Optimal design for models with semi-parametric distributions

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ABSTRACT

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

Methods: A PK model for monoxide[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 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; 7 observations/patient were sampled on one occasion in a parallel design with 3 different doses ($n = 60$ patients). D-optimal designs (OD) were found using the FO and FOCE method in PopED. Furthermore, a combined OD was found for both models. Stochastic simulations and estimation (SSE) were performed using NONMEM VI for all three designs to assess the performance of the optimal designs.

Results: The optimal sampling times for the models were different under the FO and the FOCE method. The choice of approximation method gave different designs for both models.

The ODs found under the FOCE method were quite different for the two models. The sampling times for model 1 were: 0.24, 0.32, 1.44, 3.68, 3.84, 8, 8 and for model 2: 0.24, 0.32, 0.32, 1.6, 1.6, 8, 8. The expected CVs obtained from PopED under FOCE for ka and ?ka were smaller under the design for model 1.

The optimization under FOCE for the combination of both models found the following optimal sampling times: 0.24, 0.32, 0.32, 1.6, 3.68, 8, 8. This design is 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 more precise ka and ω_{ka} with model 1.

The SSEs 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, then the combined OD and last under the OD for model 1.

Conclusions: 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.