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Physiologically Based Pharmacokinetic Modeling to Determine Haloperidol-Rifampicin Interactions (Poster Code: 005)

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INTRODUCTION

Rifampicin is an inducer of CYP3A4, which is the major metabolizing enzyme of the first-generation antipsychotic including haloperidol. Studies have shown that haloperidol plasma concentrations were reduced when the drug is co-administered with the anti- Tuberculosis drug, rifampicin. No prior physiological based pharmacokinetic study has demonstrated the interaction using the simulation software.

OBJECTIVES

The objective of our study is to simulate healthy model of individuals who are on haloperidol treatments and investigate the effects of rifampicin treatments on plasma concentration of haloperidol in TB patients using a simulation software.

METHODS

Firstly, we were able to create healthy model of individuals and population who are on haloperidol regimen (oral and intravenous dosage forms) using the PK-SIM software. We also found that there is a significant reduction on plasma levels of haloperidol in patients who are on rifampicin compared to those who are only on rifampicin therapy using the same software.

Parameter	Unit	Input value	Reported value	Reference
Physicochemical properties				
Molecular weight	g/mol	375.864	375.864	*HMD*
Effective molecular weight	g/mol	336.86	336.86	*PK-Sim*
Lipophilicity	Log	4.30	4.30	*PubChem*
Water solubility	mg/ml	0.0045	0.0045	*HMD*
pKa	--	8.66	8.66	*Drug bank*
Absorption				
Intestinal permeability	cm/min	4.50E-5	4.50E-5	*Optimized*
Distribution				
Fraction unbound	%	11.6	7.5 – 11.6	*Optimized*
Partition coefficient model	--	Berezhkovskiy	--	*PK-Sim*
Cellular permeability model	--	PK-Sim default	--	*PK-Sim*

Parameter	Unit	Input value	Reported value
Renal clearance			
GFR fraction	%	1	1
Enzymatic biotransformation			
CYP3A4 - Km (N-dealkylation to 4-FBPA)	µmol/L	62	50 – 78 (range)
CYP3A4 -Vmax (N-dealkylation to 4-FBPA)	pmol/min/mg	289	180 – 412 (range)
CYP3A4 - Km (oxidation to HPP+)	µmol/L	55.3	55.3
CYP3A4 -Vmax (oxidation to HPP+)	pmol/min/mg	48	48
Carbonyl reductase - Km (reduction)	µmol/L	250	250 ± 140 (mean ± SD)
Carbonyl reductase - Vmax (reduction)	µmol/min/g	1.50	1.50 ± 0.60 (mean ± SD)
UGT1A4 - Km (O-glucuronidation)	µmol/L	64	64.0 ± 90 (mean ± SD)
UGT1A4 - Vmax (O-glucuronidation)	nmol/mg/min	0.6	0.60 ± 00 (mean ± SD)
UGT1A9 - Km (O-glucuronidation)	µmol/L	174	174 ± 59 (mean ± SD)
UGT1A9 - Vmax (O-glucuronidation)	nmol/mg/min	2.3	2.30 ± 0.3 (mean ± SD)
UGT2B7 - Km (O-glucuronidation)	µmol/L	45	45.0 ± 90 (mean ± SD)
UGT2B7 - Vmax (O-glucuronidation)	nmol/mg/min	1.0	1.00 ± 0.1 (mean ± SD)

Table 1. Input parameters used to build the haloperidol PBPK model.

