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ORIGINAL ARTICLE

Assessment of statistical power for covariate effects in data from phase I clinical trials

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One of the important purposes in population pharmacokinetic studies is to investigate the relationships between parameters and covariates to describe parameter variability. The purpose of this study is to evaluate the model's ability to correctly detect the parameter-covariate relationship that can be observed in phase I clinical trials. Data were simulated from a two-compartment model with zero-order absorption and first-order elimination, which was built from valsartan's concentration data collected from a previously conducted study. With creatinine clearance (CLCR) being used as a covariate to be tested, 3 different significance levels of $0.001<P\leq0.01$, $0.0001<P\leq0.001$, $P<0.0001$ were chosen and 100 simulated datasets were generated using bootstrap resampling for each significance level. Then, the model with covariate (= simulation model) and the model without covariate were alternatively fit to each simulated dataset to compute ΔOFV. The power of correctly estimating CL-CLCR significance was computed as the percentage of simulated datasets using the following 3 decision criteria: ΔOFV larger than 3.84 ($P<0.05$), 6.64 ($P<0.01$), and 10.8 ($P<0.001$). When the significance level was $0.001<P<0.01$, the power becomes 81.6%, 60.2% and 34.7% for 3 decision criteria, respectively, yielding the expected model rejection ratio of higher than about 20% when the covariate that might be present in data was marginally significant. Although this work was carried out based on the data obtained from one particular clinical trial, we hope that this work can provide an insight into covariate selectivity associated with healthy volunteer data.

Introduction

One of the important objectives in population pharmacokinetic (PK) studies is to find and evaluate the relationships between parameters and covariates to characterize parameter variability in individuals.[1] For this reason, when a new drug is developed, PK data are collected from subjects participating in clinical trials and analyzed to obtain PK characteristics of the drug, including parameter-covariate relationships.

However, most of the drugs currently used in Korea are those developed by foreign drug companies, reflecting PK characteristics of foreign population only. Except for the drugs whose PK characteristics are newly obtained from separate clinical studies conducted in Koreans, many drugs currently have a shortage of PK information in the Korean populations, including the information on PK variability and covariates.

Despite such limitation with PK information in Koreans, the number of early phase clinical trials conducted in Korea has been increasing, leading to 192 Phase I clinical trials in 2014 approved by Ministry of Food and Drug Safety (MFDS) of Korea. This increase is partly due to the growth in R&D investment driven by the development of incrementally modified drugs by local pharmaceutical companies.[2] This statistics indicates, if PK data obtained from these Phase I clinical trials are properly used, it would be possible to gather the information on PK characteristics in the Korean population, although the information so-obtained would be limited in that Phase I trials are conducted in healthy volunteers.

The purpose of this study is to evaluate the model's ability to correctly detect the parameter-covariate relationship, using data simulated from a population PK model constructed from phase I clinical trials conducted in healthy Koreans.

Methods

Data were simulated from a two-compartment model with zero-order absorption and first-order elimination, which was newly developed for this work from valsartan's concentration data collected from a previously conducted PK study,[3] with creatinine clearance being used as a covariate to be tested. Figure 1 shows the concentration-time data profile for valsartan. In that study where 48 healthy volunteers participated, 14 PK samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours after dosing from each individual. The obtained PK model was formulated as below, where WT was in Kg and CLCR in mL/min:

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CL/F = THETA(1)*(WT/70)**0.75*(CLCR/125.5)
       **THETA(6)*EXP(ETA(1)) (L/h)
V1/F = THETA(2)*(WT/70)*EXP(ETA(2)) (L)
D1 = THETA(3) (h)                                   (1)
Q/F = THETA(4)*(WT/70)**0.75 (L/h)
V2/F = THETA(5)*(WT/70) (L/h)
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In the above equation, [THETA(1),…,THETA(6), ω^2_{11}, ω^2_{22}, ω^2_{12}] were estimated to be [6.18, 25.9, 4.39, 2.01, 17.4, 0.793, 0.139, 0.269, 0.094] and 125.5 denotes the mean value of CLCR. Here, [ω^2_{11}, ω^2_{22}] = [0.139, 0.269] corresponds to [37.3, 51.9] in CV (%) and ω^2_{12} = 0.094 corresponds to ρ_{12} = 0.49. In this particular example, it was found that among parameter-covariate pairs tested, only CL-CLCR pair significantly influenced the PK of valsartan.

