Design and Power of A Population Pharmacokinetic Study

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Purpose. This paper investigated the influence of critical design factors on the power of a population pharmacokinetic (PK) study for identifying subpopulations that have different drug clearance than the typical population.

Methods. A study simulation approach was used for the power estimation. The design factors included the number of subjects, sampling scheme, and compliance.

Results. The false positive rates of incorrectly identifying a subpopulation were estimated for several scenarios. The false positive rates of the population PK study was relatively low, except when the numbers of subjects with full profiles and the subjects with troughs were distributed between populations in an unbalanced manner. The total number of subjects did not seem to have as much influence on study power as the number of subjects in the subpopulation, as long as the total number of subjects was significantly larger than the subpopulation. The variability of sampling time played an important role in both the statistical power and the accuracy of the estimated difference in clearance. Taking three samples provided greater power and better accuracy than taking two samples per subject. Taking only trough samples provided little power and poor estimation of clearance difference. Adding subjects with full profiles to a study with only trough samples taken in other subjects did not satisfactorily improve the clearance estimation. It was critical to account for dosing record in the population PK analysis to achieve appropriate power and accuracy. If the variability in dosing time was accounted for in the analysis, it improved the accuracy of the estimated difference in clearance. Missing dose administrations reduced the study power and resulted in deviation of estimated clearance difference.

Conclusions. The power of a study should be determined prospectively to ensure appropriate study design for specific study objectives.

KEY WORDS: Population pharmacokinetics; study power; study simulation.

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ABBREVIATIONS: $(1-\beta_1)$, the study power with the likelihood ratio test at $p = 0.01$ level; $(1-\beta_2)$, the study power with the t-test on Cl_{slope} at $p = 0.01$ level; $(1-\beta_3)$, the study power with the likelihood ratio test at $p = 0.001$ level; $\eta_{cl,I}$, the intersubject variability of Cl for subject i; ε_{ij}, the intrasubject variability of subject i at measurement j; $\eta_{ka,I}$, the intersubject variability of Ka for subject i; $\eta_{v,i}$, the intersubject variability of V for subject i; C_{ij}, the plasma concentration of subject i at measurement j; Cl, the population mean values of clearance; Cl_0, the Cl of the typical population; Cl_i, the clearance of subject I; Cl_{slope}, the difference in Cl between the sub- and typical populations; D, the dose; G, 0 for the typical population, and 1 for the subpopulation; Ka, the population mean values of absorption rate constant; Ka_i, the absorption rate constant of subject I; V, the population mean values of volume of distribution; V_i, the volume of distribution of subject i.

INTRODUCTION

In an FDA internal survey on New Drug Application (NDAs) and Supplementary New Drug Application (SNDAs) submitted from 1994 to 1997, 37 out of 315 submissions contain population pharmacokinetics data (sparse samples). In a more recent survey of full NDAs submitted in the first quarter of 2000, 4 out of 11 contain population analyses. One of the main applications of population pharmacokinetic studies is to identify intrinsic and extrinsic factors that may influence the pharmacokinetics of drugs. The factors commonly investigated in population studies include gender, race, age, body weight, disease state, renal function, hepatic function, and drug–drug interaction. Most of the time, the pharmacokinetic parameter of interest is the clearance of drug.

Many study design factors may influence the outcomes of the population pharmacokinetics studies and their interpretations. Several recent articles discuss the important study design factors in population pharmacokinetic studies. Among the factors that have been examined in the literature are sampling strategy (1), intersubject variability (2), number of observations (3), sampling time recording (4), and study compliance (5). These articles are focused on the accuracy and precision of the parameter estimation. With regard to the power of the population PK study, two methods for testing hypotheses of comparing populations have been evaluated (6).

This article investigated the critical design factors that may influence the power of population pharmacokinetic studies for identifying subpopulations with clearance different from the typical population. These design factors included the number of subjects (in total and sub-population), sampling scheme (number of samples, nominal sampling time, fixed or variable sampling time, variability of actual sampling time, and inclusion of full profiles), and compliance (the variability of dosing time, whether the variability was recorded and accounted for in the analysis, consistent dosing pattern, missing doses, and whether the missing doses were recorded and accounted for in the analysis). The false positive rates of incorrectly identifying a subpopulation were also estimated for several scenarios. Finally, the influence of the difference in clearance between populations on the study power was investigated. A study simulation method was used to estimate the power of different study design.

METHODS

Study Design

The basic design of the population pharmacokinetic study in this investigation was a multiple-dose study (q12 hr till steady state) with the total number of subject varying from 100 to 200. The number of subjects in the subpopulation varied from 10 to 50. The number of pharmacokinetic samples varied from 2 to 3 per subject in combination with or without full profiles in some subjects. The sparse samples were taken at 1 hr, 5 hr, and/or 11.5 hr postdose, and the full profile samples were taken at 1, 3, 5, 8, and 11.5 hr. The dosing time and pharmacokinetic sampling time may vary from subject to subject and between days.