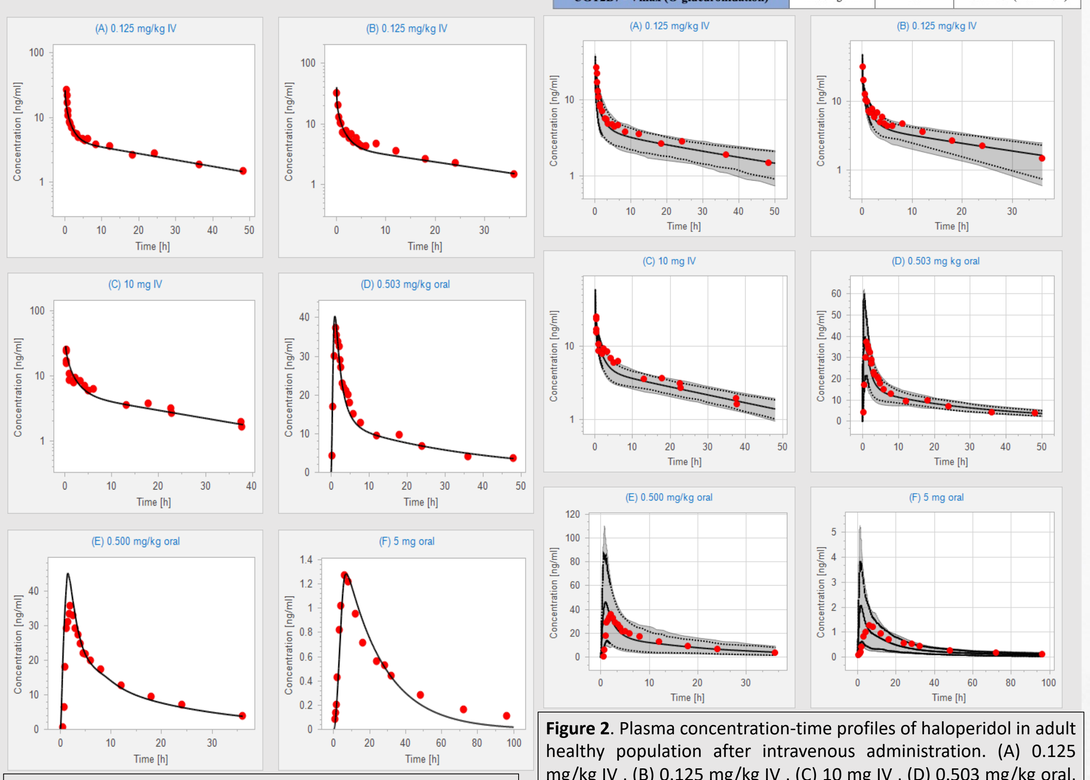

Figure 1. Fitting plots for haloperidol plasma concentration in healthy individuals for structural model assessment purposes. (A) 0.125 mg/kg IV , (B) 0.125 mg/kg IV , (C) 10 mg IV , (D) 0.503 mg/kg oral , (E) 0.500 mg/kg oral , (F) 5 mg oral .

Figure 2. Plasma concentration-time profiles of haloperidol in adult healthy population after intravenous administration. (A) 0.125 mg/kg IV , (B) 0.125 mg/kg IV , (C) 10 mg IV , (D) 0.503 mg/kg oral, (E) 0.500 mg/kg oral , (F) 5 mg oral . The observed data are depicted as red circles and the arithmetic mean of simulated data are depicted as solid black line with the 5th–95th predictive range represented as grey shaded area. The upper and lower dotted lines represent the 90th and 10th percentiles, respectively.

RESULTS

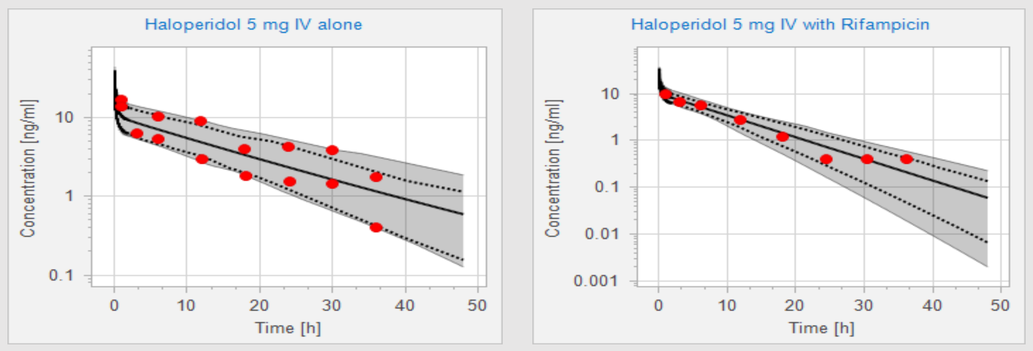

Figure 3. Population PK profiles of 5 mg haloperidol with and without rifampicin in adult psychotic-tuberculotic patients . The 3rd figure illustrate pharmacokinetic profile of the interaction of haloperidol plus rifampicin. Red sold line represents the mean plasma concentration of haloperidol alone, while the black solid line represents the mean plasma concentration of haloperidol + Rifampicin.