Then to explore the model's power or probability to correctly detect the influence of CL-CLCR which was initially assumed to be significant in the simulation model in Eq (1) when the other model parameters were fixed at the estimates reported above, 3 values of THETA(6) were chosen to impose 3 different significance levels as follows: (1) 0.001<P≤0.01, (2) 0.0001<P≤ 0.001, (3) P<0.0001, where P was CL-CLCR significance level based on Chi-square distribution for ΔOFV between the model incorporating THETA(6) (called "full model" hereafter) and the model not incorporating THETA(6) (called "reduced model" hereafter). In detail, a set of different values of THETA(6) were generated and, for each THETA(6) value, the corresponding full model (i.e., the model with THETA(6) set to the value generated) and reduced model (i.e., the model with THETA(6) set to 0) were fitted to the original dataset to compute the ΔOFV and associated P value. Among P values thus obtained, three values of THETA(6) that yield P values falling in each of 3 significance levels defined above (0.001<P≤0.01, 0.0001<P≤0.001 and P<0.0001) were manually chosen as reported in the Results section.

After THETA(6) was chosen, for each of significance levels (1)-(3), a simulated dataset was generated through bootstrap resampling from the PK model of valsartan using the same parameter values and the same experimental design as described above (i.e., the number of subjects of 48, consisting of the same demographic distributions of WT and CLCR, and the same blood sampling times). This simulation scheme was adopted to closely mimic the characteristics of study design and subjects' demographics distribution typically seen in a healthy volunteer study. Then, the simulated dataset was fit to both full and reduced models to compute ΔOFV. This process was repeated 100 times by generating 100 different simulated datasets. The power or the probability of correctly estimating CL-CLCR significance was computed as the percentage of simulated datasets using the following 3 decision criteria: ΔOFV larger than 3.84 (P<0.05), 6.64 (P<0.01), and 10.8 (P<0.001)

The simulation-estimation procedure was conducted using the stochastic simulation and estimation (SSE) method implemented in PsN version 4.2.0[4,5] and NONMEM version 7.3.0.[6] The first-order conditional estimation with interaction method (FOCE INTERACTION) in NONMEM was used to estimate the model parameters.

Results

Table 1 shows demographic characteristics of subjects who participated in the PK study of valsartan and Figure 1 shows the resulting concentration profile. THETA(6) that satisfied 3 different significance levels of CL-CLCR pre-selected in the simulation model were chosen to be 0.793, 1.12 and 1.19 with

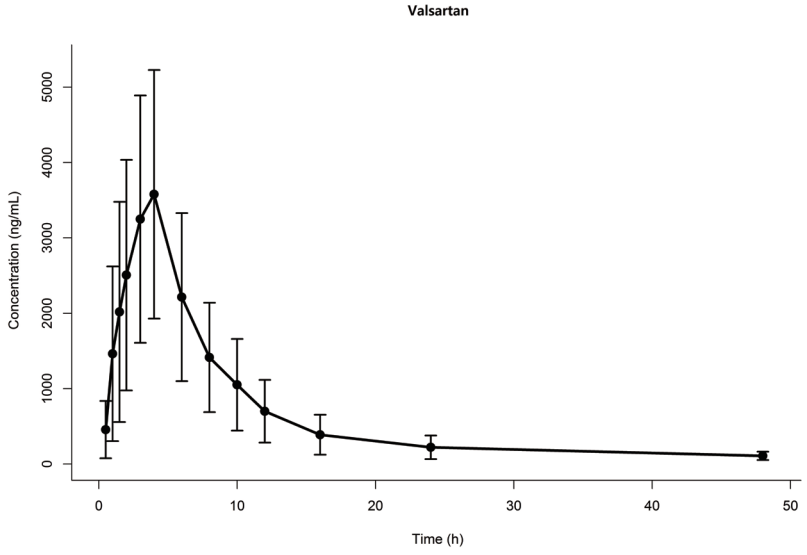

Figure 1. Observed concentration vs time for drug X. Dots and error bars represent mean and standard deviation at each time point.