Pharmacokinetic Model

The pharmacokinetics were assumed to follow the one-compartment open model with first-order absorption and

elimination rate. The plasma concentration–time profiles were described by the following equation:

$$C_{ij} = \frac{D \cdot Ka_i}{V_i(Ka_i - Cl_i/V_i)} (e^{-Cl_i/V_i \cdot t} - e^{-ka_i \cdot t}) + \varepsilon_{ij} \quad (1)$$

where C_{ij} was the plasma concentration of subject i at measurement j, D was the dose, Ka_i was the absorption rate constant of subject i, Cl_i was the clearance of subject i, V_i was the volume of distribution of subject i, and ε_{ij} was the intrasubject variability of subject i at measurement j. The variability of the three parameters were expressed in the following equations:

$$Ka_i = Ka(1 + \eta_{ka,i}) \quad (2)$$
$$Cl_i = Cl(1 + \eta_{cl,i}) \quad (3)$$
$$V_i = V(1 + \eta_{v,i}) \quad (4)$$

where Ka, Cl, and V were the population mean values of absorption rate constant, clearance, and volume of distribution, respectively, and $\eta_{ka,i}$, $\eta_{cl,i}$, and $\eta_{v,i}$ were the intersubject variability of the corresponding parameters for subject i. All the inter- and intrasubject variability was assumed to be log-normal distributions. When the clearance changed in a subpopulation, the following equation was used to describe the population mean clearance as a function of subgroup:

$$Cl = Cl_0 + Cl_{slope} \cdot G \quad (5)$$

where $G = 0$ for the typical population, and $G = 1$ for the subpopulation.

Power Estimation

The objective of this article is to investigate various factors that may influence the power of a population pharmacokinetic study for identifying any subpopulation with a different clearance than the typical population. Therefore, the null hypothesis is:

$$\text{Ho: } Cl_{slope} = 0 \quad (6)$$

The alternative hypothesis is $Cl_{slope} = 3$ in most of the scenarios investigated here. This reflects a 30% increase in clearance in the subpopulation, since the value of Cl_0 in the simulation was 10. The significance of Cl_{slope} is tested by fitting two models to the pharmacokinetic data: Model 1 is represented by Equations 1–4 and Model 2 is represented by Equations 1–5. The values of Cl_{slope} are considered different from 0 by (1) the likelihood ratio test between the two models, or (2) the t-test on Cl_{slope} in Model 2. The power of a population pharmacokinetic study is estimated based on three tests: the likelihood ratio test at $p = 0.01$ level ($1-\beta_1$), the t-test on Cl_{slope} at $p = 0.01$ level ($1-\beta_2$), and the likelihood ratio test at $p = 0.001$ level ($1-\beta_3$). The procedure of power estimation is described in the next section.

Study Simulation Process

The study simulation used for the power estimation in this investigation involved two main steps: simulating the pharmacokinetics data based on study, and fitting a population PK model to the simulated data.

Simulation

The basic pharmacokinetic model used to simulate the data was described by Equations 1–5. In addition, the following study design factors were also accounted for: the number of subjects, number of samples, nominal sampling time, whether the sampling time was fixed among subjects, variability of actual sampling time, whether full profiles were taken in some subjects, the variability of dosing time, consistent dosing pattern, and missing doses. Pharmacokinetic data in individual subjects, including sampling time, concentration, dosing time, and compliance pattern were generated via simulation in different study design scenarios.

Modeling

The PK Model 1–5 was then fitted to the simulated data. In addition to the above design factors in the simulation process, the following were also considered: whether the actual dosing time was recorded and accounted for in the analysis, and whether the missing doses were recorded and accounted for in the analysis.

Power Estimation

For each study design factor considered, 200 replicates were simulated, and the models were fitted to the simulated data. For each replicate, the three methods for estimating significance of Cl_{slope} (Equation 5) were used to test the hypothesis (Equation 6). The number of replicates (Np) was counted for those that resulted in a significant subgroup effect. The ratio of this number (Np) to the total number of replicates (200) was the estimated power of the study. In some instances, the model fitting process may not converge. To be conservative, these nonconvergent replicates were treated as studies with negative results, i.e., no difference in Cl was found between populations.

Number of Subjects

The total number of subjects in most of the simulated studies was 100. The effect of the total number of subject on study power was investigated by including 200 subjects in a study. The number of subjects in the subpopulation varied from 10 to 50 for each design factor investigated.

