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ORIGINAL ARTICLE

Random sparse sampling strategy using stochastic simulation and estimation for a population pharmacokinetic study

Xiao-hui Huang [a,1], Kun Wang [b,1], Ji-han Huang [b], Ling Xu [b], Lu-jin Li [b], Yu-cheng Sheng [b], Qing-shan Zheng [b,*]

[a] *Center of Pharmacokinetics, College of Pharmacy, Anhui Medical University, Hefei 230032, Anhui, China*
[b] *Center for Drug Clinical Research, Shanghai University of Chinese Medicine, Shanghai 20123, China*

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Abstract The purpose of this study was to use the stochastic simulation and estimation method to evaluate the effects of sample size and the number of samples per individual on the model development and evaluation. The pharmacokinetic parameters and inter- and intra-individual variation were obtained from a population pharmacokinetic model of clinical trials of amlodipine. Stochastic simulation and estimation were performed to evaluate the efficiencies of different sparse sampling scenarios to estimate the compartment model. Simulated data were generated a thousand times and three candidate models were used to fit the 1000 data sets. Fifty-five kinds of sparse sampling scenarios were investigated and compared. The results showed that, 60 samples with three points and 20 samples with five points are recommended, and the quantitative methodology of stochastic simulation and estimation is valuable for efficiently estimating the compartment model and can be used for other similar model development and evaluation approaches.

1. Introduction

The standard pharmacokinetic approaches of the compartment model estimation rely heavily on rich blood sampling data. However, it is often inconvenient or impossible for physicians and pharmacists to perform a rich blood sampling in some occasions since the number of blood sampling is limited in some special populations, such as children or older people. The population pharmacokinetic approaches are often used to solve this problem, which can use only a fewer number of drug concentration samples (sparse data) to estimate the pharmacokinetic parameters of the compartment model. However, sparse sampling designs often fail to support models derived

* Corresponding author. Address: Clinical pharmacology and pharmacometrics, Center for Drug Clinical Research, Shanghai University of Chinese Medicine, Shanghai 20123, China. Tel.: +86 021 51323006.
E-mail address: drugchina@126.com (Q.-s. Zheng).
[1] These authors contributed equally in this study.
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in the data-rich phase I and II environments (Aarons et al., 1996; Flynn et al., 2006). Therefore, it is very important to analyze and evaluate the important influential factors of model estimation (Ette et al., 1995; Hooker et al., 2007).

Sample location in a population pharmacokinetic study is an important factor. Ette et al. investigated a 2-time-point design with one-compartment IV bolus model and extended to 3- and 4-time-point designs via simulation (Roy and Ette, 2005; Ette et al., 1995). With the first time point sampled as early as possible, they found that the second sample point between 1.4 and 3.0 times the half-life of the drug produced better estimation and the exact location of the third and fourth time point for the three and four time point designs was not critical to the efficiency of overall efficiency of parameter estimation, although some parameters were sensitive to the location of these sample times. The quality of pharmacokinetic modeling and parameters' estimation of the population method usually depends heavily upon sample size and the number of sampling points. Al-Banna et al. found that the accuracy and precision of random effect parameter estimates improved dramatically when the number of sampling points increased (Al-Banna et al., 1990). For a same data set, sometimes the results show that the two-compartment model is the best model to describe the data if modeling on rich data. But sometimes, if using fewer sampling points per subject, the one-compartment model may also be the best model to fit the data. This might be because sampling points are not enough to distinguish the distribution and elimination phases (Hooker et al., 2007).

Amlodipine is a second-generation calcium channel antagonist. Some previous studies have reported that the pharmacokinetics of amlodipine conforms to the one-compartment model (Flynn et al., 2006) or one-compartment model with absorption lag time (Rohatagi et al., 2008). There are also some other pharmacokinetic studies which reported that it conforms to the two-compartment model (Faulkner et al., 1986; Cheng et al., 1996). A Limited Sampling strategy (LSS) model of amlodipine was successfully developed and validated to estimate the area under the concentration–time curve (AUC) (Suarez-Kurtz et al., 1999). In the present study, we mainly focus on the effects of the number of sampling points and sample size on the compartment model evaluation in various random sparse sampling designs. Population pharmacokinetic models of amlodipine were developed using data collected from three bioequivalence clinical trials in healthy Chinese volunteers with a total of 120 samples. A two-compartment model with lag time obtained from real clinical trial data of amlodipine was used as an example. The efficiencies of compartment model estimation in different sparse sampling scenarios were investigated and compared.

2. Materials and methods

2.1. Data

The data used for modeling and simulation were obtained from three randomized, two-period crossover bioequivalence clinical trials of amlodipine, in which the treatment phases were separated by a 14-day washout interval. Sixty healthy male volunteers ranging from 19 to 25 years of age (mean 21.7 years) and from 51 to 87 kg in weight (mean 62.8 kg) were enrolled in the study. The clinical protocol was approved by the ethics committee and all participants provided written informed consent.

The volunteers received an amlodipine 5 mg tablet with 200 ml water at 7:30 am after an overnight (> 10 h) fast. Blood samples (3 ml) were collected before the initiation of the study and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 h after the administration of amlodipine. Amlodipine concentrations were analyzed by liquid chromatography tandem mass spectrometry. The visible detection of the method was in the range of 0.2–32.0 ng/ml, and the lower limit of quantification for amlodipine was 0.2 ng/ml.

2.2. Software

Nonlinear mixed-effect methodology (NONMEM software, version 7.1.0, Icon Development Solutions, Ellicott, MD, USA) was used to fit the population model. The Perl speak to NONMEM toolkit (PsN version 4.2.3, Uppsala University, Sweden) was used in conjunction with NONMEM. Data manipulation and graph drawing were accomplished by R 2.13, Xpose (version 4.3.0, Uppsala University, Sweden) and Lattice (Sarkar, 2008).

2.3. Candidate models

Compartment model estimation proceeded from a one-compartment model with first-order input and first-order elimination (1-cp model). The pharmacokinetic parameters were estimated. Subsequently, one-compartment with absorption lag time model (1-cp-lag model), two-compartment model (2-cp model) and two-compartment with absorption lag time (2-cp-lag model) were evaluated. The approximate maximum likelihood technique known as the first-order conditional estimation (FOCE) method was used to estimate the model parameters. The likelihood ratio (LR) test and graphical tools were used as the criteria of compartment model selection to assess whether a model is good enough to describe the data. The LR test is based on the difference of objective function value (OFV) of two compared models. The difference of OFV approximately follows a χ^2 distribution, and the degree of freedom is equal to the different numbers of parameters between the two compared models. Difference in OFV of 3.84, 5.99 and 7.81 corresponds to $P < 0.05$ for 1, 2 and 3 degrees of freedom, respectively.

2.4. Statistic model

Random components are assumed to be derived from an exponential distribution. An individual parameter (P_j) is distributed according to

$$P_j = TVP \times e^{\eta j} \quad (1)$$

where, P_j is the parameter of subject i, TVP is the typical parameter value and η_j is the random effect which is normally distributed around zero with variance ω^2 reflecting the inter-individual variability.

Three error models tested in this study, additive (2), proportional (3) and mixed (4) error models, were postulated as:

$$C_{i,obs} = C_{i,pred} + \epsilon_i \quad (2)$$

$$C_{i,obs} = C_{i,pred} \times \epsilon_i \quad (3)$$