Population pharmacokinetic-pharmacodynamics modelling of the QTc prolongation of Moxifloxacin and Levofloxacin in healthy volunteers: selection of the positive control in mandatory QT/QTc studies

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Introduction

Several classes of non-antiarrhythmic drugs induce lengthening of the QT interval. QT interval length is considered as a biomarker of ventricular tachiarrhythmia (Torsade de pointe). Regulatory agencies require QT/QTc studies to evaluate cardiac safety of non anti-arrhythmic drugs (1). Because of multiple sources of variability in Individual corrected QT (QtcI) intervals for the investigation of any potential drug effect, population pharmacokinetics/pharmacodynamics (PK/PD) modeling approach is more and more used in order to split the overall variability into components (2). Moxifloxacin and levofloxacin are often used as positive control to validate the sensitivity of the QT/QTc studies. The positive control should have an effect on the mean QT/QTc interval of about 5ms.

Objectives

The aim is to help to choose a positive control and the dose to be administered in thorough QT/QTc study, by comparing population QTc PKPD model parameter estimates after moxifloxacin and levofloxacin administrations.

Methods

QtcI data coming from two phase I studies (moxifloxacin 400mg and levofloxacin 1000 or 1500mg) including a total of 160 healthy volunteers under placebo were used to build the population model for the QTc. ECGs were recorded during 24h with an average 10 records per period and per subject (Figure 1).

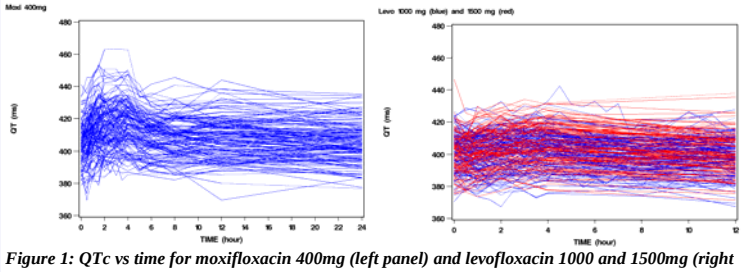

Figure 1: QTc vs time for moxifloxacin 400mg (left panel) and levofloxacin 1000 and 1500mg (right panel)

Estimation of the population parameters characterizing the QTc baseline was performed using NONMEM VI with the FOCE-I method. Then several models were investigated to evaluate any potential drug effect.

Baseline model

QTcI intervals *versus* time are subject to within-day (circadian) variations. A circadian rhythm model for the QTcI interval previously developed by Piotrovsky (2005) was applied in the present study:

$$QTcI = QTcIm * [1+CIRC] \quad (1)$$

With $CIRC=A1*\cos[2\pi(t-tlag1)/24] + A2*\cos[2\pi(t-tlag2)/12]+A3*\cos[2\pi(t-tlag3)/6]$

QTcIm is the mesor value of the QTcI interval; A1, A2 and A3 are the amplitudes; tlag1, tlag2 and tlag3 are the acrophase parameters; t is the time and 24, 12 and 6 represent the periods (in hours). Inter-individual and inter-occasion variabilities were tested on QTcIm, A1, A2, A3, tlag1, tlag2, tlag3 parameters. Proportional (res_prop) and/or additive (res_add) error models were tested for the residual error model.

Placebo model

$$QTcI = QTcIm * [1+CIRC+Placebo\_effect] \quad (2)$$

Drug effect

Predicted increases of concentrations (Cpred), obtained by PK models from moxifloxacin and levofloxacin concentrations, were then tested on QTcIm in the baseline and placebo model. These concentration effects were modeled as a linear effect (Sr_effect) or through an Emax model:

$$QTcI = QTcIm * [1+CIRC+Placebo\_effect+Sr\_effect*Cpred] \quad (3)$$

$$QTcI = QTcIm * [1+CIRC+Placebo\_effect+(Sr\_Emax*(Cpred))/(EC50+(Cpred))] \quad (4)$$

Model evaluation

The adequacy of the models to describe the data was assessed based on basic evaluation methods such as standard goodness-of-fit (GOF) plots and assessment of uncertainty on parameter estimates (relative standard errors or RSE), and advanced evaluation methods such as VPC and NPDE.

