MODEL-BASED PREDICTION OF DOMPERIDONE AND KETOCONAZOLE INTERACTION AND IT'S IMPACT ON QTc PROLONGATION

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Introduction

Domperidone (DOMP), a dopamine antagonist, has been shown to prolong cardiac repolarisation by blocking the rapid component of delayed-rectifier potassium current (I_{kr}, see Fig. 1) in a concentration dependent manner. Recent studies, in healthy volunteers, have shown a threefold increase in the exposure of DOMP, in the presence of ketoconazole (KETO), possibly due to the inhibition of CYP3A4 mediated metabolism [1]. This study was conducted to establish the usefulness of modelling and simulation approach in predicting the extent of the proarrhythmic potency of DOMP in the presence of a CYP3A inhibitor, KETO.

Methods

Physiologically Based Pharmaco-kinetic (PBPK) models within Simcyp® (v11.1) were used to predict population PK behaviour in healthy volunteers. A compound file for DOMP was developed within Simcyp using published *in vitro* data [3, 4]. Subsequently, the observed clinical data [5] were fitted by obtaining optimal values for the intestinal permeability, intrinsic clearance and renal clearance (using the Parameter Estimation module within Simcyp). The DOMP compound file was validated against published clinical data from various sources [5, 6, 7] for both IV and oral dosing given in fasted and fed states. To assess the proarrythmic potency of DOMP alone and in the presence of KETO the plasma concentration values at the same time points as reported by Boyce *et al.*, were recorded from the Simcyp outputs and used as inputs in the ToxComp platform (v1.3) to simulate the drug induced QTcF (Fridericia correction) interval change [8, 9]. The *in vitro* I_{Kr} ionic current inhibition data for both drugs were taken from the literature [10, 11], and the I_{Ks} current inhibition was predicted with the QSAR model [12].

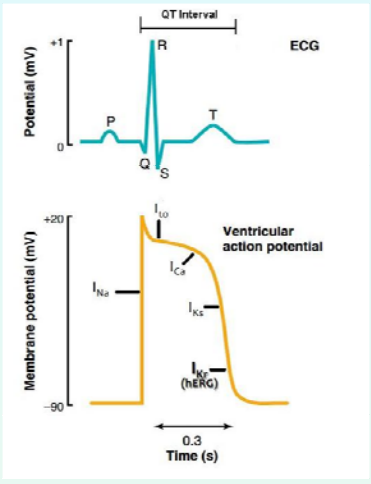

Figure 1. (Top) Schematic representation of a normal electro-cardiogram (ECG) trace or sinus rhythm. (Bottom) monophasic ventricular action potential of single cell, showing the different currents responsible for each phase [2]. (I_{Na}: Na^+ ion influx, I_{to}: K^+ and Cl^- ion efflux, I_{Ca}: Ca^{2+} influx, I_K: K^+ influx, I_{ks} and I_{kr} slow and rapid delayed rectifier currents respectively)

Results and Discussion

The steady-state (day 7) predicted DOMP concentration-time profile superimposed with observed data with and without co-administration of CYP3A inhibitor KETO, for men and women are presented in Fig. 2 & 3. Table 1 presents a comparison of the observed and simulated pharmacokinetic parameters for DOMP in presence and absence of KETO. The predicted plasma concentration values were further utilized to predict the QTcF for males (M) and females (F) following DOMP alone and DOMP+KETO treatments in healthy volunteers. The simulated QTc values superimposed with observed values (Mean ± SD) on Day 7 (steady state) after administration of DOMP in absence and presence of KETO, for male and female volunteers, are presented in Fig. 4 & 5 respectively. The average QTcF (Obs) to QTcF (Sim) ratios at various time points were close to unity. The QTcF ratio for DOMP alone treatment in men was 1.11 and in women was 0.97 and the QTcF ratio for the combined treatment in men was 1.09 and in women was 0.95.

Table 1. Observed (Obs) vs. Simcyp simulated (Sim) PK parameters for single DOMP and DOMP+KETO combination.