False Positives

The false positive rates of the population PK analysis were investigated under several scenarios: studies with sparse samples, studies with sparse samples and full profiles, and studies with a subpopulation having different absorption rates but the same clearance than that of the typical population. For each of the scenarios, 200 replicates of study data were generated by assuming no subgroup effects, i.e., $Cl_{slope} = 0$ in Equation 5. Then the number of replicates falsely showing significant subgroup effects were counted. The ratio of the number of false significance subgroup effects to the total number of replicates (200) was the estimated false positive rate.

Sampling Scheme

Several components in sampling schemes were studied: number of samples, nominal sampling time, whether the sampling time was fixed among subjects, variability of actual sampling time, and whether full profiles were taken in some subjects. The number of sparse samples varied from 2–3 per subject, and the number of samples in full profiles was 5 within a 12 hr dosing interval. A 10% variability (log-normal) was assigned to sampling time in all scenarios except for one where the effects of fixing sampling time on the study power was investigated.

Compliance

The following factors relevant to study compliance were investigated: fixed dosing time, the variability of dosing time, whether the variability was recorded and accounted for in the analysis, missing doses, and whether the missing doses were recorded and accounted for in the analysis. The dosing time was assumed to randomly distribute around the scheduled time.

Basic Study Design and Parameter Set

This article deals with several simulation objectives. These objectives are discussed individually in the Results section. Under each objective, a specific design factor was investigated. Several scenarios with different values of the design factor were simulated. The influence of the design factors on the power of population pharmacokinetic studies was evaluated.

The following is the basic study design for most of the simulation objectives. A total of 100 subjects were enrolled in the study. Two samples were taken from each subject at 1 hr and 11.5 hr postdose on day 10 with a variability of 10% (CV) in sampling time. No full profile was taken in any of the subjects. The perfect compliance was assumed, i.e., exact dosing time every 12 hours and no missing dose. Any deviation from the basic study design for a particular simulation objective will be specified in the Results section.

Each simulation objective was evaluated by fixing a set of basic parameter values for all scenarios, with the exception of one or more parameters which differed among scenarios. In most of the simulations conducted, the following set of typical parameters were used:

$$\begin{aligned} D &= 100\ mg,\ Ka = 0.5\ hr^{-1},\ Cl = 10\ L/hr, \\ V &= 100\ L,\ \eta_{ka} = 25\%,\ \eta_{cl} = 25\%, \\ \eta_v &= 25\%,\ \varepsilon_{ij} = 20\%, \\ Cl_0 &= 10\ L/hr,\ Cl_{slope} = 3\ L/hr \end{aligned} \tag{7}$$

Other basic study design factors were: dosing time fixed at the nominal sampling time, 12 hr dosing interval, sparse samples taken at 1 and 11.5 hr, full profiles taken at 1, 3, 5, 8, and 11.5 hr, and 10% variability of sampling time.

Software

The software S-Plus 2000 was used to conduct the study simulation. The function (NLME) was used for the population pharmacokinetic analyses.

RESULTS

False Positive Rate of Studies with 1-hr/Trough Samples

The false positive rate of incorrectly identifying a subpopulation was investigated. The basic study design was assumed, with the typical set of parameters (Equation 7). The only exception to the typical parameter values was that $Cl_{slope} = 0$. The above study design was then simulated. The false positive rates estimated from the three methods were: 2% for the t-test on Cl_{slope} at $p = 0.01$, 1% for the likelihood ratio test at $p = 0.01$, and 0.5% for the likelihood ratio test at $p = 0.001$ with a subject number of 10 in the subpopulation. When the number of subjects in the subpopulation increased to 20, the false positive rates dropped to 1.5, 0.5, and 0%, respectively.

The Number of Subjects in the Subpopulation

The influence of the number of subjects in the subpopulation on study power was investigated. The basic study design and pharmacokinetic parameters (Equation 7) were assumed. The study power of identifying 30% difference in clearance between typical and subpopulations are shown in Fig. 1. The power was estimated for a different number of subjects in the subpopulation with the total number of subjects fixed. The mean and standard deviation of the estimated difference in clearance between typical and subpopulations are also shown in the same figure. Apparently, the likelihood ratio test at $p = 0.01$ level ($1-\beta_2$) gave the greatest study power. It required 20 subjects in this case to reach 80% power

