Optimal two-stage design for a population pharmacokinetic study in children

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Introduction

Pharmacokinetic (PK) studies in children

- Are mainly analysed by nonlinear mixed-effect models (NLMEM) [1,2] as recommended in guideline [3]
- Approaches based on the Fisher information matrix (M_F) [4] can be used to optimize their designs and are based on *a priori* information
- PK data in children are often not available and methods as allometry or PBPK are used to predict 'initial' PK parameters

➡ Adaptive designs [5,6], among which two-stage designs, are useful to provide flexibility and two-stage designs are easier to conduct

Objectives

1) To analyse concentration-time data obtained from PBPK simulations in children after oral absorption of a drug X in development
2) To develop and evaluate the impact of two-stage designs when children 'true' parameters are different from initial ones

Methods

1) Data and modelling

- Parent PK profiles obtained by simulation in scaling the existing PBPK model in adults to children using the software SIMCYP (version 9) [7]
- 100 children between 6 months and 18 years old
- Oral absorption of a dose equal to 0.1 mg/kg
- Simulated data analysed by NLMEM (FOCEI algorithm in NONMEM 7.2 [8])
- Dose and parameters per kg

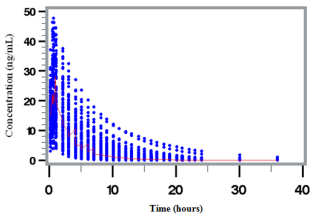

Figure 1: Simulated pharmacokinetic profiles

2) Two-stage design

- Assumption here: same elementary design (ξ) for all subjects
- Notations

- Ψ_0: initial parameters
- Ψ^*: true parameters
- ξ_1: optimized design obtained with parameters Ψ_0 for N_1 subjects
- Ψ_1: estimated parameters from data Y_1 with design ξ_1 and N_1 subjects
- ξ_2: optimized design obtained with estimated parameters Ψ_1 for N_2 subjects
- Ψ_2: estimated parameters from data Y_2, obtained with design ξ_2 for N_2 subjects, and Y_1

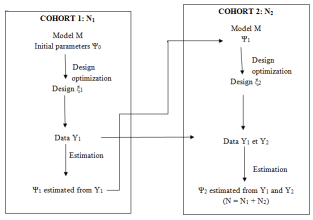

Figure 2: Two-stage design

- M_F for a two-stage design

First stage: ξ_1 is the design which optimizes the following M_F

$$M_F(\Psi_0, N_1\xi) = N_1 M_F(\Psi_0, \xi)$$

Second stage: ξ_2 is the design which optimizes the following M_F using estimated Ψ_1

$$M_F(\Psi_1, N_1 \xi_1 + N_2 \xi) = N_1 M_F(\Psi_1, \xi_1) + N_2 M_F(\Psi_1, \xi)$$

3) Simulation study

- Application to drug X for a trial with N = 60 children
- 'Initial' parameters Ψ_0 are different from the 'true' parameters Ψ^*
- Steady-state bid and dose equal to 0.1 mg/kg
- Optimization

- according to the D-optimality criterion with PFIM [9,10] in R
- 5 sampling times among the possible sampling times 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

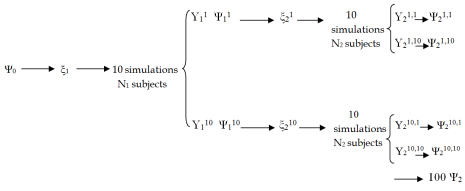

Figure 3: Simulation plan

- Estimation of Ψ_1 and Ψ_2 with saemix [11] in R
- Comparison of the relative bias and relative root mean square error (RMSE) for the estimated Ψ_1 (first stage) and the estimated Ψ_2 (second stage)

Results

1) PK model and parameters estimated for the parent drug

- Two-compartment model (five parameters)

Parameters (units)	Estimates (RSE %)	Ψ_0	Ψ^*
ka (h^{-1})	3.0 (20.0)	3.0	3.0
CL ($L.h^{-1}.kg^{-1}$)	1.3 (7.5)	1.3	3.4
V1 ($L.kg^{-1}$)	2.1 (13.0)	2.1	2.1
Q ($L.h^{-1}.kg^{-1}$)	0.91 (8.5)	0.91	0.91
V2 ($L.kg^{-1}$)	1.3 (7.3)	1.3	1.3
ω^2_{ka}	1.4 (14.5)	1.4	1.4
ω^2_{CL}	0.53 (11.4)	0.53	0.53
ω^2_{V1}	1.1 (13.9)	1.1	1.1
COV/CORR(CL ;V1)	0.55 (14.7) / 0.73 (7.1)	0.00	0.00
σ_{inter} ($\mu g.L^{-1}$)	0.00060 (17.5)	0.13	0.13
σ_{slope}	0.12 (8.1)	0.12	0.12

Table 1: Population PK parameter values

2) Two-stage design

Ξ_0: N = 60 and ξ_0 = 0.25, 0.75, 2, 5, 12 (optimal for Ψ_0)
Ξ^*: N = 60 and ξ^* = 0.25, 0.75, 2, 4, 7 (optimal for Ψ^*)
Ξ_{2S}: N_1 = 30 with ξ_0 and N_2 = 30 with ξ^*

