8 mg/Kg	14

Table 2. Demographics of ABC-treated subjects and corresponding dosing regimens. Some subjects received multiple doses. All data were included in the analysis.

The pharmacokinetics of ABC was described by a one-compartment model with first-order absorption with a lag-time and first-order elimination . Inter-individual variability was defined with an exponential model:

$$P_i = \Theta_i \cdot \exp(\eta_i)$$

Residual errors in plasma concentrations were estimated with a slope/intercept model:

$$C_{obs,ij} = C_{pred,ij} + \varepsilon_{ij,1}\sqrt{1+\Theta^2 \cdot C_{pred,ij}^{\ 2}}$$

Preliminary Results

Figure 3 shows the goodness-of-fit plots.
Differences in parameter distributions were estimated prior to a stepwise covariate analysis. Weight was identified as the only factor influencing the pharmacokinetics of ABC (Fig. 4).

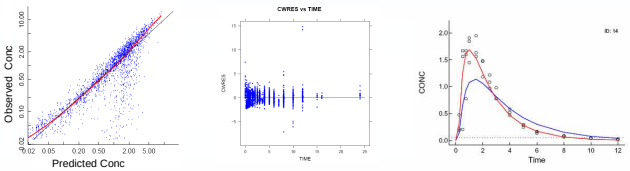

Figure 3. Diagnostic plots for ABC data fitting: observed vs. individual predictions, conditional weighted residuals (CWRES) and an example of individual fit (blue line = population, red line = post hoc).

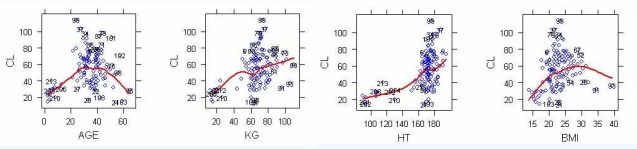

Figure 4. Correlation between demographic variables and ABC clearance.

In the final model, an exponential equation was used to describe the correlation between clearance, volume and body weight in the population:

$$CL = 36.8\left(\frac{weight}{70}\right)^{0.558} \qquad V = 74.7\left(\frac{weight}{70}\right)^{0.63}$$

Dosage adjustments were derived for the paediatric population assuming that similar drug exposure is required to ensure efficacy levels as observed in the reference group (Tab. 3).

WEIGHT	DOSE (mg)	SD (mg)
10 kg (~1 year old)	110	85 - 135
20 kg (~2 years old)	160	123 - 197
40 kg (4-12 years old)	235	181 - 289

Table 3. Example of a dosing regimen for a paediatric population to achieve and maintain exposure levels of AUC = 8.79 +/- 2.02 mg h/L. Model estimation does not include the effect of bioavailability due to change in formulations. The current recommended dose in children is 8 mg/kg twice daily.

Conclusions

The current results show that pharmacokinetic parameter distributions can be accurately estimated for a new population by integrated data analysis. This method provides a feasible alternative to dose selection in early paediatric development. These findings also suggest that pharmacokinetic parameter estimation is more sensitive to population size than to sampling frequency for drugs showing pharmacokinetic disposition according to a one-compartment model.