INFLUENCE OF ESTIMATION OF INTER-OCCASION VARIABILITY ON DETECTION OF TIME-VARYING COVARIATES

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ABSTRACT

Purpose To explore the influence of the estimation of inter-occasion variability (IOV) on the ability to detect time-varying covariates influencing PK parameters from a population PK (PPK) analysis using NONMEM.

Methods Based on a published PPK model developed using data from a phase III clinical trial of a drug which exhibits enzyme auto-induction, 10 replicated clinical trial data sets, each consisting of 430 patients and 18 measurements per patient following repeated oral dosing over 9 weeks were generated using stochastic simulation. The PPK model is a one-compartment model with first-order absorption and elimination, with clearance expressed as a function of time (to characterize the induction process) and body weight, and volume expressed as a function of body weight. IOV was introduced on clearance at a moderate level relative to IIV (IOV CV%/IIV CV%: 0.83). The simulation model was fitted to the simulated data sets using two different approaches: estimating or ignoring IOV in clearance. Backward elimination of covariate effects was then performed on each dataset. The final models achieved from the different approaches were compared with respect to the bias and precision of the parameter estimates. The detection of the time-varying covariate was judged by its statistical significance during backward elimination.

Results Except parameters associated with volume, bias of fixed effect parameters from the analyses estimating IOV was generally improved over the analyses where IOV was ignored by up to 1 % decrease in mean percentage error (-0.7 ~ 6.1% versus -1.6 ~7.2%). As expected, precision of random effect parameters in IOV models was improved compared to models ignoring IOV by up to 7% decrease in mean absolute percentage error (4.8 ~11.3% versus 9.6 ~17.9%). The time-varying covariate, time on therapy, was a statistically significant predictor (P < 0.0001) in all datasets regardless of whether IOV was included.

Conclusions As expected, incorporation of IOV generally warrants better estimation of parameters in the cases studied here. In addition, in the presence of IOV with a moderate magnitude relative to IIV, the estimation of IOV does not preclude the ability to detect a time-varying covariate.

INTRODUCTION

- For a time-dependent kinetics, the time-dependent variability in pharmacokinetic (PK) parameters may be separated into two parts: systemic changes due to some physiological processes such as age (in neonates) or enzyme auto-induction and non-systemic random fluctuations across sampling occasions which is not predictable for individuals.
- Time-varying covariates means that the covariates change over time. The magnitude or the frequency of systemic changes in time-varying covariates can properly account for the variation in population pharmacokinetic (PPK) or pharmacodynamic (PD) modeling. If properly included in the PPK-PD model, time-varying covariates may provide more valuable information than time-constant covariates.[1]
- Variability in PPK may be divided into inter-individual variability (IIV) and residual variability (RV). As part of RV, inter-occasion variability (IOV) also known as between occasion variability includes the variability in the PK parameters within an individual between occasions. Neglecting such inter-occasion variability may cause significant bias in any of the fixed-effect population parameter estimates.[2]
- To model time-dependent PK, we can either find time-varying covariates that explain the variation in PK and incorporate the time-varying covariates in the fixed effect model; or use IOV as "a fudge factor" to account for the variation in PK by explicitly modeling it in the random effect model. The concern is whether the model would still be able to discern the variation caused by time-varying covariates from natural variability (noise) when IOV is explicitly incorporated in the model.
- In this study, modafinil, a drug which exhibits enzyme auto-induction, for which duration of treatment is modeled as a time-varying covariate of clearance in population PK analysis, is used as a model drug.[3] The effect of IOV estimation on the ability to detect duration of treatment as a time-varying covariate were examined using stochastic clinical trial simulation based on realistic random error (IIV, IOV and RV) distributions.

METHODS

Creation of Virtual Objects

- 430 virtual patients were created. Covariates for these patients, such as body weight, gender, age, BMI, were randomly sampled from demographic data of real phase III studies using re-sampling techniques. Correlated covariates, such as, age and weight, BMI and weight, were sampled together to maintain the correlation.

