A Simple Method for Approximating Population Pharmacokinetic Parameters

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Background

Population pharmacokinetic (PK) models are useful for describing time-concentration data, but often there is little time and no budget to engage corporate or external experts to analyze data and determine these values. The analysis often involves rather specialized software such as NONMEM, S-ADVMIXED, or the nlmef package in R.

In several recent engagements, we needed to test our models with "reasonable" drug time-concentration profiles to facilitate trial simulation methods development, and wanted to see if a simple method could be used to approximate population PK models without having to teach scientists, not specializing in PK, a new programming language. This effort is necessary because often physiologically-based pharmacodynamic (PhysioPD™) modeling occurs simultaneously or prior to the development of rigorous PK models. The PK information is needed to build and test the physiological model and clinical trial design may be necessary before data from concurrent clinical trials is available. While there are programs available to estimate individual and population PK, we needed a program that could be used by scientists, without specialized training, and at little cost.

We describe a simple method to generate approximate central tendencies and measures of distribution for PK/PD model parameters. A mean and covariance description of parameters allows experimentally. We have used the technique to allow the preliminary evaluation of our PhysioPD popPK parameters: "Spaghetti plot" of predicted time-concentration curves matched well, parameters less so. This method does not account for parametric covariance, and problems in those predictions are known (1-3). However, the model parameters generated by the Rosa Excel macro were very useful for testing of the complex PhysioPD models.

PhysioPD models are used in a decision process:
- What compounds to develop practically and clinically?
- Which compounds should be leads, and which should be backups?
- What is the optimal design for a clinical trial?
- What assets/compounds to in-license/out-license?
- How to prevent/mitigate/manage safety issues and potential adverse events?
- What collaborations/partnerships to undertake?
- What companies/compounds to acquire/divest?

Methods

This experiment was done as two steps. The first step was to evaluate the available software for use by individuals who were not trained pharmacologists. The second step was to evaluate the results from the software itself. Published data for glyburide and metformin were selected to use as supply data for comparative examples. We attempted to generate individual PK and popPK for each subject using Monolix, POPPK, and a ROSA PK Macro. To keep an understandable form available each system was used for someone not trained in PK, and was developed, installed, and run as such program. Each program was tested in its own context, and on different results, and cost. The results from each program were then compared to published or NONMEM generated models.

Because MxT's/MxT's were used to capture the areas for each compound and dose, we utilized the MxT's/MxT's Visual Basic macros functions to obtain the AUC over time. We used the藥物 PK parameters for a PK/MK model to generate a series of matched, uniform time-concentration curves to provide PK models parameters for a standard one or two-compartment model. The results were then compared to the results of the weighted squares errors. These optimizations were done using the Steiner function (based on a Generalized Reduced Gradient method of Microsoft Excel). The system function with single dose or multiple doses of drug for each dose during the day displaying different kinetics. The individual peaks for each dose were determined by classic "peak stripping" techniques. For the population analysis, a TID dosing of a new compound with three meals experiment. Results plotted are mean values. PK data generated by Monolix. In general, approximate and rigorous time-concentration curves matched well, parameters less so.

Conclusions

A system was designed to allow a simple method to fit individual PK model parameters using concentration data and to approximate population PK parameters using widely available software. The system utilized either single dose data or multiple dose data and provided reasonable PK model parameters for each dataset tested. The population PK models generated by the system provided parameters and variance values that were useful in testing Rosa's PhysioPD models. The ease of generating approximate estimates for these parameters for testing the PhysioPD model and trial simulations was useful to our scientists. The method implemented has the advantage of utilizing standard worksheet software for those users who do not have access to and training in specialized software or the time of expert pharmacologists.

We emphasize that this is an approximation, with some deficiencies that are well known. However, this approximation has been used to test our PhysioPD models prior to the availability of rigorous popPK, and the approximate values were used as initial estimates for the more rigorous analysis. The agreement of the concentration-time profiles was very good, and the approximate parameter values were useful as starting points for the rigorous popPK analyses.

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References: