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 in a lesser extent by CYP3A4. It is administered orally either as 20 mg or 40 mg dose and 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.

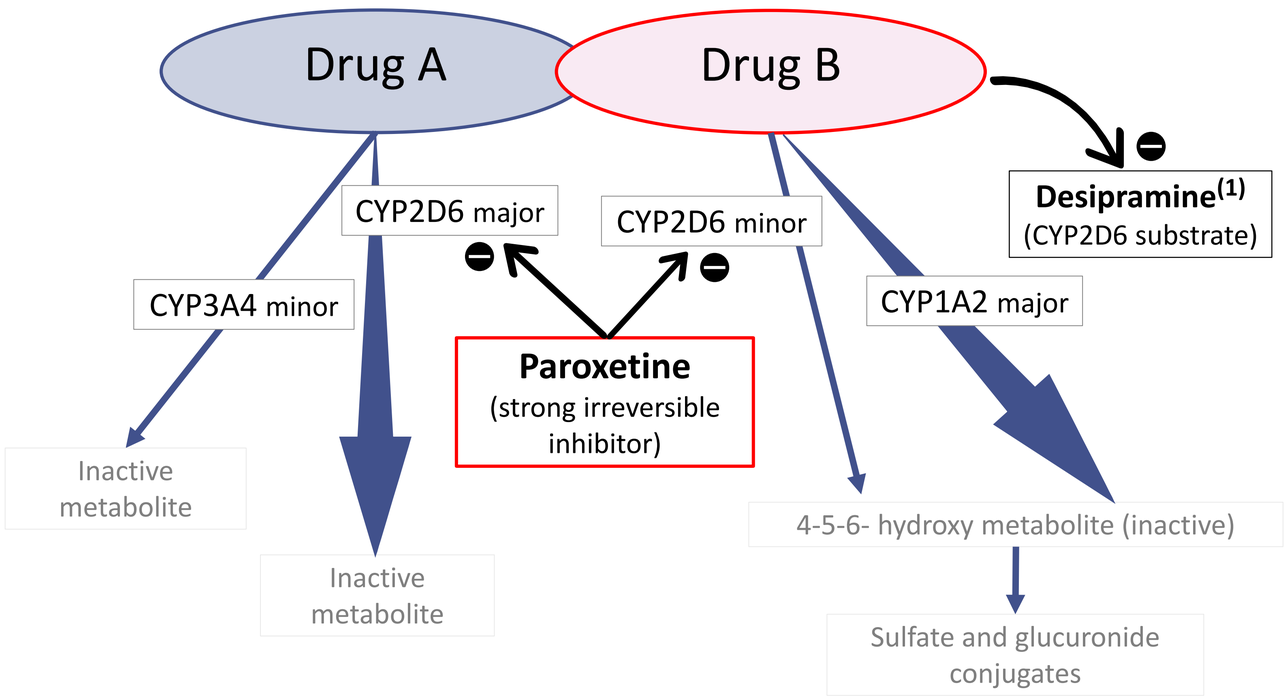

Figure 1. Schematic view of the metabolism pathways of the drugs of interest and their interactions with paroxetine and desipramine. (1) Desipramine PBPK model was downloaded from *Samant et al. 2017*

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 a substrate of 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

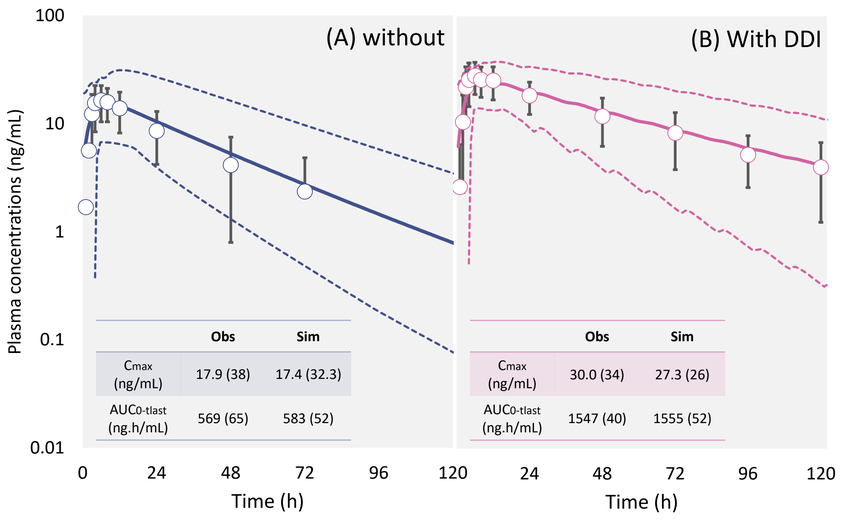

Figure 2. Mean simulated (solid lines, N= 50 subjects) and observed (2) (open symbols ±SD) Cp-time profiles of desipramine after an oral administration of 50 mg without (A) or with (B) pre-treatment with drug B 60 mg for 7 days. Dotted lines represent the 5th and 95th percentiles