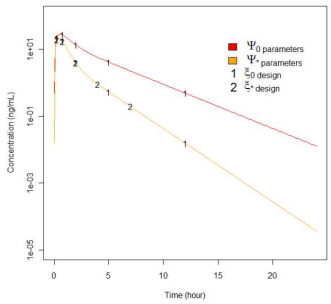

Figure 4: Mean profiles in semi-log scale

Parameters / Design	Ψ_0 Ξ_0	Ψ^* Ξ_0	Ψ^* Ξ^*	Ψ^* Ξ_{2S}
Criterion (Determinant)$^{1/10}$	78.8	47.0	61.7	58.6
Predicted RSE (%)				
ka	20.8	**63.2**	27.9	**30.8**
CL	9.5	9.5	9.5	9.5
V1	17.5	**60.1**	24.8	27.9
Q	19.9	**74.1**	19.8	25.8
V2	13.0	27.0	11.2	12.6
ω^2_{ka}	20.0	24.3	23.4	23.8
ω^2_{CL}	18.4	18.5	18.5	18.5
ω^2_{V1}	19.2	23.2	22.5	22.8
σ_{inter}	24.1	8.8	12.1	10.1
σ_{slope}	10.4	13.5	12.9	13.0

Table 2: Design influence on parameter estimation (PFIM predictions)

➡ One-stage design Ξ_0 when parameters are different (Ψ^*) shows a loss of efficiency. The 'ideal' two-stage design, with N_1 = N_2 = 30, allows to partly compensate this loss of information

3) Simulation study

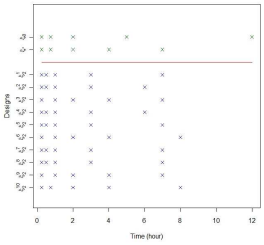

Figure 5: The ten second-stage designs (ξ_2) optimized from the ten estimated Ψ_1

Parameters	First stage (Ψ_1) Relative bias (%)	First stage (Ψ_1) Relative RMSE (%)	Second stage (Ψ_2) Relative bias (%)	Second stage (Ψ_2) Relative RMSE (%)
ka	24.2	**94.0**	1.87	**43.6**
CL	-4.15	9.31	-3.73	6.52
V1	-26.2	**40.9**	-24.1	**32.1**
Q	-3.79	12.2	-2.38	10.0
V2	-1.15	13.3	0.627	9.07
ω^2_{ka}	21.7	**131**	-6.44	**55.0**
ω^2_{CL}	-7.49	18.8	-9.60	16.8
ω^2_{V1}	18.1	49.5	32.6	**66.7**
σ_{inter}	0.420	13.0	0.420	8.90
σ_{slope}	-2.07	14.9	-2.07	10.2

Table 3: Relative bias (%) and RMSE (%) for estimated Ψ_1 and Ψ_2

➡ Seven designs are different and the other are identical. None of them are identical to ξ^* nor ξ_0

➡ Relative bias and RMSE are lower for Ψ_2 than for Ψ_1. The two-stage design improves the estimation

Conclusion

- Two articles in other contexts [12,13] discussed that two-stage designs could be more efficient than fully adaptive designs
- Two-stage designs are a good alternative for designing PK studies in children

- Perspectives

- To study the impact of the two-stage design with the metabolite
- To investigate the choice of the ratio of the sample sizes between the two stages

References

[1] Mentré F, Dubruc C, Thénot JP (2001). *J Pharmacokinet Pharmacodyn*, 28: 299-319.
[2] Tod M, Jullien V, Pons G (2008). *ClinPharmacokinet*, 47: 231-243.
[3] EMEA (2006). Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. *Scientific guideline*.
[4] Mentré F, Mallet A, Baccar D (1997). *Biometrika*, 84: 429-442.
[5] Foo LK, Duffull S (2012). *Pharmaceutical Research*, 29: 1530-1543.
[6] Zamuner S, Di Iorio VL, Nyberg J, Gunn RN , Cunningham VJ, Gomeni R and Hooker AC (2010). *ClinPharmacol & Ther*, 87: 563–571.
[7] Jamei M , Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A (2009). *Expert Opin Drug Metab Toxicol*, 5: 211-223.
[8] Dumont C, Chenel M, Mentré F (2011). *Population Approach Group in Europe*, Abstr 2160 [www.page-meeting.org/?abstract=2160].
[9] Bazzoli C, Retout S, Mentré F (2010). *Comput Methods Programs Biomed*, 98: 55-65.
[10] www.pfim.biostat.fr.
[11] Comets E, Lavenu A, Lavielle M (2011). *Population Approach Group in Europe*, Abstr 1695 [www.page-meeting.org/default.asp?abstract=2173].
[12] Federov V, Wu Y, Zhang R (2012). *Stat Med*, 31: 217-234.
[13] Chen TT (1997). *Stat Med*, 16: 2701-2711.