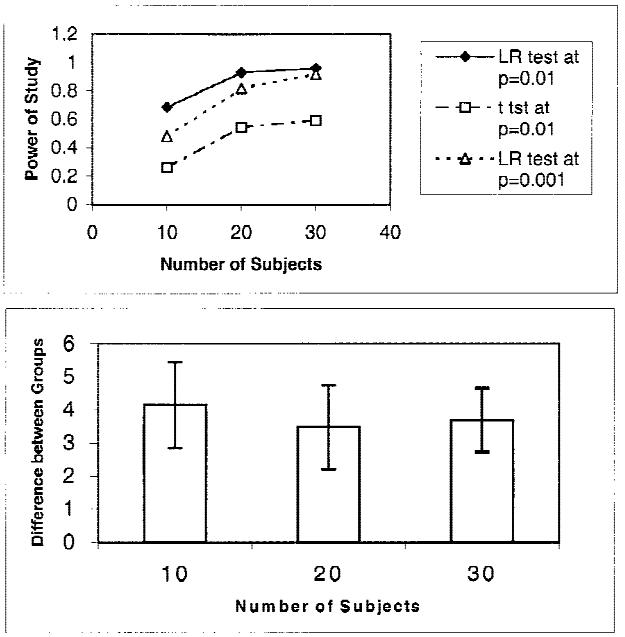

Fig. 1. The influence of the number of subjects in the subpopulation on (1) the study power of identifying a 30% difference in clearance between the sub- and typical populations, and (2) the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects, two samples taken from each subject at 1 hr and 11.5 hr postdose on day 10 with a variability of 10% CV in sampling time, no full profile taken in any of the subjects, and perfect compliance.

$(1-\beta_2)$. The mean estimated difference (34%) in clearance between groups with 20 subjects was relatively close to the true value (30%).

The Total Number of Subjects

The influence of total number of subjects on the study power was investigated. The basic study design and parameter values (Equation 7) were used. The only change in study design here was the total number of subjects, which was increased to 200. The study power of identifying 30% difference in clearance between the typical and the subpopulations are shown in Fig. 2. The mean and standard deviation of the estimated difference in clearance between typical and subpopulations are also shown in the same figure. Similar to the study design with 100 subjects (Fig. 1), the likelihood ratio test at $p = 0.01$ level $(1-\beta_2)$ gave the greatest study power, and 20 subjects in the subpopulation provided 80% power to the study. In this case, doubling the total number of subjects did not provide any advantage in the study power.

Fixed Sampling Time

The power of a population pharmacokinetic study with fixed sampling time among subjects (i.e., intersubject variability in sampling time was 0), was investigated through simulation. The basic study design and parameter values (Equation 7) were used in the simulation. The exception to the design was that two samples were taken from each subject exactly at 1 hr and 11.5 hr postdose on day 10. The power of identifying a 30% difference in clearance between sub- and typical populations are shown in Fig. 3, along with the mean and SD of the estimated difference in clearance between populations. The power estimated with the likelihood ratio test at $p = 0.01$ and $p = 0.001$ levels appear not to change much from the early simulation study with 10% variability in sampling time (Fig. 1), while power estimated by testing the significance in covariate effects $(1-\beta_2)$ reduced to almost 0. In addition, the mean estimated difference in clearance between populations grossly deviated from the true value. This poor performance in study power may reflect the fact that only two (exact) time points were measured and three parameters in the structure model were to be estimated.

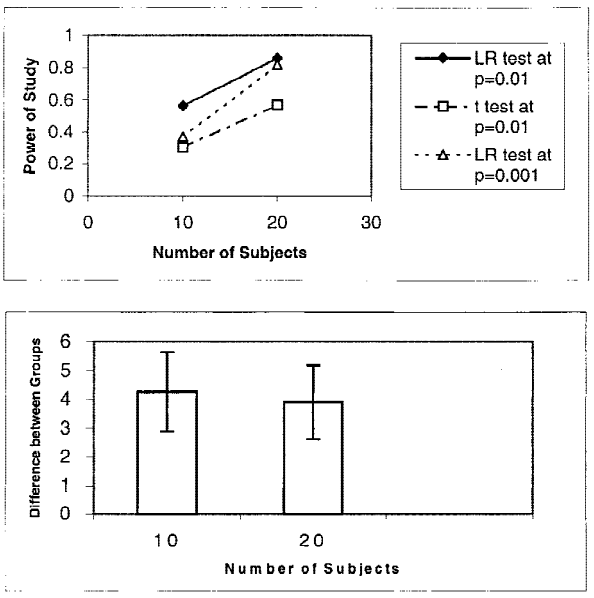

Fig. 2. The influence of the total number of subjects on (1) the study power of identifying a 30% difference in clearance between the sub- and typical populations, and (2) the estimated difference in clearance between the two populations. The same study design in Fig. 1 was applied here, with an increase of total number of subjects to 200.