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

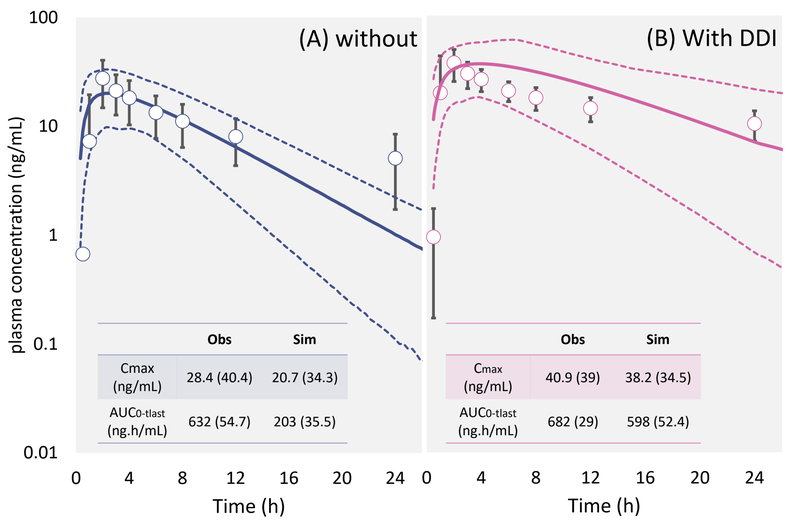

Figure 3. Mean simulated (solid lines, N= 50 subjects) and observed (3) (open symbols ±SD) Cp-time profiles of drug A after an oral administration of 20 mg without (A) or with (B) pre-treatment with paroxetine 20 mg for 6 days. Dotted lines represent the 5th and 95th percentiles

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

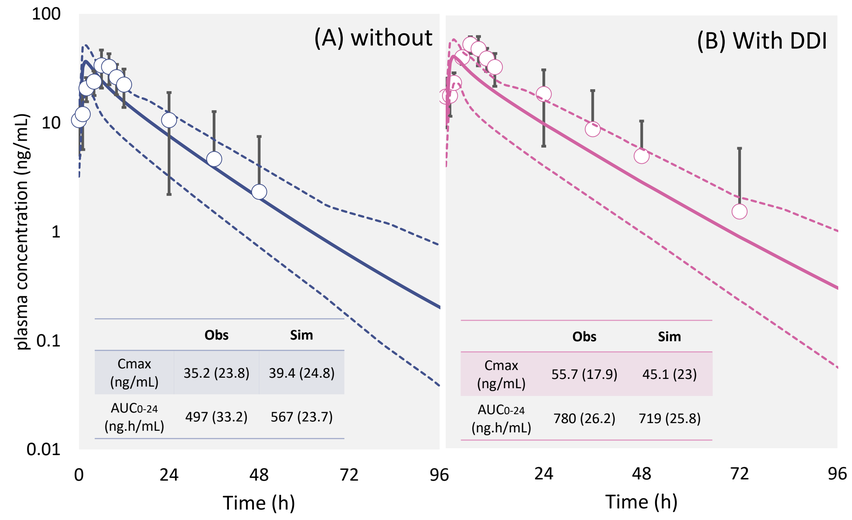

Figure 4. Mean simulated (solid lines, N= 50 subjects) and observed (2) (open symbols ±SD) Cp-time profiles of drug B after an oral administration of 40 mg without (A) or with (B) pre-treatment with paroxetine 20 mg for 20 days. Dotted lines represent the 5th and 95th percentiles

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 error range (0.5 – 2)

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

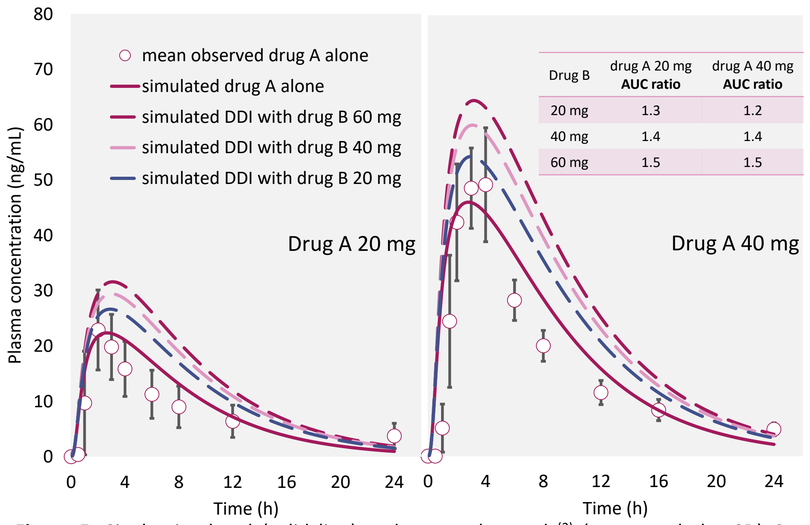

Figure 5. Single simulated (solid line) and mean observed (3) (open symbols ±SD) Cp-time profile of drug A after a single oral administration of 20 mg (left panel) and 40 mg (right panel). Simulated exposure (dotted lines) of drug A with co-administration of drug B at different dose levels

- ✓ 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