Development of QT prolongation model in guinea pig with hERG assay-in vivo PK-in vivo QT effect to guide decision making in early drug discovery

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Introduction

hERG assay is one of a traditional approaches for evaluating cardiac safety of drug in early drug discovery. But this assay has major limitation that it does not consider PK properties of drug candidates, leading to a weak correlation between in-vitro (hERG IC50) and in-vivo (QTcF) tests. For accurate prediction of QT prolongation in early drug development process, much improved evaluation method is required. In this study, we built the model for predicting QT prolongation considering hERG assay and PK parameters as well as in-vivo QT prolongation in guinea pig.

Method

Pharmacokinetics study design
- Selection of drugs for developing QT prolongation model
  - For developing QT prolongation prediction model, drugs were selected from each of the four groups that were classified based on safety margin (IC50/Cmax = 30/100) and hERG IC50 (< 10 µM) values.
  - 13 drugs were selected and were classified as high (Group 1), moderate (Group 2), low (Group 3) and no (Group 4) risk groups.
  - Test dose of each drug was converted to animal dose from human maximum daily dose.

Pharmacodynamics study design
- For measuring ECG of guinea pig, lead 2 Hugo Sachs Electronik ECG (Hugstetten-March, Germany) was used. ECG were measured after administration of drug only after heart rate was stabilized.
- Blood collection until analysis.
- Plasma were centrifuged at 15,000 rpm, 4°C for 10min. Plasma was separated and stored at -70°C until analysis.
- Analysis of samples was done with API 2000 (Applied Biosystems, USA) and Analyst software ver.5.1.
- Pharmacokinetic parameters (AUC0→∞, Cmax) were estimated using Phensins ver. 6.4.0 (Pharsight, USA).

Pharmacokinetic & Pharmacodynamic study results
- Using final model, we suggest draft decision tree for predicting and evaluating of QT prolongation using in-silico method. This draft version of the decision tree will be updated with future studies.

Pharmacokinetic & Pharmacodynamic study results
- From PK study (n=5, each drug, PK parameters (AUC0→∞, Cmax) of each drug were estimated by noncompartmental analyts.
- From PD study (n=5, each drug), maximum ΔQTc interval (QTF, QTF (inf), QTF (max)) of each drug were calculated.
- Simple regression analysis
  - 4 models were tested in R and the second model (Y=c1x+c0) was selected because of r² value (0.2294) and significance of variables.

Results

Final model of simple regression analysis:
- Plane equation and paraboloid equation were 0.1421 and 0.2504, respectively.

- Nonlinear mixed effect model for prediction of QT prolongation
  - Model for identifying nonlinear relationship between hERG IC50, and ΔQTc interval was developed using NONMEM and in-AUC0→∞, Cmax were selected as covariate of alpha parameter.
  - Estimated values from final model and visual predictive check were shown below.

- Draft decision tree about in-silico prediction and evaluation of QT prolongation
  - With the results from PK and PD study, simple regression and multiple nonlinear regression analysis were successfully developed.
  - Equations from these regression analysis are simple but show low r² values, and cannot explain high variance of PK and PD parameters.
  - Regression model of hERG IC50 and ΔQTc interval, considering PK parameters as covariate was successfully developed using NONMEM.
  - Natural log transformed AUC0→∞, Cmax were found to be significant covariate for ΔQTc interval.
  - Our final model can estimate the ΔQTc interval considering hERG IC50 value as well as PK parameters of given drugs.
  - Final model was used to update our model with PK and PD data from more drugs.
  - Using final model, we suggest draft decision tree for predicting and evaluating of QT prolongation using-in-silico method. This draft version of the decision tree will be updated with future studies.

Discussion

- With the results from PK and PD study, simple regression and multiple nonlinear regression analysis were successfully developed.
- Equations from these regression analysis are simple but show low r² values, and cannot explain high variance of PK and PD parameters.
- Regression model of hERG IC50 and ΔQTc interval, considering PK parameters as covariate was successfully developed using NONMEM.
- Natural log transformed AUC0→∞, Cmax were found to be significant covariate for ΔQTc interval.
- Our final model can estimate the ΔQTc interval considering hERG IC50 value as well as PK parameters of given drugs.
- Our study had limited number of drugs in each of the classified risk groups, so we plan to update our model with PK and PD data from more drugs.
- Using final model, we suggest draft decision tree for predicting and evaluating of QT prolongation using-in-silico method. This draft version of the decision tree will be updated with future studies.

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