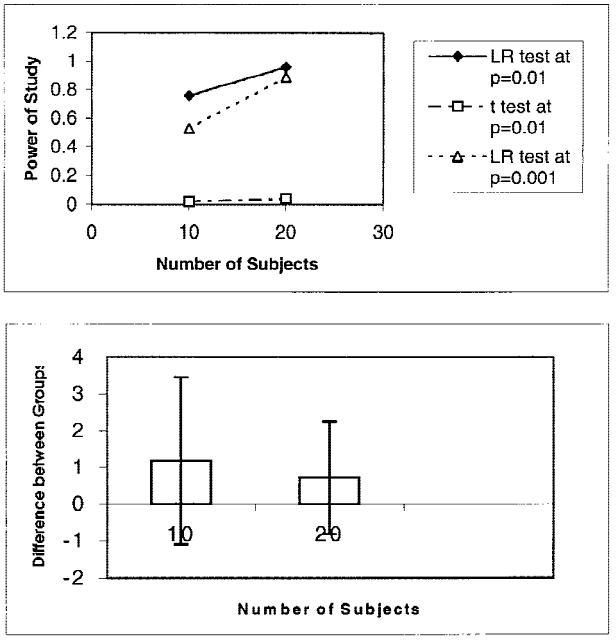

Fig. 3. The study power was investigated for a population pharmacokinetic study with fixed sampling time among subjects. The upper panel shows the study power of identifying a 30% difference in clearance between the sub- and typical populations; the lower panel shows the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects; two samples taken at exactly 1 hr and 11.5 hr postdose on day 10 in all subjects; no full profile taken in any of the subjects, and perfect compliance.

Three Sparse Samples

The power of population studies with three PK samples was estimated through the simulation method. The basic study design and parameter values (Equation 7) were used in the simulation. The exception to the design was that the samples were taken at 1, 5, and 11.5 hr postdose on day 10, with a 10% intersubject variability. The estimated power of the study for identifying subgroup effect are shown in Fig. 4, along with the mean and SD of the estimated difference in clearance between populations. The power of the study dramatically increased with three samples (Fig. 4) compared to the study with only 2 PK samples (Fig. 1). With three samples, only 10 subjects were required to achieve 80% power. Also noticed was the better precision of the mean estimated difference in clearance compared to the early scenarios.

Two Troughs

Frequently, only trough concentrations are measured in the population studies, due to certain limitations of the study design and conduct. The power of such study designs was

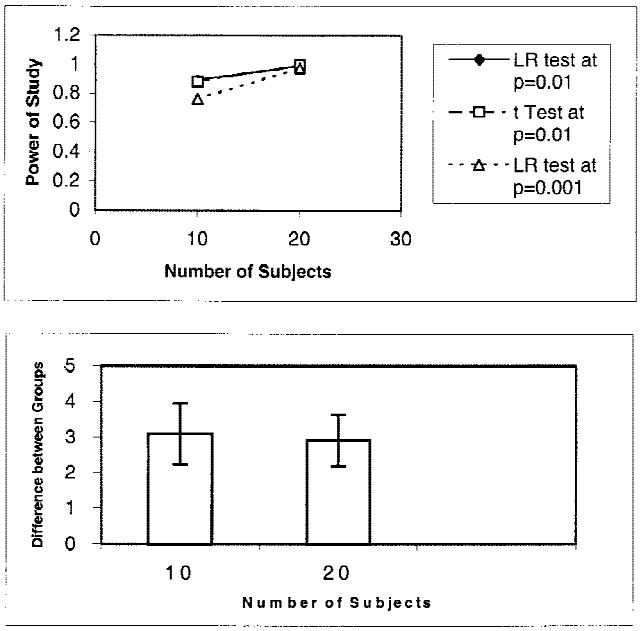

Fig. 4. The study power was investigated for a population pharmacokinetic study with three samples taken from each subject. The upper panel shows the study power of identifying a 30% difference in clearance between the sub- and typical populations; the lower panel shows the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects; three samples taken from each subject at 1, 5, and 11.5 hr postdose on day 10 with a variability of 10% CV in sampling time; no full profile taken in any of the subjects, and perfect compliance.

