A comparison of relative exposure estimates from single trough, multiple trough, and full population PK sampling designs

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Introduction/Objectives

In clinical studies it is often of interest to estimate how drug exposure changes with patient characteristics. Pharmacokinetic (PK) exposure information can be obtained using single trough, multiple trough, or full population PK sampling designs [1]. The last design is considered the most informative one but requires patients to stay at the site for the duration of the sampling. Collecting trough samples only is often preferred in practice. It is therefore of interest to study if estimates of relative exposure derived from single trough, multiple trough, and full population PK sampling designs are comparable.

Methods

Exposure metrics

The three different sampling designs require different exposure metrics and data analysis models. In trough sampling designs the ratio of steady state trough samples (C_{min}) is used to describe the exposure of a patient with certain covariate characteristics relative to a reference patient. For full population PK sampling designs the most commonly used exposure metric is the ratio of the Areas Under the Curve (AUCs). Data from single trough designs are typically analysed with a linear model while linear and nonlinear mixed effect models are employed for the repeated trough and full population PK design, respectively.

PK model

We performed a simulation study to compare estimates of relative exposure from the different sampling designs. The PK model was assumed to be a one compartment model with CL=0.58 L/h, V=10 L, ka=0.2 1/h, Dose=100, tau=12 h. Note that the half-life of the drug ($t_{1/2}$=12 h) matches the dosing interval (tau). We used exponential between subject and residual error models with standard deviations of $\omega_{CL} = \omega_V = 0.3$, $\sigma_{Res} = 0.2$.

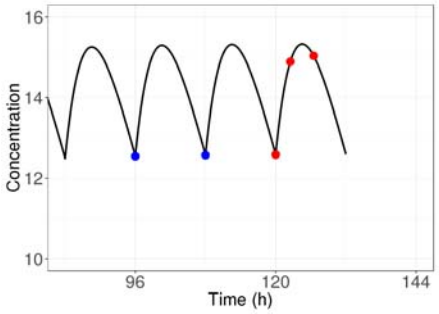
Covariate Model

We looked at two different covariate models. Covariate Model 1 was an allometric scaling model in which weight affects apparent clearance and volume of distribution according to $CL_i = CL \cdot (WGT_i/70)^{0.75}$ and $V_i = V \cdot (WGT_i/70)^1$. Weight was normally distributed WGT~N(70,15^2). We want to estimate the exposure of a 120 kg subject relative to 70 kg. Covariate Model 2 described an effect of Globular Filtration Rate (GFR) on apparent clearance, $CL_i = CL \cdot (GFR_i/90)^{0.5}$, where GFR was uniformly distributed U(30, 120). We want to estimate the exposure of a subject with GFR=45 mL/min/SA (moderate renal impairment) relative to a subject with GFR=90 mL/min/SA (normal renal function).

Simulation Design

We simulated 500 studies with 100 subjects each. For the single and multiple trough designs we generated 1 and 3 steady state samples. For the full population PK design we simulated 3 samples at steady state pre-dose, 2.5 h, and 6.5 h. This sampling scheme was defined by fixing one sample at pre-dose and optimizing the times for the other two samples with PopED 0.3.2 [2], not taking into account covariates. For each simulated study we estimated the relative exposure using a linear model for the single trough design ($\log C_{min,i} = a+b \cdot \log WGT_i+\varepsilon_i$), a linear mixed model with a random effect u_i at subject level for the multiple trough design ($\log C_{min,ij} = a+b \cdot \log WGT_i+u_i+\varepsilon_{ij}$), and a nonlinear mixed effect model implemented in Monolix 2018R1 [3].

Figure 1 Structural PK model and sampling times for serial (red dots) and trough samples (blue dots and first red dot)



Results

In Covariate Model 1 (Table 1), the relative exposure of a subject with 120 kg relative to a 70 kg subject was estimated. The mean estimates over the n=500 simulated studies were 0.68, 0.68, and 0.67 for the single trough, multiple trough, and full population PK sampling design. Relative standard errors (RSEs) were 7.5%, 6.8%, and 6.4%.

Table 1 Estimates of relative exposure 120 kg vs 70 kg (Covariate Model 1)

Design	Exposure metric	True value of exposure metric	Mean (%RSE)* 90% Confidence Interval
Single Trough	Cmin Ratio	0.68	0.68 (7.5%) (0.60, 0.76)
Multiple Trough	Cmin Ratio	0.68	0.68 (6.8%) (0.61, 0.75)
Full PopPK	AUC Ratio	0.67	0.67 (6.4%) (0.60, 0.74)

*) Summary statistics for n=500 simulated estimates of relative exposure, RSE = Relative Standard Error

In Covariate Model 2, the exposure of a subject with GFR=45 mL/min/SA (moderate renal impairment) relative to a subject with GFR=90 mL/min/SA (normal renal function) was estimated. The mean estimates over the n=500 simulated studies were 1.44, 1.45, and 1.45 for the single trough, multiple trough, and full population PK sampling design. Relative standard errors were 5.9%, 5.7%, and 7.0%.

Table 2 Estimates of relative exposure of subject with Globular Filtration Rate GFR=45 mL/min/SA (moderate renal impairment) relative to a subject with GFR=90 mL/min/SA (normal renal function) (Covariate Model 2)

Design	Exposure metric	True value of exposure metric	Mean (%RSE)* 90% Confidence Interval
Single Trough	Cmin Ratio	1.47	1.44 (5.9%) (1.31, 1.58)
Multiple Trough	Cmin Ratio	1.47	1.45 (5.7%) (1.33, 1.59)
Full PopPK	AUC Ratio	1.41	1.45 (7.0%) (1.31, 1.65)

*) Summary statistics for n=500 simulated estimates of relative exposure, RSE = Relative Standard Error

Conclusions:

In the scenarios studied in our simulations the estimates of relative exposure generated from the different sampling designs were comparable in terms of location and precision. Single trough designs are not encouraged by FDA [1]. If the objective of a PK study is to estimate relative exposure then our results indicate that multiple trough designs can be a valid alternative to full population PK designs. However, our findings may not generalize to situations where the dosing interval of a drug is substantially longer than its half-life or more complex (e.g. nonlinear) models are required to describe the kinetics of the drug.

References

1. FDA. Guidance for Industry, Population Pharmacokinetics. 1999. https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf
2. Nyberg J et al. Comput Methods Programs Biomed, 108: 789-895, 2012.
3. Monolix 2018R1, user guide. http://monolix.lixoft.com/single-page/

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