A PBPK model-based drug interaction study to inform the dose selection of a new compound

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Background

Drug A is a molecule metabolized mainly by cytochrome P450 2D6 (CYP2D6) and CYP3A4. It is administered orally either as 20 mg or 40 mg dose and it is currently developed to be co-administered with Drug B as a modulator.

Drug B is a molecule essentially metabolized by CYP1A2 and CYP2D6 and is a moderate inhibitor of CYP2D6.

A PBPK approach was employed to study the influence of drug B on the exposure of drug A to determine an optimal dosing for the combo drug.

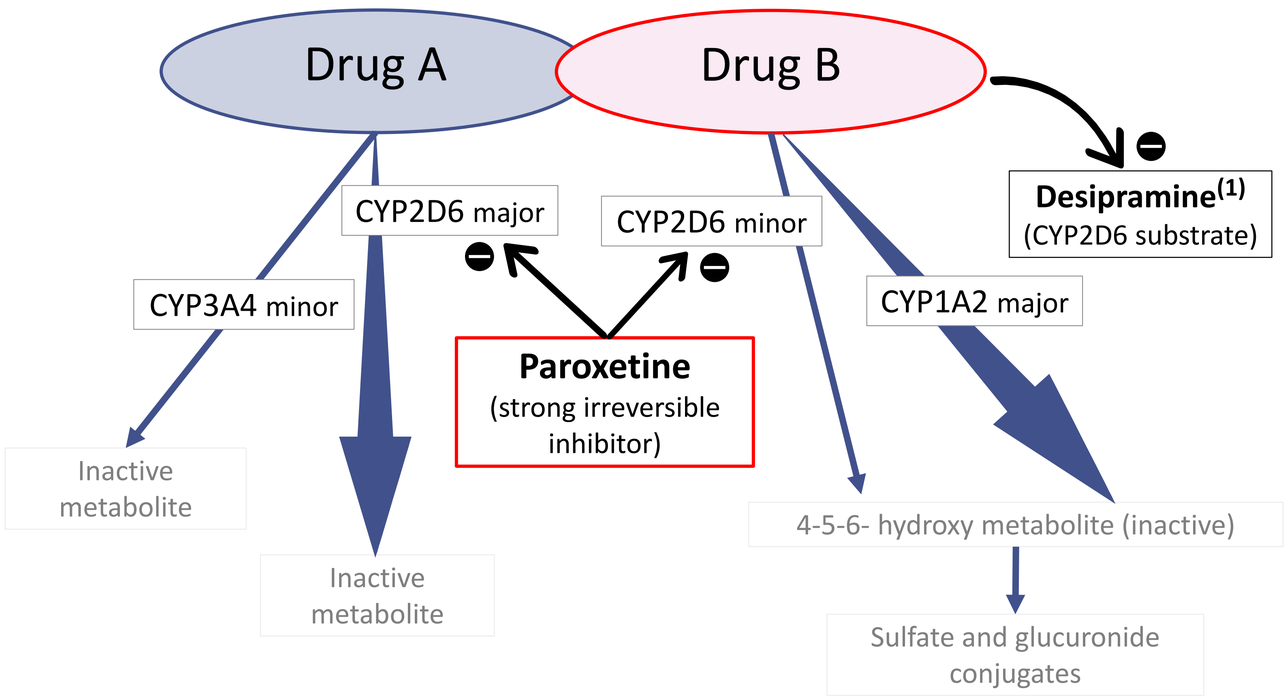

Figure 1. Schematic view of the metabolism pathways of the drugs of interest and their interactions with paroxetine and desipramine. NB: Desipramine PBPK model was downloaded from *Samant et al. 2017*

Objectives

The aim of the study was to determine an optimal dosing for the combo drug A+B thus the different objectives were as follow:

- Develop a PBPK model for both drugs (A and B)
- Validate drug B as a perpetrator on a CYP2D6 substrate (desipramine) (1)
- Develop a model for paroxetine to validate drug A as a CYP2D6 substrate (2) and verify the contribution of CYP2D6 in the metabolism of Drug B (3)
- Perform model-based DDI predictions of drug B on drug A (4)

PBPK models development steps

Model development	Input of physico-chemical data and in vitro drug metabolism
	Simulations after IV dosing Adjustment of distribution volume and systemic clearance
	Simulations after PO dosing Characterization of pre-systemic disposition
Model verification	Validation of Oral disposition (external PK datasets)
	Population simulations (50 subjects), goodness of fit with 95% confidence interval
DDI validation and prediction with intended use	Validation of Drug B as a perpetrator on a CYP2D6 substrate Validation of drug A as substrate on CYP2D6 (paroxetine)
	Predictions of DDI with Drug B as a perpetrator and drug A