Dosing Regimen

- Patients were orally administered study drug during a 9-week study. The dose started at 85 mg/day and then titrated up to 340 mg/day for patients weighing less than 30 kg or 425 mg/day for patients weighing at least 30 kg.

Pharmacokinetic Sample collection

- Sparse samples were collected at 1, 2.5, and 9 hours after dosing at weeks 1, 2, 3, 5, 7, and 9. Protocol deviations on measurement times were simulated using normal distribution model with a standard deviations of 0.25, 0.25, and 0.8 hours for the 1, 2.5, and 9-hour samples, respectively.
- Implementation of the covariate distribution model and the trial execution model (models accounting for the nominal trial protocol and deviations) were performed using standard statistical software, SAS®, version 8.2.

Simulation of Concentration-time Profiles

- Simulated datasets were generated from a 1-compartment model with first-order absorption and elimination including an empirical model for clearance that accounts for the auto-induction using the computer package NONMEM®, Version 5.1.1. The simulation model was described by equation 1 through 10 as below.

Structural model		Random effect model	
$C(t)=\frac{D\cdot ka}{V(ka-\frac{CL}{V})_i}\left[\exp(-\frac{CL}{V}t)-\exp(-ka\cdot t)\right]$	(1)	$ka_j = TVka_j$	(7)
$TVka_j = 1.35$	(2)	$CL_{jk} = TVCL_j \cdot e^{\eta_{cl,j}+\kappa jk}$, $\eta_{cl,j} \sim N(0, 0.0276)$, $\kappa_{jk} \sim N(0, 0.019)$	(8)
$CL_{ij} = 2.79 \cdot (WT_j/39)^{0.410}$	(3)	$V_j = TVV_j \cdot e^{\eta v,j}$, $\eta_{v,j} \sim N(0, 0.087)$	(9)
$CL_{pj} = 1.35 \cdot (WT_j/39)^{0.751}$	(4)	$C_{ij,\,obs} = C_{ij,\,pred} \bullet (1 + \varepsilon_{ij})$, $\varepsilon_{ij} \sim N(0, 0.114)$	(10)
$TVCL_j = CL_{ij} - (CL_{ij} - CL_{pj}) \cdot e^{0.052 \cdot Time}$	(5)		
$TVV_j = 28.8 + 0.747 \cdot (WT_j - 39)$	(6)		

Where:
CL_{ij} = the maximum value of induced CL (L/hr) for the j^{th} patient;
CL_{pj} = the pre-induced CL (L/hr) for the j^{th} patient;
TVX_j = the typical value of the X parameter for the j^{th} patient;
WT_j = the body weight (kg) of the j^{th} patient;
Time = time on therapy (days).

Population Pharmacokinetic Analysis

- For each simulated data set, we estimated the population pharmacokinetic parameters with the first order conditional estimation method (FOCE) method of NONMEM, using the same population structural model as for the simulation (see equations 2 – 6) and two different random effects model, including IOV or not including IOV (see equations 7 – 10). For the model not including IOV, κ_{jk} was removed from equation 8.

Covariate Analysis

- The potential influence of body weight and time on therapy on apparent oral clearance (CL/F) and volume of distribution (V/F) of modafinil was evaluated.
- Univariate forward selection analyses were performed, followed by stepwise backward elimination.

Statistical Analysis

- Statistical significance: univariate forward-selection, P *value* < 0.01, backward elimination, P *value* < 0.001
- Goodness-of fit of each NONMEM® analysis was assessed by examination of precision of the parameter estimates as measured by the percent standard error of the mean (%SEM = standard error of the parameter estimate/parameter estimate · 100%)
- Bias and precision of parameter estimates were measured as mean percentage error (MPE) and mean absolute percentage error (MAPE) about the percent prediction error for parameter (PE).[1]

RESULTS

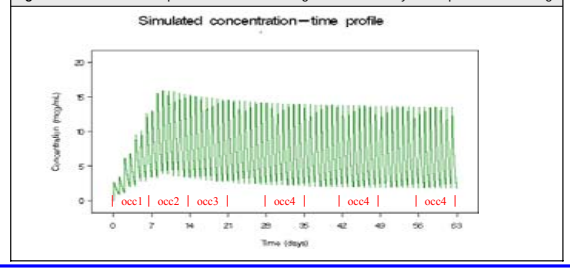
- In total, 10 replicate data sets were simulated using the selected level of IOV (IIV/IOV=1.2) in drug clearance. For each of the 10 data sets, plasma samples (approximately 3 samples per patient per visit) were simulated for 430 patients.

