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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.

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

## **PBPK models development steps**



#### **PBPK analysis Results**

#### **PBPK models development**

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DDI	Interaction ratio			
	Observed Cmax	Simulated Cmax	Observed AUC	Simulated AUC
Cimetidine - Metformin	1.41	1.67	1.47	1.56

Simulated vs. observed metformin concentration DDI cimetidine - metformin

**Interaction ratio** DDI Observed C<sub>max</sub> Simulated C<sub>max</sub> Observed AUC Simulated AUC 1.27 1.22 1.02 1.21 **Cimetidine - Ranitidine** 

Simulated vs. observed ranitidine concentration

DDI cimetidine - ranitidine



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#### Conclusion

References

Both PBPK models were successfully developed and verified (both compounds with C<sub>max</sub> and AUC fold-error within 0.75 and 1.3).

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.

[1] Woodings, E P et al. - Gut vol. 21,3 (1980): 187-91. [2] Garg, Dyal C. et al. - Journal of Clinical Pharmacology 25.6 (1985): 437-443. [3] Van Crugten et al. - Journal of Pharmacology and Experimental Therapeutics 236.2 (1986): 481-487. [4] D'Angio R et al. - British Journal of Clinical Pharmacology 21.5 (1986): 515-520 al. - European Journal of Clinical Pharmacology Somogyi *et* 19.5(1981): 343-347 [6] Wiebe S et al. - Clinical Pharmacokinetics. 59.12 (2020) : 1627-1639