PBPK analysis Results

(1) Validation of drug B as a CYP2D6 perpetrator on desipramine

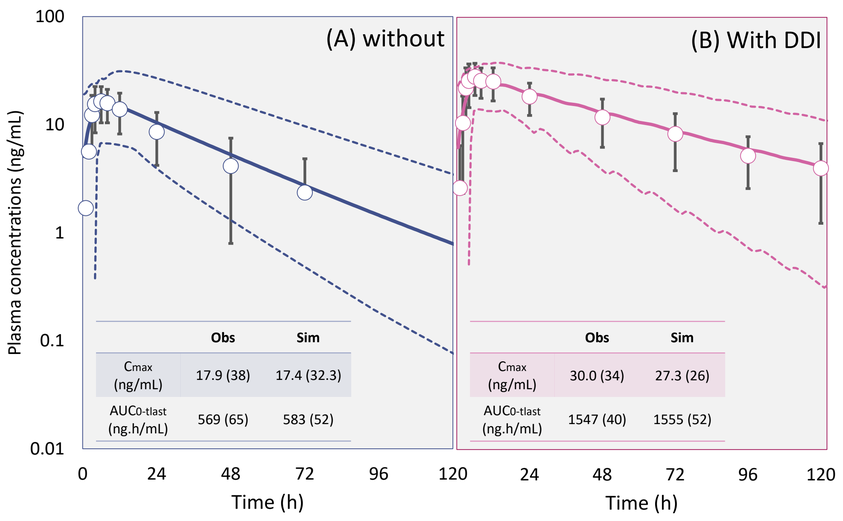

Figure 2. Mean simulated (solid lines, N= 50 subjects) and observed [2] (open symbols ±SD) Cp-time profiles of desipramine after an oral administration of 50 mg without (A) or with (B) pre-treatment with drug B 60 mg for 7 days. Dotted lines represent the 5th and 95th percentiles

(2) Validation of Drug A as a CYP2D6 substrate with paroxetine

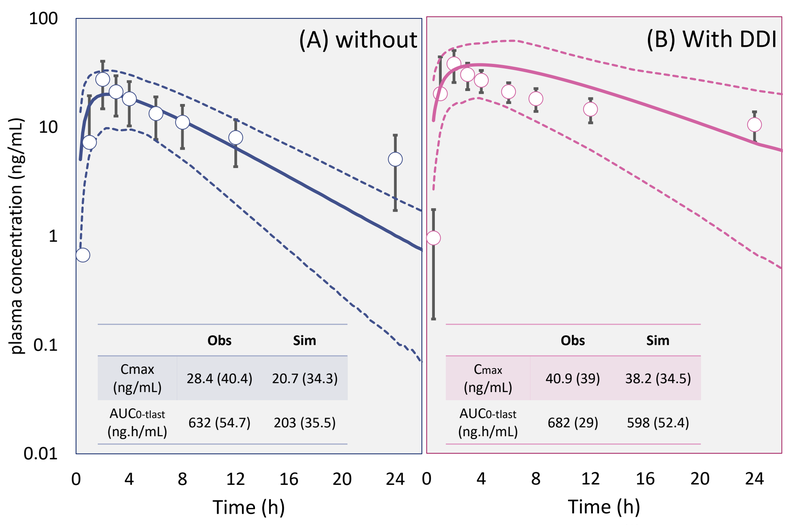

Figure 3. Mean simulated (solid lines, N= 50 subjects) and observed [3] (open symbols ±SD) Cp-time profiles of drug A after an oral administration of 20 mg without (A) or with (B) pre-treatment with paroxetine 20 mg for 6 days. Dotted lines represent the 5th and 95th percentiles

