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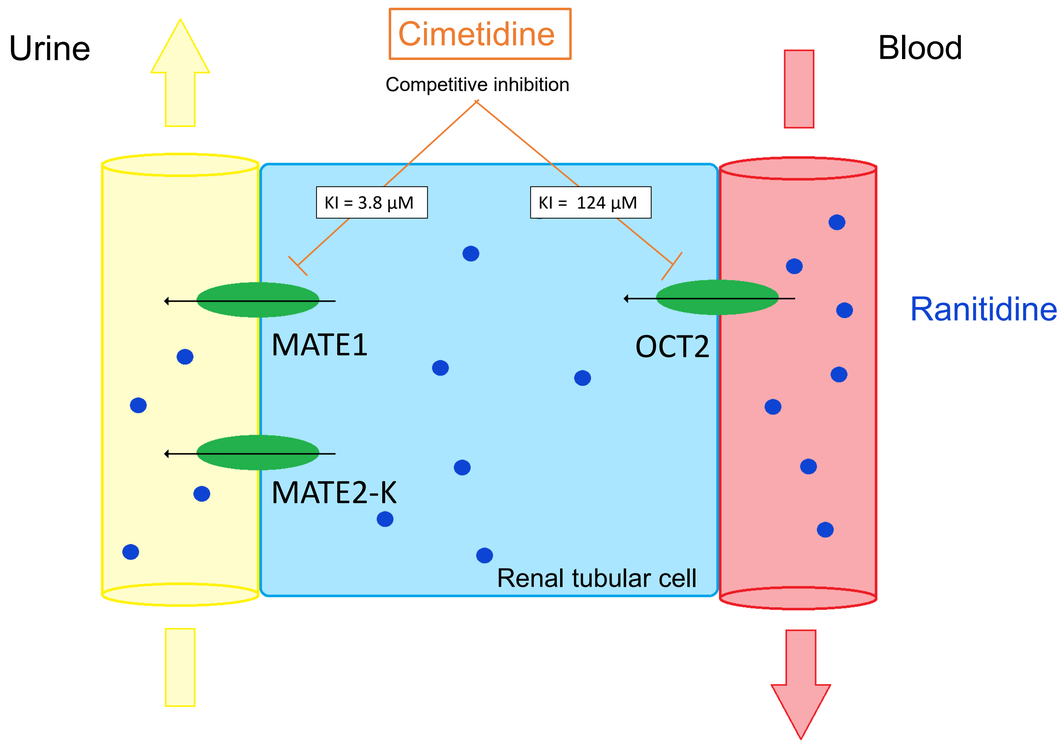
Development of a kidney transporter-mediated drug-drug interaction between cimetidine (perpetrator) and ranitidine (substrate) using PBPK modeling

Background

Tubular secretion for renal clearance relies on carriers and transporters that are subdivided in 2 groups, ATP binding cassette (ABC) and Solute Carriers (SLC). SLC transporters being more abundantly expressed in the kidney and include (as most abundant) OAT1, OAT3, OCT2 and MATE1. These transports have been listed by the Food and Drug Administration (FDA) as well as the international transporter consortium recommendation for drug-drug interaction (DDI) evaluation but also to evaluate the impact of endogenous compound-drug-drug interaction. PBPK modeling and simulation was used in this study to assess the PK of 2 OCT2 and MATE1 substrates, ranitidine and cimetidine and their competitive interaction.



Objectives

The aim of the study was the model building of 2 OCT2/MATE1 substrates, ranitidine and cimetidine, and predict their coadministration as cimetidine is also a perpetrator for the transporter tandem.

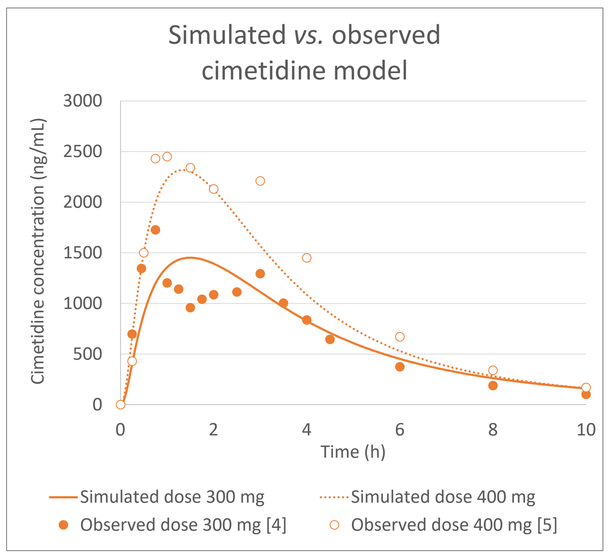
1. Develop a PBPK model for both drugs
2. Validation of Cimetidine as a perpetrator on a OCT2/MATE1 substrate (metformin)
3. Perform DDI predictions of cimetidine as perpetrator on ranitidine as victim