Results

The circadian QTc rhythm was modeled as a mesor and a sum of three cosine terms (one amplitude and one lag-time per cosine term), representing three periods of 24, 12 and 6 h. Thus, the population model consisted of 7 fixed-effect parameters with inter-individual variability parameters and a proportional residual error model. The lag-time for the period of 12h was fixed to zero in the model. No placebo effect was found here. Moxifloxacin and levofloxacin effects were modeled as linear effects. The estimated population parameters, the precision of their estimation (RSE) and the coefficient of variation (CV) are given in Table 1 for the final model.

Paramater	VALUE	RSE(%)	CV(%)
QTclm(msec)	402	0.23	
A1	0.003	14	
tlag1 (h)	6.59	7.5	
A2	0.005	7.3	
tlag2 (h)	9.2	1.9	
A3	12.4	4.6	
tlag3 (h)	3.53	0.28	
SLOPE_MOXI	0.012	4.3	
SLOPE_LEVO	0.00096	15	
IIV_QTclm	0.00076	9.1	2.8
IIV_A1	0.62	26	79
IIV_tlag2	2.8	18	166
IIV_A3	0.084	23	29
IIV_tlag3	0.094	25	31
IOV_QTclm	0.000078	9.9	0.89
IOV_A1	0.21	38	46
Res_add (%)	4.2	2.1	

Table 1: Population PK parameters for the final model

The VPC and NPDE were satisfactory for both moxifloxacin and levofloxacin (Figure 2 and 3)

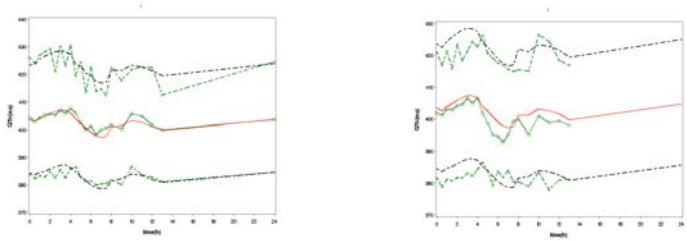

Fig.2: QTc vs time; The dashed lines represent the 5th,and 95th percentiles of 1000 simulations; The solid green lines represent the 5th, 50th, and 95th percentiles of observations for moxifloxacin (left panel) and levofloxacin 1500mg (right panel)

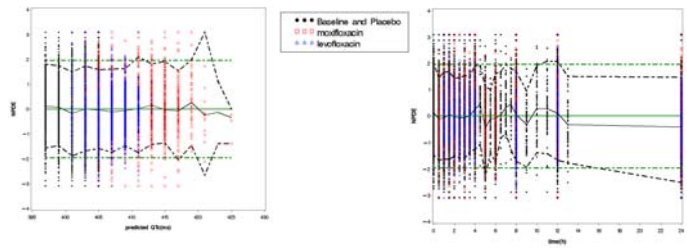

Fig.3: NPDE vs time (left panel) and NPDE vs predicted QTc (right panel); The dashed lines represent the 5th,and 95th percentiles of NPDE; The solid green lines represent the 50th percentiles of NPDE;green lines represent the references lines.

Moxifloxacin and levofloxacin effects were modeled as linear effects. In this model, the effect of moxifloxacin (400mg) predicted mean maximum concentration (mean Cmax=2.5mg/L) corresponded to a change of QTcI from baseline of 11.8ms. For Levofloxacin (mean Cmax=9.6mg/L for dose 1000mg and 13mg/L for 1500mg), the change of QTcI were 3.7 and 5ms, respectively.

Conclusions

This population PK/PD analyses allowed us to characterize the effects of moxifloxacin 400mg and levofloxacin 1000 or 1500mg on the QTc baseline. Simulations will be the next step to determine both the optimal dose and the number of subjects to assure a mean QT/QTc interval of about 5ms with each positive control.

References:

(1) International Conference on Harmonisation; guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; availability. Notice. Fed Regist. 70.202 (2005): 61134-35

(2) Piotrovsky V. *et al*. Pharmacokinetic/Pharmacodynamic modeling on the data analysis and interpretation of drug-induced QT/QTc prolongation. AAPS J. 7(3): E609-24, review (2005).