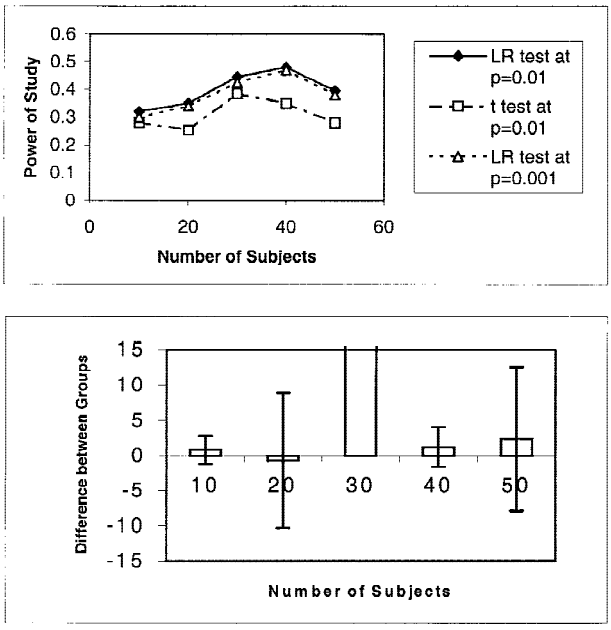

Figure 5. The study power was investigated for a population pharmacokinetic study with two trough samples taken from each subject. The upper panel shows the study power of identifying a 30% difference in clearance between the sub- and typical populations; the lower panel shows the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects; two samples taken from each subject both at 11.5 hr postdose on day 10 with a variability of 10% CV in sampling time; no full profile taken in any of the subjects, and perfect compliance.

investigated. The basic study design and parameter values (Equation 7) were assumed in the simulation. The exception to the design was that two samples were taken from each subject both at 11.5 hr postdose at steady state with an intersubject variability of 10% CV in sampling time. The estimated power of the study for identifying subgroup effects are shown in Fig. 5, along with the mean and SD of the estimated difference in clearance between populations. Apparently, the study power reduced from the previous design with 1-hr and trough samples (Fig. 1). Even with 50 subjects in the subpopulation, only approximately 40% power can be achieved. The estimation of the difference in clearance between populations was also poor.

Troughs Plus Full Profile

With the poor performance of the study design that measured only trough concentrations, it was interesting to investigate if taking full profiles from some subjects can help increasing the power of the study. A simulation study was performed with the same study design as above in Fig. 5. The only difference was that full pharmacokinetic profiles were taken in 25 out of the 100 subjects, and these 25 subjects all belong to the typical population (for example, the full profile may be obtained in Phase I/II studies, and trough samples from Phase III studies). The full profiles were taken at 1, 3, 5, 8, and 11.5 hr postdose with a 10% intersubject variability. Only two trough samples were taken from the subjects in the subpopulation. The power of this study design is shown in Fig. 6, along with the mean and SD of estimated difference in clearance between populations. The power of the study determined by testing the significance in covariate effects ($1-\beta_2$) increased from the previous design (without the full profile). With the full profiles obtained in some subjects, it required 30 subjects in the subpopulation to achieve 80% power. However, the estimation of the difference in clearance was still poor and with a large SD.

False Positive Rate for Design with Troughs Plus Full Profile

Since adding the full profiles in the study design seemed to improve the power of the study, as shown above, the potential false positive rate was then investigated. The same pharmacokinetic parameters and study design as above (Fig. 6) were applied here for the false positive rate estimation, except for that $Cl_{slope} = 0$. The estimated false positive rate ranged from 10–25%, 10–15%, and 7–15% for the likelihood ratio test at $p = 0.01$, t-test on Cl_{slope} at $p = 0.01$, and the likelihood ratio test at $p = 0.001$, respectively, with the number of subjects in the subpopulation varying from 10 to 40. These were relatively higher than the false positive rate for study without full profile.

False Positive Rate for Design with 1-Hr/Trough Samples Plus Full Profile

The false positive rates for study design with 1-hr and trough samples in some subjects and full profiles in others

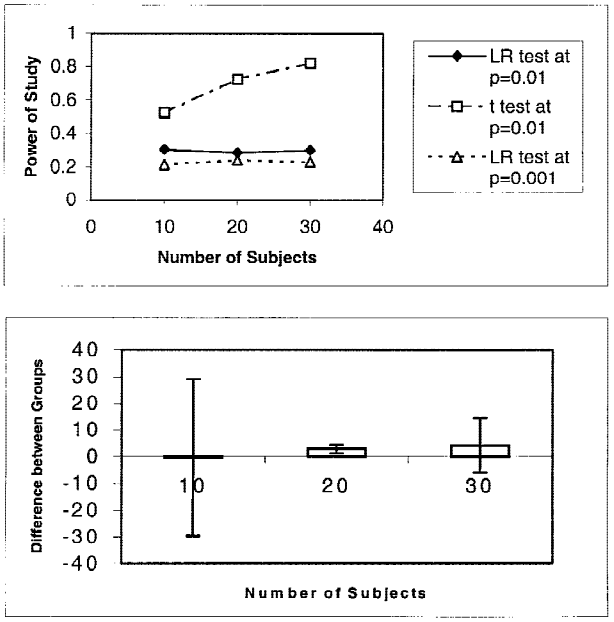

Fig. 6. The study power was investigated for a population pharmacokinetic study with two trough samples taken from some subjects and full PK profiles taken from other subjects. The upper panel shows the study power of identifying a 30% difference in clearance between the sub- and typical populations; the lower panel shows the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects; two samples both at 11.5 hr postdose taken from 75 subjects on day 10; full profile at 1, 3, 5, 8, and 11.5 hr postdose was taken on day 10 from 25 subjects, all of which belonged to the typical population, all sampling time assumed to have a variability of 10% CV, no full profile taken in any of the subjects, and perfect compliance.

