Oral

[O27-2] O27-2: Pharmacometrics (2)

Chairs: Fumiyoshi Yamashita, Japan / Toshimi Kimura, Japan
Wed. Sep 27, 2017 11:15 AM - 12:00 PM Room C1 (1F)

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[O27-2-1] Multiple-model optimization of sparse sample phenotyping of drug disposition utilizing population modeling

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Keywords: pharmacokinetic population modeling, multiple-model optimal sampling, phenotyping, drug disposition

Background

The use of probe drugs for *in vivo* phenotyping of drug disposition require extensive sampling over a relatively long time period to properly describe the probes pharmacokinetics (PK). The aim of this study was to develop an optimal sparse sampling strategy for two probe drugs often included in phenotyping cocktails, rosuvastatin (OATP1B1) and digoxin (P-glycoprotein), by utilizing PK population modeling and multiple-model optimization.

Methods

Non-parametric PK population models for digoxin and rosuvastatin were developed in the Pmetrics package for R using 24-hour PK profiles (18 samples per profile) from 38 subjects. The determination of optimally timed samples was based on the multiple model optimal sampling (MMopt) algorithm included in Pmetrics, weighted for AUC and limited to a sampling time between 0 to 6 hours after dose administration. AUC_{0-24} estimates were obtained from different MMopt-strategies (2-, 3- and 4 samples) and from the full 18-sample data sets based on the population models as well as from non-compartmental analyses (NCA).

Results

Digoxin: The median (IQR) AUC_{0-24} estimated from the full data set (18-sample) was 101% (99 to 103%) of the NCA AUC_{0-24}. Optimal sampling strategies using either 2-, 3- or 4 samples estimated AUC_{0-24} well. In the 3-sample strategy the median (IQR) AUC_{0-24} estimate was 100% (87 to 113%) of the model estimated AUC_{0-24} using the full data set.
Rosuvastatin: The population model slightly underestimated AUC_{0-24} compared to NCA; AUC_{0-24} was 94% (90 to 98%) of the AUC_{0-24} from NCA. The AUC_{0-24} estimated from the 4-sample strategy was in best agreement with the estimate from the full data set, showing AUC_{0-24} of 95% (81 to 105%)

Conclusions

For both digoxin and rosuvastatin, AUC_{0-24} estimates obtained from sparse sampling in a limited sampling interval, adapted to what is easily implementable in a research setting (6 hour investigation), were in good agreement with full data-based $AUC_{0-24.}$ Model-based optimal design strategies can be employed to perform cocktail phenotyping studies more efficiently and less costly.