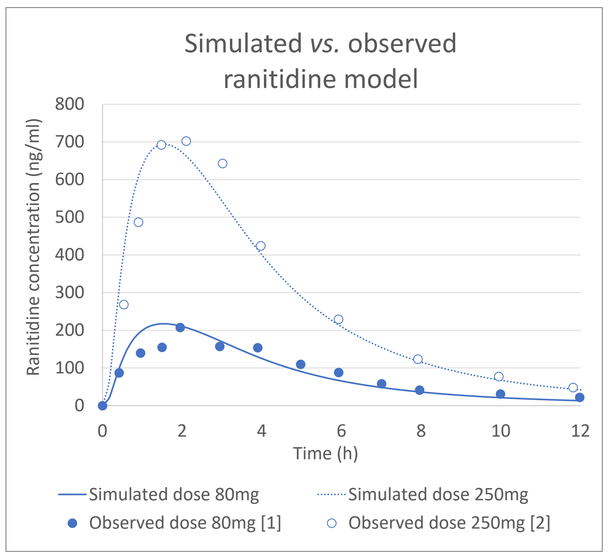
PBPK models development steps

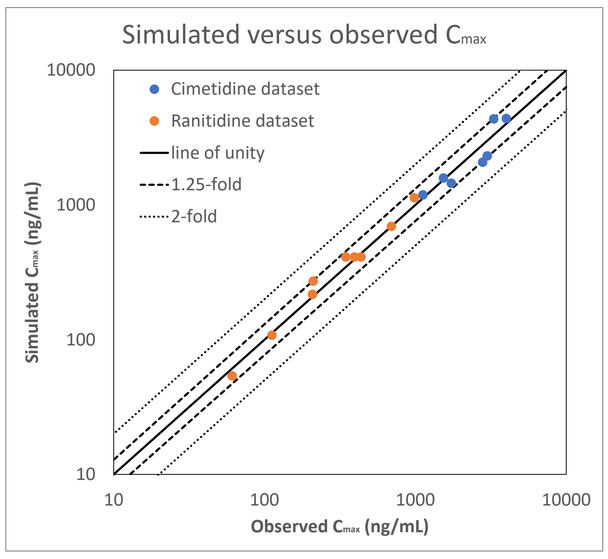
Model development	Input of physico-chemical data and *in vitro* drug metabolism
	Simulations after IV dosing Adjustment of distribution volume and systemic clearance
	Simulations after PO dosing Characterization of pre-systemic disposition
Model verification	Validation of Oral disposition (external PK datasets)
DDI validation and prediction with intended use	Validation of cimetidine as a perpetrator on a OCT2/MATE1 substrate (metformin)
	Predictions of DDI with cimetidine as a perpetrator and ranitidine.