Table 1. Summary statistics of body weight for the virtual patients and real patients

Body Weight (kg)	Population of virtual patients (n = 430)	Population of real patients (n = 405)
Mean (SD)	42.1 (16.0)	41.9 (16.4)
Median	39.0	38.6
Range (Minimum - Maximum)	19.5 - 85.0	18.6 - 98.4

- The concentrations of modafinil were computed using the typical values of pharmacokinetic parameters in the simulation (errorless data). The whole study period was divided into 4 occasions. Occasion 1, 2, 3, and 4, is represented by occ1, occ2, occ3, and occ4.

Figure 1. Pharmacokinetic profile of modafinil during the 9-week study with repeated oral dosing



RESULTS

- In the subsequent backward elimination analyses, the effects of body weight on clearance and volume, and duration of treatment on clearance remained significant (Table 2).

Table 2. Summary of backward elimination results

Model	Parameter	Covariate	ΔOBJF [a] (mean±SD)	Δdf [b]	p-value
IIV[c]	CL	Body Weight	1025 ± 44.3	2	< 0.0001
	CL	Time on Therapy	560.6 ± 38.9	3	< 0.0001
	V	Body Weight	457.2 ± 69.0	1	< 0.0001
IOV[d]	CL	Body Weight	631.9 ± 38.9	2	< 0.0001
	CL	Time on Therapy	563.3 ± 59.8	3	< 0.0001
	V	Body Weight	419.3 ± 65.2	1	< 0.0001

Annotation
[a] Increase in the objective function in comparison to the full model.
[b] Differences in degrees of freedom between reduced and full model.
[c] Only IIV was modeled for clearance.
[d] Both IIV and IOV were modeled for clearance.

- Precision of random effect parameters in IOV models was improved compared to models ignoring IOV by up to 7% decrease in mean absolute percentage error (4.8 ~11.3% versus 9.6 ~17.9%). (Figure 2 and 3)
- Except parameters associated with volume, bias of fixed effect parameters from the analyses estimating IOV was generally improved over the analyses where IOV was ignored by up to 1 % decrease in mean percentage error (-0.7 ~ 6.1% versus -1.6 ~7.2%). (Figure 4 and 5)

Figure 2. Precision of the estimated fixed effect model parameters

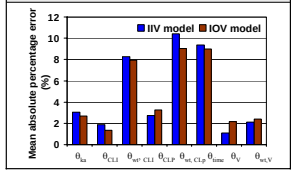


Figure 3. Precision of the estimated random effect model parameters

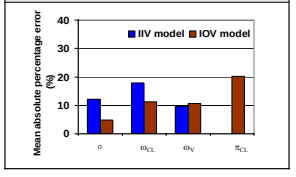


Figure 4. Bias of the estimated fixed effect model parameters

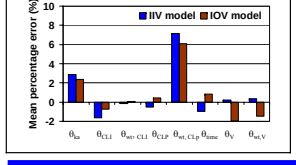
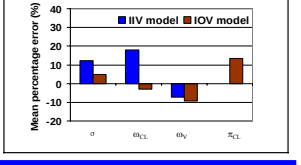


Figure 5. Bias of the estimated random effect model parameters



CONCLUSIONS

- Incorporation of IOV generally warrants better estimation of parameters in the cases studied here.
- In the presence of IOV with a moderate magnitude relative to IIV, the estimation of IOV does not preclude the ability to detect a time-varying covariate.

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ACKNOWLEDGEMENTS

- We gratefully acknowledge Dr. William Jusko and D. Wojciech Krzyzanski for their insightful comments.
- We also thank Mona Darwish, Joel Owen, and the Cognigen project team for developing the model.