Table 1. Demographic characteristics of the study subjects

Characteristics	Subjects (n = 48)
Age, y	
Mean (SD)	26.8 (6)
Range	20-45
Weight, kg	
Mean (SD)	68.7 (7.7)
Range	53.5-85
Height, cm	
Mean (SD)	174.3 (4.9)
Range	163.6-185.2
Smoking, no. (%)	
Smoker	20 (42)
Nonsmoker	28 (58)
Creatinine clearance (mL/min)	
Mean(SD)	125.5 (21.1)
Range	78.3-169.7
Alcohol drinking, no. (%)	
Drinker	31 (65)
Nondrinker	17 (35)
Caffeine user, no. (%)	
Yes	21 (44)
No	27 (56)

corresponding P- values of 0.0048, 0.00047 and $3.86*10^{-6}$, respectively.

Table 2 lists the resulting power of the estimation model computed at selected decision criteria for each case. The table shows that at the significance level of $0.001<p<0.01$, the power becomes 81.6%, 60.2% and 34.7% for 3 decision criteria, respectively, yielding the expected model rejection ratio of higher than about 20% when the covariate that might be present in the data is marginally significant.

Discussion

This report investigated a NONMEM-based, model's ability to identify the significance of a covariate for the population data obtained from a healthy volunteer PK study. To do so, taking CL-CLCR as an example, 3 different levels of covariate significance were tested, along with 3 different levels of decision criteria. As expected, the lower the significance level of CL-CLCR was in the simulation model, the less it was selected by the estimation model. Only when the covariance significance was very strong, the model rejection ratio did not exceed 10% at all decision criterion levels. This finding indicates that in healthy volunteer studies it would be difficult to correctly detect the covariate significance through model building unless the significance level of the covariate is substantial. In this work, we tried to identify the power of selecting a covariate using the study design and subject demographics typically seen in phase I study to preserve relevance to real data and the simulated data used were generated accordingly.

Covariate selection bias of the full model has been reported previously. Ribbing et al. studied the covariate effect in PK models from the aspect of power, selection bias and predictive performance. In the study, they analyzed the effect of competing covariates, the influence of variation of covariate coefficients and the number of subjects. They concluded that the small dataset with a weak covariate effect could lead to a very high selection bias, thus making the proposed full model useless.[7]

In contrast to previous works such as the one cited above, which usually relate to the patient data, most of phase I studies in Korea are conducted for developing incrementally modified drugs, recruiting a fixed number of healthy volunteers based on the bioequivalence criterion required by MFDS i.e., Type I error 5%, Type II error 20%, and the equivalence margin 20%. As a result, enrolled subjects become less heterogeneous in covariate distributions as compared with patients group, leading to a limitation in adequately finding the significance of covariate effects.

This work was carried out based on the data obtained from one particular clinical trial and more study will be needed to generalize the result. Nevertheless, we hope that this work can provide an insight into the covariate selectivity associated with healthy volunteer data. Although not covered in this work, Type I or alpha error in a model's covariate selectivity can be similarly explored.

Table 2. Power for detecting the significant effect of CL-CLCR at different significance levels used in simulations and model decision

	Significance level used in model decision		
Significance level used in simulation (P value used)	ΔOFV<3.84 (p<0.05)	ΔOFV<6.64 (p<0.01)	ΔOFV<10.8 (p<0.001)
$0.001<p\leq0.01$ (0.0048)	81.6%	60.2%	34.7%
$0.0001<p\leq0.001$ (0.00047)	94.9%	81.8%	56.6%
$p\leq0.0001$ ($3.86x10^{-6}$)	98.0%	96.9%	89.8%

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Conflict of Interest

All the authors declare no conflict of interest.

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