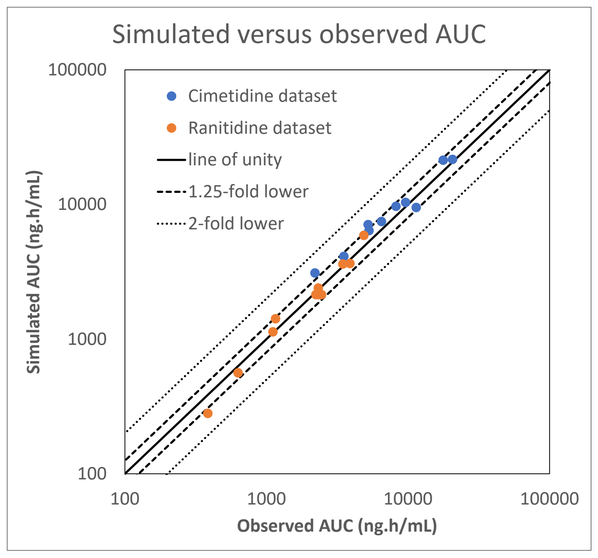
PBPK analysis Results

1 PBPK models development



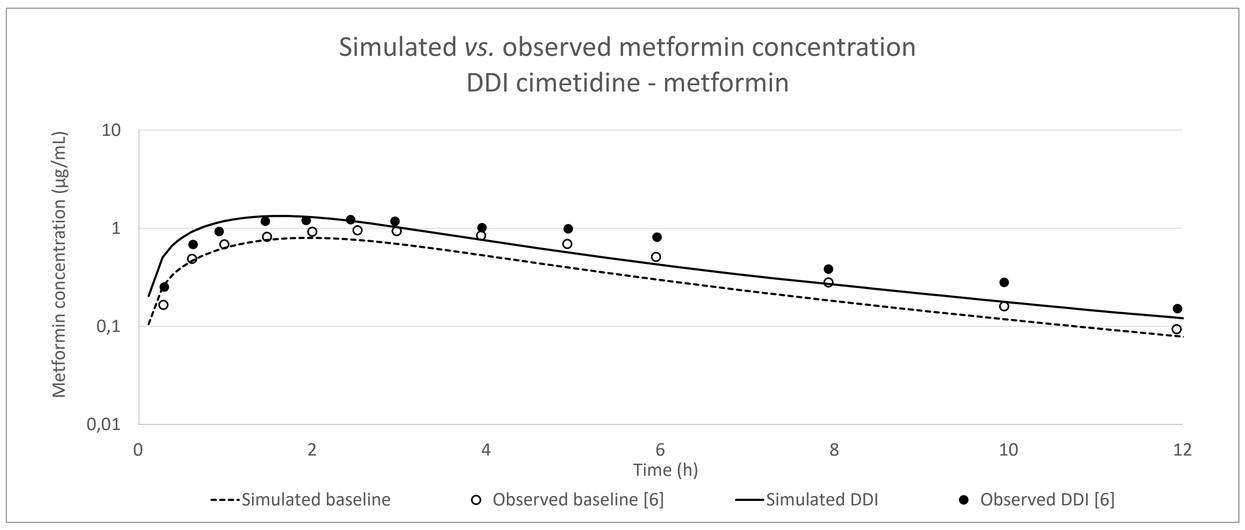






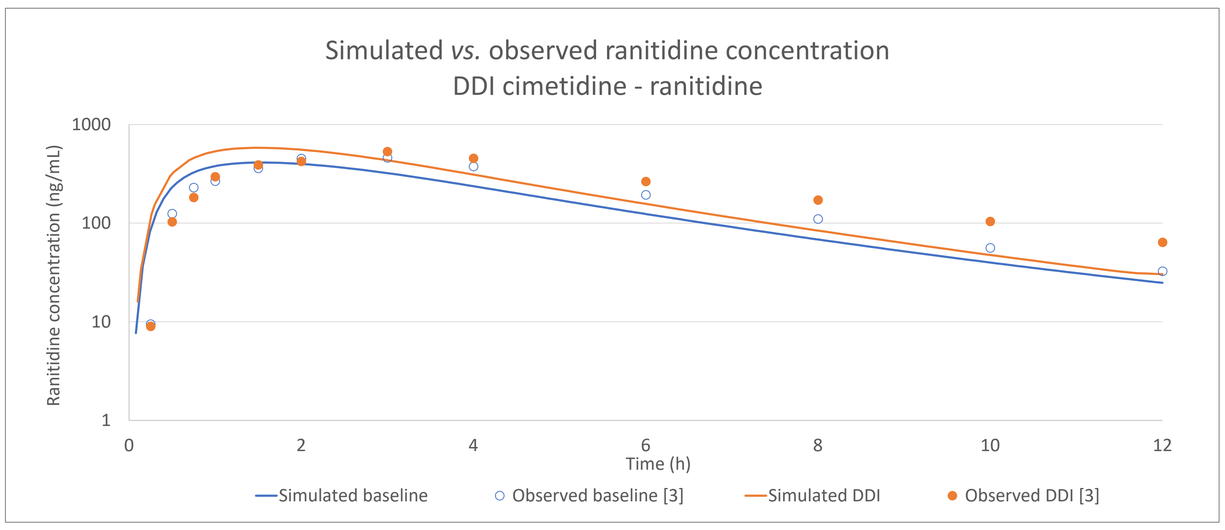
2 Validation of cimetidine as a perpetrator on a OCT2/MATE1 substrate (metformin)

DDI	Interaction ratio			
	Observed C_{max}	Simulated C_{max}	Observed AUC	Simulated AUC
Cimetidine - Metformin	1.41	1.67	1.47	1.56



3 Perform DDI predictions of cimetidine as perpetrator on ranitidine as victim

DDI	Interaction ratio			
	Observed C_{max}	Simulated C_{max}	Observed AUC	Simulated AUC
Cimetidine - Ranitidine	1.02	1.21	1.27	1.22



Conclusion

1. Both PBPK models were successfully developed and verified (both compounds with C_{max} and AUC fold-error within 0.75 and 1.3).
2. Cimetidine as perpetrator on OCT2/MATE1 was validated with fold error on interaction ratio of DDI cimetidine–metformin around 1.2 for C_{max} and 1.06 on AUC.
3. Predictions of DDI with cimetidine as a perpetrator and ranitidine was accurate with fold error of interaction ratio around 1.2 for C_{max} and 0.96 for AUC.

➢ The successful results of theses simulations confirmed the ability of PBPK modeling to assess the contribution of transporters in compound's PK profile and prediction of interactions with substrates of the OCT2/MATE1 tandem.

References

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