Dose	Cmax (ng/mL)	SD	Tmax (hr)	SD/Range	AUC (ng*hr/mL)	SD	AUC Ratio	SD
Obs DOMP	23.5	7.4	9.0	0.5 to 14	249	65		
Sim DOMP	23.3	2.6	12.7	0.04	260	38		
Obs DOMP+KETO	67.9	21.1	5.0	0.5 to 14.1	878	268	3.53	
Sim DOMP+KETO	56.7	4.4	12.8	0.03	738	71	2.88	0.44

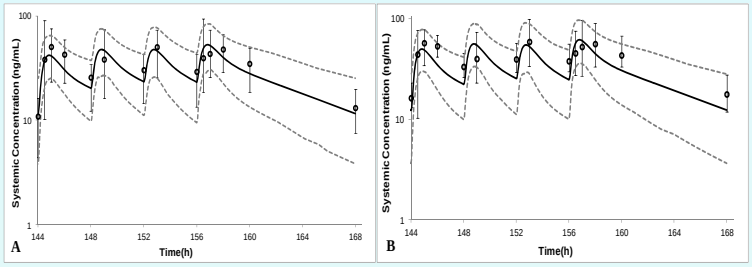

Figure 2. Predicted steady state plasma concentration (solid line) superimposed with observed data (open circles) without KETO in healthy **A:** men and **B:** women volunteers (with 5th & 95th percentiles)

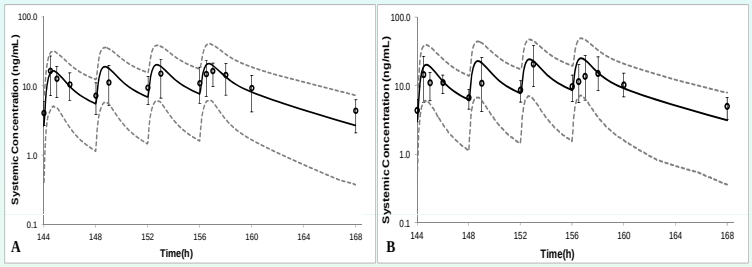

Figure 3. Predicted steady state plasma concentration (solid line) superimposed with observed data (open circles) with KETO in healthy **A:** men and **B:** women volunteers (with 5th & 95th percentiles)

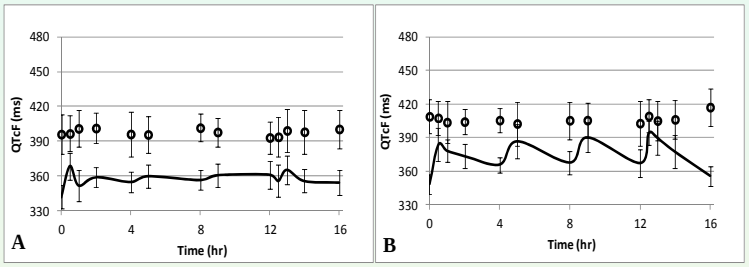

Figure 4. Predicted QTcF values (solid line) superimposed with observed data (open circles) without KETO in healthy **A:** men and **B:** women volunteers (Mean ± SD)

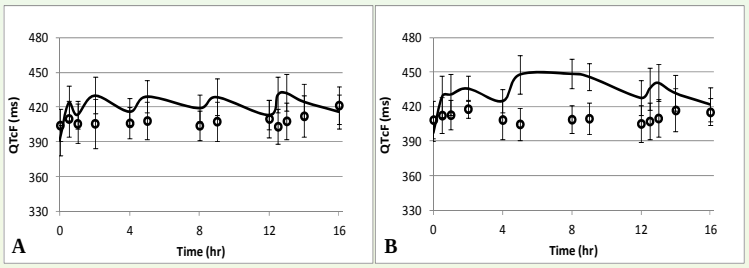

Figure 5. Predicted QTcF values (solid line) superimposed with observed data (open circles) with KETO in healthy **A:** men and **B:** women volunteers (Mean ± SD)

Conclusions

The combination of mechanistic PBPK and Tox modelling and simulation tools (Simcyp and ToxComp) was able to recover Pharmacokinetic and toxicological effect of a single drug, DOMP and its combination with a pharmacokinetically and pharmacodynamically interacting drug, KETO. ToxComp tends to under predict QTc for males and over predict QTc for females which can be due to the heart rate variability. This may require developing and implementing a circadian heart rate variability model which is planned for the future releases of the ToxComp system. In general model-based drug development proved to be a valuable cardiac safety assessment tool.

References:

1. Boyce *et al.*, Br J Clin Pharm, 2012; **2.** Vander *et al.* in *Human Physiology - The mechanism of body function*. 2001; **3.** Chang et.al., Xenobiotica, 2010.; **4.** Ward *et al.*, Br J Clin Pharmacol, 2004.; **5**. Huang, *et al.*, J Clin Pharm, 1986.; **6.** Heykantset.al. Eur J Drug Metab PK, 1981; **7.** Kobylinska and Kobylinska , J Chromatogr, 2000; **8.** Polak *et al.* Toxicol Mech Met, 2012a; **9**. Polak *et al.*, www.Tox-Portal.net; **10**. Claassen and Zunkler, Pharmacology, 2005; **11.** Ridley *et al.*, FEBS Lett, 2006.; **12.** Polak *et al.*, J Appl Toxicol, 2012b.