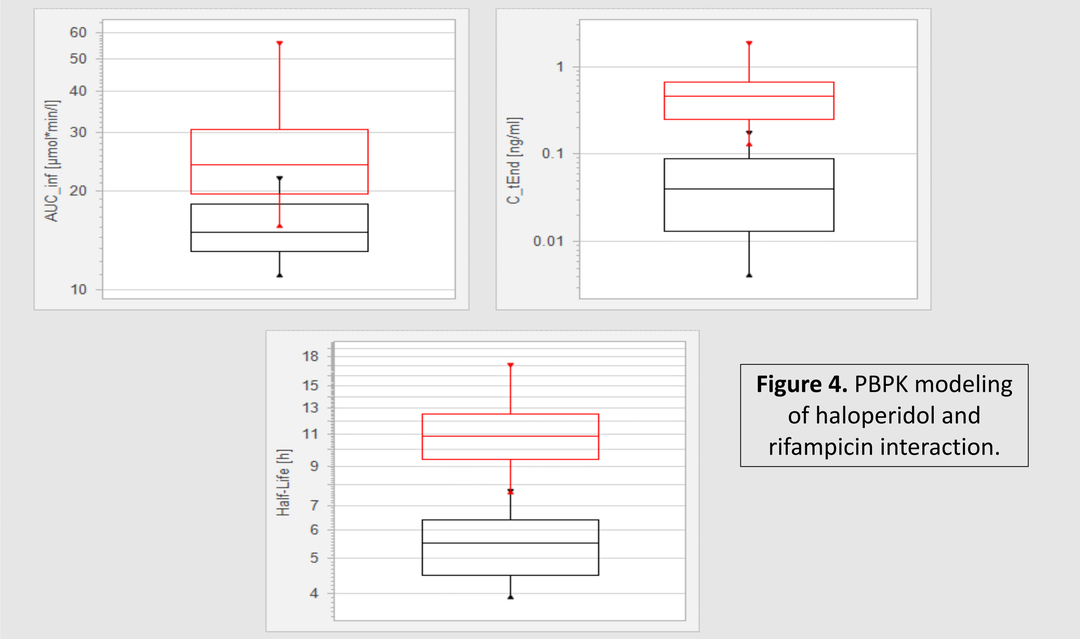

Figure 4. PBPK modeling of haloperidol and rifampicin interaction.

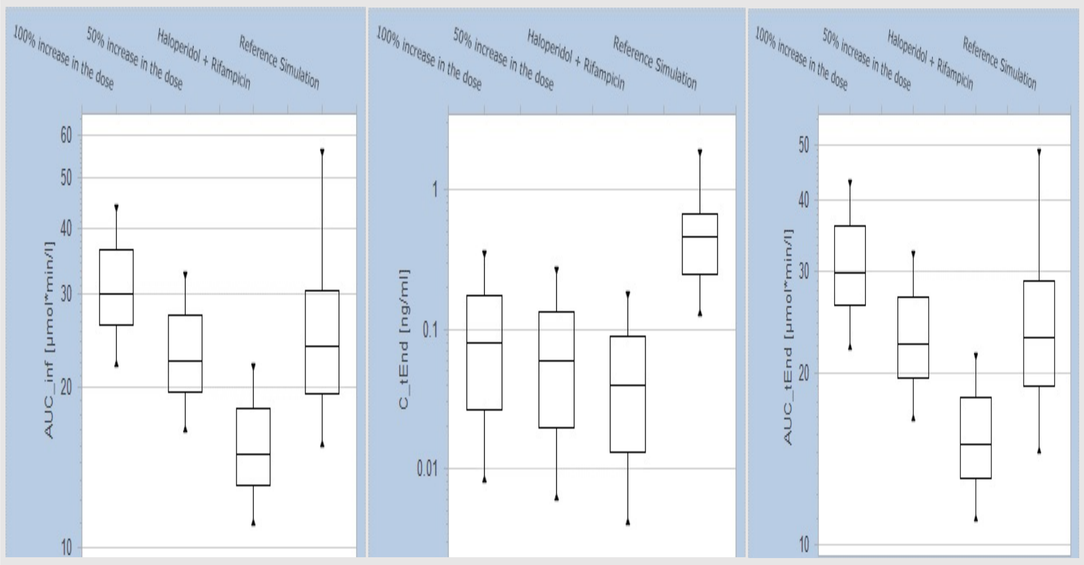

Figure 5. *PK analysis of haloperidol with increasing the dose by 50% and 100%.*

CONCLUSION

We conclude here that dose optimizations of haloperidol might be considered and studied to provide more antipsychotic efficacy in TB patients.

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