PK/PD MODELING OF QTcF DURATION FOR VARDENAFIL & SILDENAFIL FOLLOWING CONCOMITANT ADMINISTRATION WITH GATIFLOXACIN IN HEALTHY VOLUNTEERS

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Introduction

PDE-5 inhibitors such as vardenafil (V) and sildenafil (S) that are prescribed for erectile dysfunction cause small, nonclinically relevant increases in the QTc interval. Since patients may be concomitantly treated with others medications that have the potential to prolong QTc interval, this study evaluated the effects of concomitant dosing of V and S with gatifloxacin (G) on cardiac conduction.

Objective

The primary objective of this analysis was to characterize the PK/PD relationship between V, S and G plasma concentrations (Cp) and QTc interval following single oral administration of V, S and G or when V and S were co-administered with G.

Methods

This was a double-blind, randomized, single dose, six (6)-period, period-balanced crossover study conducted in 44 healthy adult males (18-51 years of age). Each subject received either placebo (P), V (10 mg), S (50 mg), G (400 mg) alone or V and S in combination with G with in a randomized, crossover fashion with a minimum washout period of at least 3 days between sessions. ECGs were measured in triplicate at -1, -0.75, -0.5, -0.25, 0.5, 1.5, 2.5, 4, 6, 8, 12, 16 and 24 hours and at 1 hour post-dose 6 ECGs were required. The baseline QTc for each regimen was calculated from the average of the four pre-dose values measured on Day 1 of each session. The primary endpoint was change from baseline in Fridericia's corrected QTc (QTcF) at 1 hour post-dose. S, V and G Cp were measured up to 16 hours post-dose. In order to utilize all of the observed QTcF measurements, Cp for all of the three drugs were predicted at 24 hours post-dose.

Model Development

The PK/PD relationship between Cp and QTcF was modeled using NONMEM V (level 1.1). The PK/PD model development was initiated using only the P data to incorporate a circadian time-dependent change in QTcF in the model. A variety of cosine functions with one or two cyclic components using different cycle times (i.e., 4, 6, 8, 12 and 24 hours) were examined to characterize the time-dependent changes in QTcF interval. After accounting for the diurnal variation in P, various direct effect PK/PD models were investigated to describe the PK/PD relationship for each of the three drugs (index dataset), and to assess for the presence of a less than additive effect (partial antagonism) or a greater than additive effect (synergy) (full dataset). The full dataset included 2660 PK/PD observations. The first order method was used for all analyses. The predictive performance of the final population PK/PD model was evaluated by Monte Carlo (MC) simulation using NONMEM. MC simulation was performed to simulate QTcF for 100 studies based on the final population PK/PD model. The observed QTcF values were compared with the 95% prediction intervals.

Results

The PK/PD model that best described the data is given below:

$$QTcF = QTcF_0 + AMP_1 * Cos[(t-tmax_1)*(2\pi/12)] \text{ for } t < 12 \text{ hrs}$$
$$+ AMP_2 * Cos[(t-tmax_2)*(2\pi/24)] \text{ for } t \text{ 12-24 hrs}$$
$$+ S_v * Cp_V + S_s * Cp_S + S_G * Cp_G$$

where $QTcF_0$ is the baseline QTcF; S_V, S_S and S_G are the slopes for the regressions describing the linear increase in QTcF with increase in Cp for V, S and G; AMP_1, AMP_2, $tmax_1$ and $tmax_2$ are the amplitudes and the acrophase (peak) times of the first and second periodic components of circadian variation in QTcF over the 12 and 24 hour cycles, respectively.

Table 1. Final PK/PD Model Parameter Estimates

Parameter	Population Mean (% CV[3])	% Inter-Individual Variability (% CV[3])	95% CI based on ΔOBJ Mapping
$QTcF_0$ (msec)	389 (0.5)	3.18 (24.9)	388.6 – 392.9
S_V (msec/ng/mL)	0.552 (21.4)	32.1 (349)	0.508 – 0.574
S_S (msec/ng/mL)	0.0165 (26.3)	119.6 (74.8)	0.0160 – 0.0241
S_G (msec/ng/mL)	0.00219 (8.0)	15.5 (121)	0.00186 – 0.00252
AMP_1	3.96 (12.0)	69.1 (25.7)	2.97 – 4.95
AMP_2	1.88 (27.2)	122.5 (74.0)	0.846 – 2.914
t_{max1} (hours)	2.07 (7.4)	36.6 (47.8)	1.76 – 2.38
t_{max2} (hours)	13.0 (3.0)	111.8 (59.4)	12.2 – 13.8
IOV on $QTcF_0$[1]	0.83 (21.6)		
Residual Error[2] (%CV)	6.16 (5.4)		

