Optimal design for models with semi-parametric distributions

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Background and Objective

To investigate the influence of semi-parametric parameter distributions on optimal study designs.

Methods

A PK model for moxonidine [1] was originally presented with a normal η-distribution on the absorption rate parameter (ka). However, recently, the same model was found to be improved using a box-cox transformation of the η_{ka}. [2]

We used this example to investigate the feasibility of including such a shape parameter in models implemented in PopED v.2.0 (http://poped.sourceforge.net) for finding an optimal study design. The model was implemented in PopED using both a normal (model 1) and a semi-parametric box-cox-transformation distribution with a shape parameter of 0.769 (model 2). The design setup was adapted from the original study. Seven observations/patient were sampled on one occasion in a parallel design with 3 different doses including 60 patients. D-optimal designs (OD) were found using the FO and FOCE method in PopED. Furthermore, a combined OD was found for both models together using the FOCE method.

Stochastic simulations and estimation (SSE) were performed using NONMEM VI for all three designs to assess the performance of the optimal designs.

Results and Discussion

Figure 1 shows the different optimal sampling times for the models when using the FO or the FOCE method. The choice of approximation method gave different designs for both models.

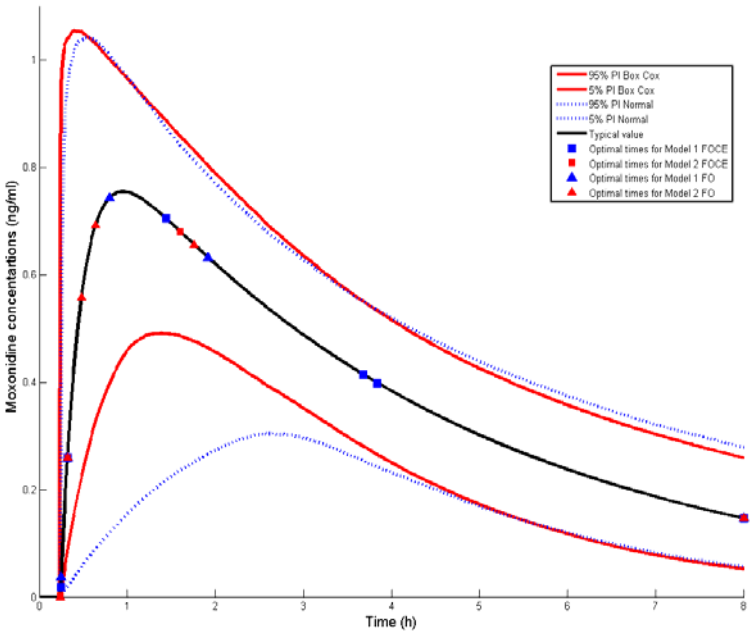

Figure 1. *Optimal designs for a model with a log-normal ka distribution (Model 1: blue) versus a Box-Cox transformed ka distribution (Model 2: red) using the FO (triangles) or the FOCE (squares) method*

The optimal sampling times found were:

	FO	FOCE
Model 1	0.25, 0.32, 0.80, 0.80, 1.92, 8, 8	0.24, 0.32, 1.44, 3.68, 3.84, 8, 8
Model 2	0.24, 0.32, 0.48, 0.64, 1.72, 8, 8	0.24, 0.32, 0.32, 1.60, 1.60, 8, 8
Combined Design (Model 1 & Model 2)		0.24, 0.32, 0.32, 1.60, 3.68, 8, 8

The ODs found under the FOCE method were quite different for the two models. The expected CVs obtained from PopED under FOCE for ka and ω^2_{ka} were smaller under the design for model 1 (Table 1).

		FO		FOCE			
						Combined Design	
	parameter value	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
CL	26.60	3.2%	3.3%	2.9%	3.2%	2.9%	3.1%
V	1.43	3.6%	3.9%	3.1%	3.4%	3.2%	3.3%
ka	4.32	3.7%	3.9%	1.4%	2.6%	1.5%	3.3%
t_lag	0.24	0.11%	0.04%	0.05%	0.00%	0.04%	0.05%
box-cox shape	0.77		1.5E+10		1.0%		2.0%
ω^2 CL	0.04	31.0%	31.5%	31.1%	31.3%	30.7%	29.9%
ω^2 V	0.02	74.8%	89.1%	68.1%	58.6%	61.3%	56.4%
ω^2 ka	2.71	21.0%	1.8E+02	20.9%	22.3%	20.6%	22.6%
RUV prop	0.08	10.8%	11.6%	10.4%	10.4%	10.3%	10.5%

Table I. *Expected CVs obtained from PopED under FO and FOCE for the optimal designs*

The OD for the combination of both models was found to be more similar to the OD for model 2, which is likely due to influential individuals with fast absorption rates. Under this design the expected CVs for all parameters in model 1 and 2 are very similar in comparison. However, again, with a trend to estimate ka and ω^2_{ka} more precise with model 1 (Table 1).

Table 2 shows the results of the SSEs, which confirmed that the most precise estimates for model 1 were obtained under the OD for model 1, followed closely by the combined OD and then under the OD found for model 2. Similarly, the precision of the estimates for model 2 was highest when simulated and estimated under the OD found for model 2, followed by the combined OD and lastly under the OD for model 1.

	Model 1 Design OD			Model 2 Design OD		
	Design OD M1	Combined	Design OD M2	Design OD M2	Combined	Design OD M1
Parameters	RSE (%)			RSE (%)		
CL	3.28%	3.19%	3.71%	3.39%	3.33%	3.21%
V	4.22%	4.69%	5.75%	3.62%	3.71%	3.63%
ka	19.13%	19.10%	22.76%	18.75%	25.13%	26.37%
t_lag	0.13%	2.37%	2.75%	0.00%	0.05%	0.20%
box-cox shape				19.62%	22.74%	22.85%
ω2 CL	23.00%	26.71%	30.39%	22.43%	19.60%	20.78%
ω2 V	61.70%	57.78%	74.42%	44.26%	53.76%	55.23%
ω2 ka	16.57%	17.60%	18.63%	24.89%	27.67%	26.78%
RUV prop	9.62%	11.00%	13.78%	9.47%	8.89%	9.66%
SUM	**137.64%**	**142.43%**	**172.18%**	**146.43%**	**164.89%**	**168.70%**

Table II. *RSE (%) for all estimated parameters in NONMEM (FOCE) after 100 SSEs of model 1 under the optimal design (FOCE) found for model 1, model 2 and the combined design for both models. Similarly, the results after the 100 SSEs of model 2 under the optimal design (FOCE) found for model 1, model 2 and the combined design for both models.*

Conclusion

The choice of the parameter distribution and the approximation method used influences the outcome of the OD and will also influence the possibility of estimating semi-parametric distributions. This could be confirmed with SSEs in NONMEM.

References:

1. Karlsson MO, et al. J Pharmacokinet Biopharm 1998; 26: 207-46.
2. Savic RM. Improved pharmacometric model building techniques. Paper VII Uppsala: Uppsala University, 2008.