(3) Verification of CYP2D6 contribution on drug B with paroxetine

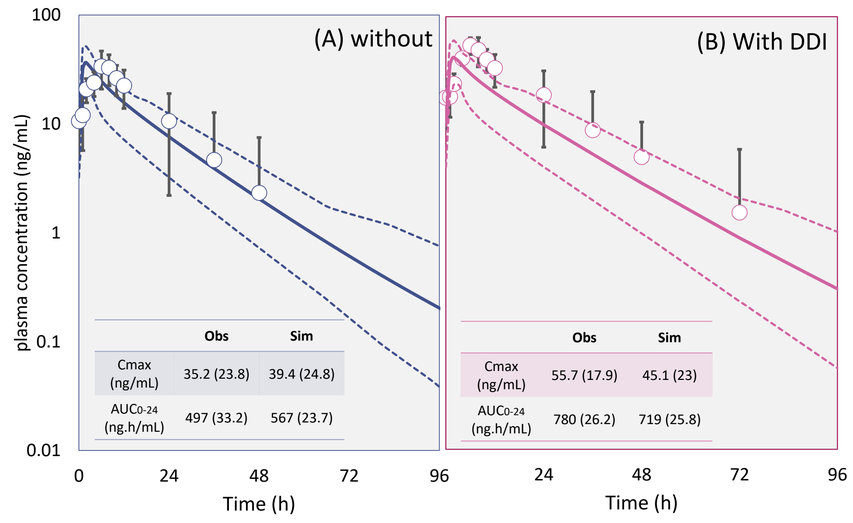

Figure 4. Mean simulated (solid lines, N= 50 subjects) and observed [2] (open symbols ±SD) Cp-time profiles of drug B after an oral administration of 40 mg without (A) or with (B) pre-treatment with paroxetine 20 mg for 20 days. Dotted lines represent the 5th and 95th percentiles

Ratios of simulated versus observed of the DDI studies

		Cmax Ratio Sim / Obs	AUC 0-t Ratio Sim / Obs
(1)	Desipramine 50 mg without	0.97	1.02
	Desipramine 50 mg with drug B 60 mg	0.91	1.00
(2)	Drug A 20 mg without	0.73	0.56
	Drug A 20 mg with paroxetine 20 mg	0.93	0.88
(3)	Drug B 40 mg without	1.11	1.14
	Drug B 40 mg with paroxetine 20 mg	0.81	0.92

Table 1. Ratio of simulated over observed PK parameters Cmax and AUC0-t of the different drug-drug interaction studies. The model was deemed acceptable if the ratio was contained within the 2-fold range error range (0.5 – 2)

(4) Predictions of the DDI effect of drug B on drug A

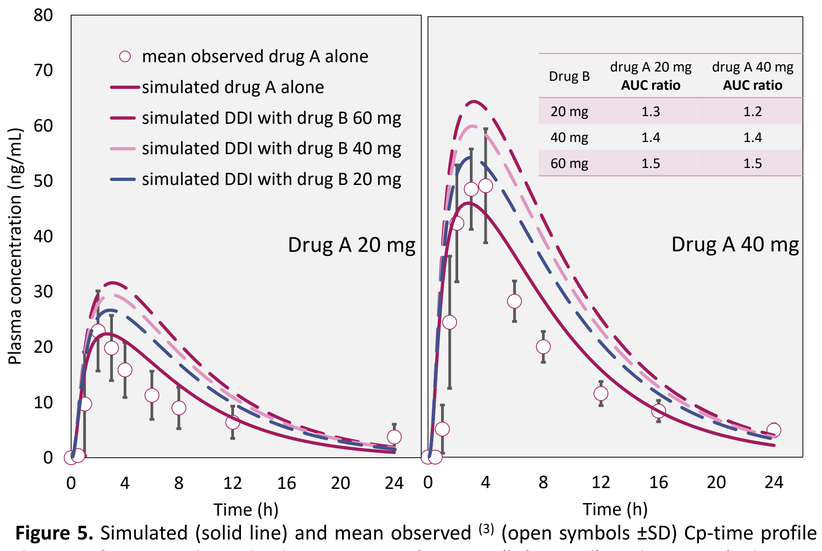

Figure 5. Simulated (solid line) and mean observed [3] (open symbols ±SD) Cp-time profile of drug A after a single oral administration of 20 mg (left panel) and 40 mg (right panel). Simulated exposure (dotted lines) of drug A with co-administration of drug B at different dose levels

- ✓ The model-based DDI simulations accurately described the observations with all ratios (Sim/Obs) contained in the 2-fold error range (table 1)
- ✓ The results of the predictions suggested that the administration of drug A (20 or 40 mg) would result in a 1.5-fold increase of the AUC when administered with 60 mg of drug B
- ✓ The administration of drug A 40 mg with drug B 60 mg should be taken with caution
- ✓ These results were satisfying and instructive enough to make a decision

Conclusion

The PBPK models successfully developed were able to contribute to the dose selection. Therefore the PBPK modelling approach could be used as a valuable tool in the drug development and help in the decision making.

References

Modelling and simulations performed with GastroPlus version 9.6

(1) *Samant et al. 2017* development and qualification of physiologically based pharmacokinetic models for drugs with atypical distribution behaviour: a desipramine case study

(2) *Skinner et al. 2003* duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers

(3) Clinical study data provided by the sponsor