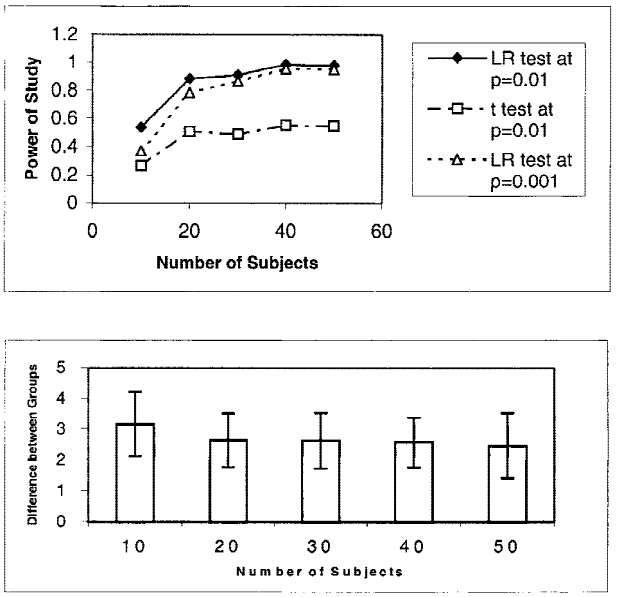

Fig. 7. The study power was investigated for a population pharmacokinetic study with missing dosing record. The upper panel shows the study power of identifying a 30% difference in clearance between the sub- and typical populations; the lower panel shows the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects; two samples taken from each subject at 1 and 11.5 hr postdose on day 10 with a variability of 10% CV in sampling time, no full profile taken in any of the subjects, and the doses administered within ±1 hr of the scheduled dosing time. The dosing record was missing and the scheduled dosing time was used in the population pharmacokinetic analysis.

were investigated. The same pharmacokinetic parameters and study design as the above scenario were assumed, with the exception that one 1-hr and one trough (rather than 2 trough) samples were taken from those subjects with sparse samples. The estimated false positive rate ranged from 15–17%, 0%, and 13–14% for the likelihood ratio test at $p = 0.01$, t-test on Cl_{slope} at $p = 0.01$, and the likelihood ratio test at $p = 0.001$, respectively, with the number of subjects in the subpopulation varying from 10 to 20. Apparently, replacing one trough with a 1-hr sample did not reduce by much the false positive rate estimated based on the likelihood ratio test.

Missing Dosing Record and Variability in Dosing Time

The influence of missing dosing record on the study power was investigated. The basic study design and parameter values (Equation 7) were assumed. The exception is that the doses were assumed to be administered within ±1 hr of the scheduled dosing time. In addition, the dosing record was assumed to be missing, and the scheduled dosing time was used in the population pharmacokinetic analyses. The estimated power for this scenario is shown in Fig. 7, along with the mean and SD of the estimated difference in clearance between populations. The power of the study did not appear to be influenced much by the missing dose record, compared to the scenario where the doses were given at the scheduled time (Fig. 1). The mean estimated difference in clearance was slightly lower in this scenario compared to the previous one (Fig. 1).

Another scenario was simulated where the variability in dosing time was accounted for in the population PK analysis. The power of the study remained similar. An 80% power for the likelihood ratio test at $p = 0.01$ was reached with 20 subjects in the subpopulation. The estimated difference in clearance improved a little.

Missing Doses

The influence of missing doses on the study power was investigated through simulation. The basic study design and parameter values (Equation 7) were assumed. The exception is that the doses were assumed to be taken within ±1 hr of the scheduled dosing time. It was further assumed that half of the patients took all doses, and the other half missed 30% of their doses randomly. Then the following scenario was considered: where the dosing record was missing, and without the dosing record, the PK data were analyzed by assuming all doses were administered at the scheduled time. The estimated power for this scenario is shown in Fig. 8, and the estimated difference in clearance is also shown in the same figure. Clearly, the power of this study conduct and analysis was much lower than that without missing doses (say, as in Fig. 1). The mean estimated difference in clearance between populations also grossly deviated from the true value.