1. IOV expressed as % coefficient of variation
2. Expressed as msec
3. Precision expressed as % coefficient of variation

Figure 1. Individual Predicted QTcF versus Observed QTcF For V & V + G

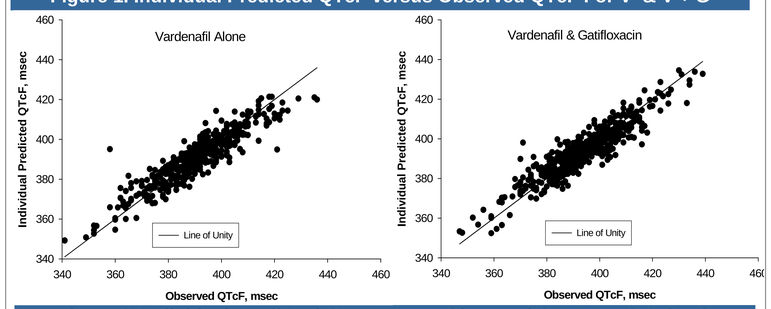


Figure 2. Individual Predicted QTcF versus Observed QTcF For S & S + G

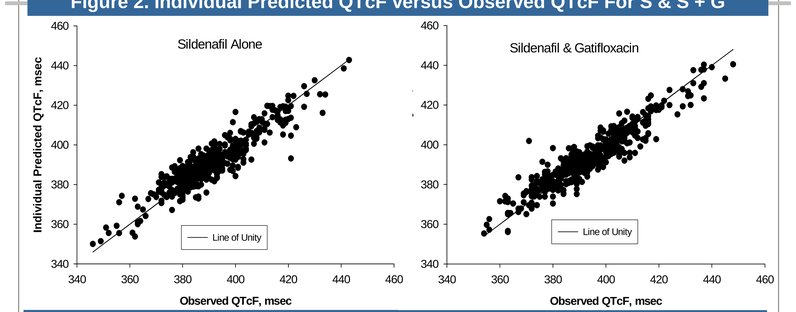


Figure 3. Individual Predicted QTcF versus Observed QTcF For G & P

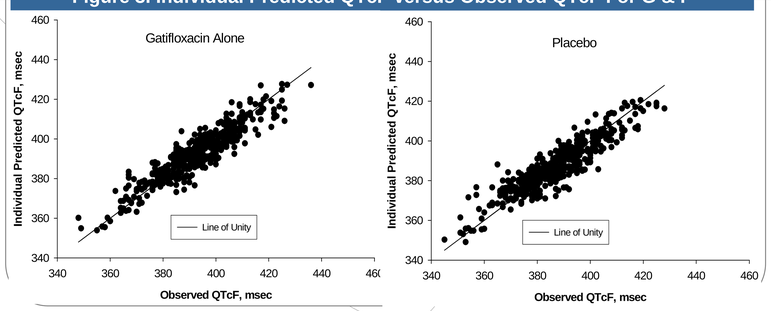


Figure 4. Model Predicted and Observed QTcF For V & V + G

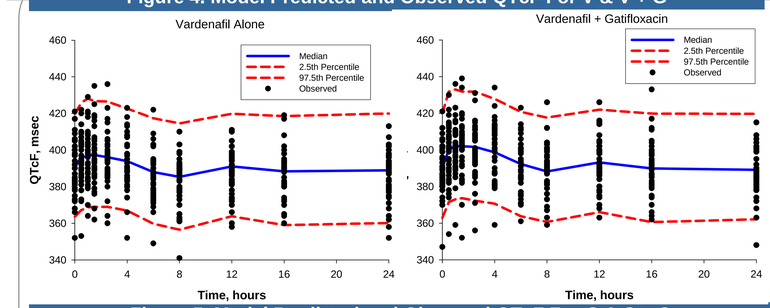


Figure 5. Model Predicted and Observed QTcF For S & S + G

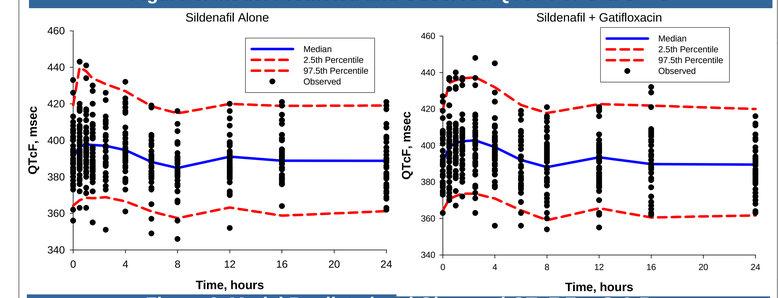
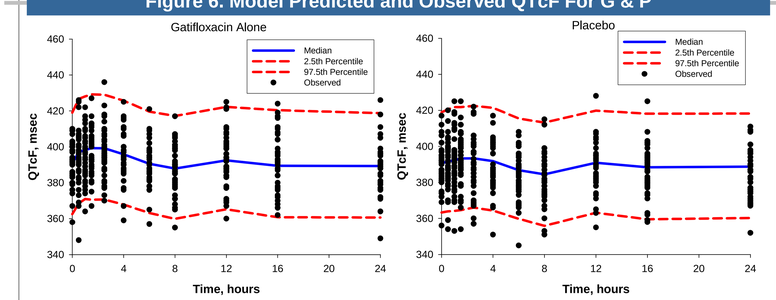


Figure 6. Model Predicted and Observed QTcF For G & P



Conclusions

- After accounting for the diurnal variation in QTcF, the PK/PD relationship between Cp and QTcF prolongation for V, S and G was described using direct effect slope models. The QTcF prolongation for the combination treatments was explained by an additive effect model.
- Based on the model derived individual predicted QTcF, the mean (SD) change from baseline at 1 hour (corrected for placebo) for V, S and G were 4.4 (2.3), 3.6 (3.5) and 6.2 (1.2) msec, respectively. Assuming an additive effect model, the mean change from baseline at 1 hour (corrected for placebo) for V and S when co-administered with G were 9.1 (3.5) and 7.9 (4.1) msec.
- These additive effects on QTc duration should be considered when prescribing vardenafil and sildenafil to patients who are taking other medications known to prolong the QTc interval.

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