Design optimisation of a pharmacokinetic study in the paediatric development of a drug

Cyrielle Dumont [1], Marylore Chenel [2] and France Mentré [1]

(1) UMR 738 INSERM and University Paris Diderot, Paris, France.

(2) Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Paris, France.

Introduction

Pharmacokinetic (PK) studies in children:

- Paediatric Investigation Plan [1] : facilitates the drug's development for paediatric use since 2007
- Conducted in patients
- Limitation on the blood volume which can be taken in children

⇨Appropriate estimation method: nonlinear mixed effect models (NLMEM)

- Increasingly used during drug development and for analysis of longitudinal data in clinical trials
- Very useful in paediatrics PK [2]
- Allow to limit the number of samples per subject

Choice of the PK design:

- Important on the study results (precision of parameter estimates)
- Balance between number of subjects and number of measures/subject, choice of sampling times
- Approaches to assess/optimise the designs for NLMEM

- Based on simulation: time consuming
- Based on the calculation of the Fisher information matrix (FIM) and the optimisation of its determinant (det(FIM)) [3]

- Several software packages including PFIM in R [4,5]

Objective

To optimise the PK sampling time design for the paediatric trial of a drug X in development, taking into account clinical constraints

Methods

Data:

- Parent and metabolite PK profiles were obtained by simulation in scaling the existing PBPK model in adults to children using the software SIMCYP version 9 [6]
- 400 children
- Intravenous bolus dose of 0.1 mg/kg

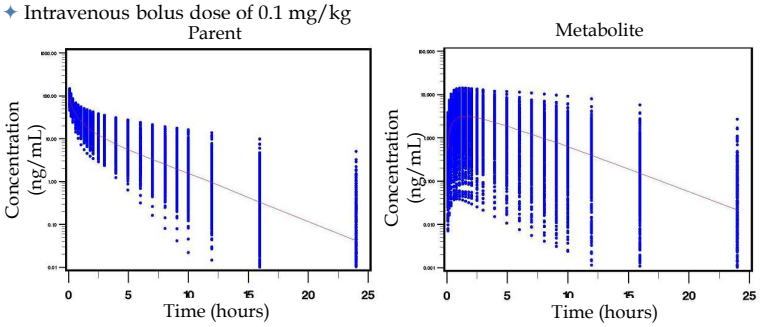

Figure 1: Simulated pharmacokinetic profiles for the parent (left) and for the metabolite (right)

PK model estimated for the parent and the metabolite:

- Simulated data analysed by NLMEM (FOCE algorithm in NONMEM VI)
- Three compartments for the parent and one compartment for the metabolite

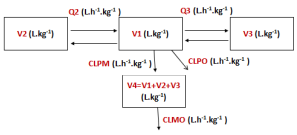

Figure 2: Structural PK model with 4 compartments

- Variabilities on CLPO, V1, CLPM, CLMO (all correlated but not considered here)
- Combined residual error model
- Dose and parameters are expressed per kilogramme
- Estimation of parameters using NONMEM and use of these parameters and of the model for design optimisation
- Implementation of the model in PFIM as an analytical solution

Design optimisation:

Constraints of the design:

- Single intravenous bolus (30 seconds) dose of 0.1 mg/kg
- PK ancillary study : 82 children between 2 and 18 years old
- For each sample, measured concentrations of parent and metabolite

Clinical constraints:

- No sample allowed between 0.3 and 1.5 h
- As far as possible, similar design in all children
- Possible earliest last time to avoid stay at hospital and if late, in few subjects

Comparison and evaluation of designs on the relative standard errors (RSE) predicted by PFIM on the four parameters with variabilities, ie CLPO, V1, CLPM and CLMO (RSE < 30% are satisfying)

Consideration of Limit Of Quantification (LOQ):

- LOQ = 0.25 ng/mL
- Not considered during design optimisation as the mean simulated concentrations were not below the LOQ but important to consider them for final evaluation of design
- Monte Carlo simulations of concentrations at optimal times of the design were performed

Evaluation of the design where some sampling times in a proportion of subjects corresponding to the simulated LOQ proportion were omitted (if more than 10%)

Results

Design optimisation:

- Optimised design with 4 points before 5h:

- RSE very high (> 500% for CLPM for example)
- Necessity to add a late time

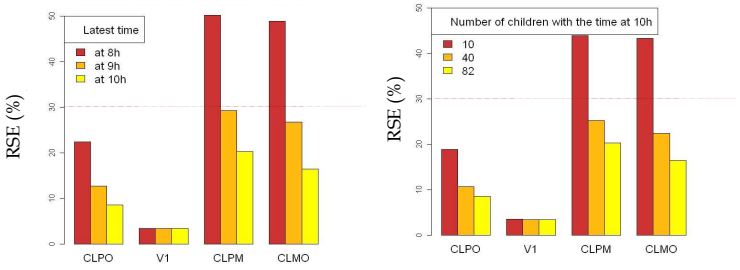

Figure 3: RSE (%) showing the influence of the timing of the late sample (left) and illustrating the influence of the proportion of subjects with the late time (right)

- Influence of the late time and of the proportion of subjects with the late time:

- Late times before 10h are not satisfying because RSE are too high
- 10 children with the late time are not sufficient while 40 children can be acceptable but it is preferable to have all children with the late time

- Compromise between optimisation and constraints: sampling times at 0.1, 1.8, 5 and 10h for all children

Handling LOQ:

- Predicted mean concentration at 10h: 1.99 ng/mL for the parent and 0.54 ng/mL for the metabolite

Time (in hour)	0.1	1.8	5	10
Parent	0.0	0.0	0.6	8.4
Metabolite	34.1	3.3	9.7	33.2

Table 1: Proportion (%) of subjects with concentrations below LOQ at the sampling times of the optimal design

- According to the simulations (Table 1), decision to omit assumption of LOQ for the parent only
- Evaluation of the proposed design taking into account LOO

0.1 h	1.8 h	5 h	10 h	Number of subjects	Percentage of subjects
x	x	x	x	43	52
x	x	x		11	13
	x	x	x	12	15
	x	x		16	20

Table 2: Design evaluated to take into account LOQ data for the metabolite

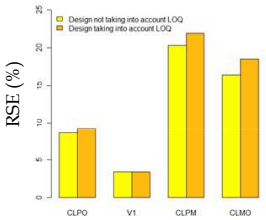

Figure 4: RSE (%) showing the comparison of designs assuming or not LOQ

- To assume LOQ slightly damages the design but the difference in predicted RSE is small

Conclusion and prospects

- Compromise between optimisation and clinical constraints: evaluation within the given time thanks to PFIM
- Optimal design with the time at 10h for all children
- "Pseudo-data" analysed to propose a design in children
- Use of an ad hoc method for data below LOQ: calculation of FIM considering these data
- Limited influence of the LOQ on the design
- Reevaluation of the design after inclusion of 20 children: work on adaptive design [7] in NLMEM
- Proposition of different designs according to the weight

References

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