Another scenario was simulated where the dosing record

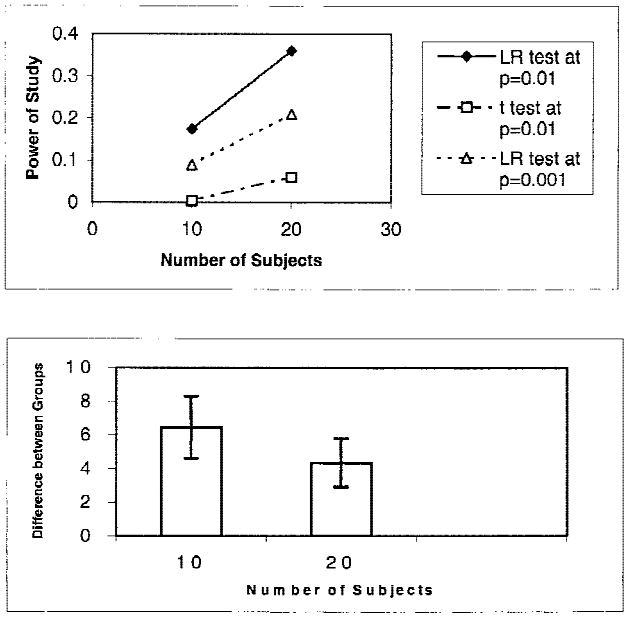

Fig. 8. The study power was investigated for a population pharmacokinetic study with missing doses in subjects and the dosing record not available. The upper panel shows the study power of identifying a 30% difference in clearance between the sub- and typical populations; the lower panel shows the estimated difference in clearance between the two populations. The basic set of parameter values in Equation 7 was used in the simulation. In addition, the following study design was considered: A total of 100 subjects; two samples taken from each subject at 1 and 11.5 hr postdose on day 10 with a variability of 10% CV in sampling time, and no full profile taken in any of the subject. Half of the subjects missed 30% of their doses randomly, and the other half took all the doses. All the doses, if taken, were administered within ±1 hr of the scheduled dosing time. The dosing record was missing and all doses were assumed taken and the scheduled dosing time was used in the population pharmacokinetic analysis.

was available, and the missing doses were accounted for in the population pharmacokinetics analysis. In this case, the power appeared to be slightly improved. However, with 50 subjects in the subpopulation, only 50% power can be reached with the likelihood ratio test at $p = 0.01$ level. The mean estimated difference in clearance was reasonably close to the true value.

Difference in Clearance

The power of population pharmacokinetics study was estimated for various differences in clearance between populations. The scenario with 30% difference in clearance is shown in Fig. 1. With the same study design as that in Fig. 1, the power for identifying 50% difference in clearance was also estimated. A 90% power was reached with 10 subjects in the subpopulation for both likelihood ratio tests at $p = 0.01$ and $p = 0.001$. As expected, the study power increased when a greater difference in clearance was to be identified by the same study design.

False Positive Rate with Difference in Absorption

The false positive rate was estimated for the scenario where the absorption rate differed but the clearance was the same between the sub- and the typical populations. The objective of this simulation was to determine if any difference in absorption kinetics could be falsely translated into a difference in clearance through study design or data analysis. The basic study design and parameter values were assumed in the simulation. The estimated false positive rate was below 2% for all three tests with 10–20 subjects in the subpopulation.

DISCUSSION

Many study design factors may have significant influences on the power of a population pharmacokinetics study for identifying subpopulations with different clearances. The false positive rates for identifying difference in clearance by the population PK study are relatively low (< 2% for the likelihood ratio test at $p = 0.01$ level) for sparse sampling design with 1-hr and trough samples. A difference in absorption rate in the subpopulation does not impact on the false positive rate. However, including full pharmacokinetic profile in some subjects increases the false positive rate. The total number of subjects does not seem to have as much influence on the study power as the number of subjects in the subpopulation, as long as the total number is significantly large (in this case, it is 100). The variability of sampling time plays an important role in both the study power and the accuracy of the estimated difference in clearance. With fixed sampling time (0 intersubject variability), the power is low and the estimate is poor. With 10% variability in sampling time, the power and accuracy improve.

Taking three sparse samples provides greater power and better accuracy than taking two sparse samples. Taking only trough samples provides little power and poor estimation of clearance difference. Adding subjects with full profiles to a study with only trough samples does not satisfactorily improve the estimation of clearance difference. It is critical to account for the dosing record in the population PK analysis to achieve appropriate power and accuracy. If accounted for in the analysis, variability in dosing time improves the accuracy of the estimated difference in clearance. If not accounted for, missing dose administrations reduces the study power and results in deviation of estimated clearance difference.

Based on these simulation results, the ideal population pharmacokinetics study design for pharmacokinetics following the basic model (Equations 1–5 & 7) appears to be one with at least two samples around the 1-hr and trough samples, sufficient variability in sampling time and dosing time, as good compliance as possible, doing time and any missing dose recorded, and sufficient numbers of subjects. Cautions must be taken when including full profile in the analysis. Finally, the power of a study should be determined prospectively to ensure appropriate study design for specific study objectives.

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