Human PBPK model of a S compound metabolized by UGTs

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Introduction: The compound S is currently in phase I of development. It has a low absorption due to a low solubility, a metabolic clearance via UDP-Glucuronosyltransferases (UGTs) and no renal clearance. In order to help drug development, to have information about elimination and to test UGTs function in SimCYP® a physiologically-based pharmacokinetic model has been developed.

Materials&Method

- First, absorption and distribution model were validated using an *in vivo* oral clearance CL_{po}, then enzyme intrinsic clearances were introduced.
- Software : SimCYP® 11.01
- Compound S:

  Properties:
  - Small molecule
  - Very lipophilic
  - Low solubility in water

  In vitro data:
  - Blood to plasma ratio : 0.55
  - fu = 0.3%
- Absorption: Compartmental Absorption and Transit (CAT) model with P_{eff} predicted by apparent permeability on Caco-2 cells.
- Distribution: Full PBPK model
  - $P_{t:p}$ predicted by the method of Poulin and Theil
  - $P_{t:p}$ muscle increased (from 6 to 20)
- Elimination:
  - *1st model*: *In vivo* clearance CL_{po} = 16388 L/h (from clinical data)
  - *2nd model*: Enzyme intrinsic clearances were introduced (CL_{int} for UGT1A1, UGT1A9, UGT1A4, CYP1A2, CYP2C8, CYP2C9, CYP3A4) from *in vitro* data.
- Simulation – Trial design:
  - Population Sim-Healthy Volunteers
  - 18-45 years old males
  - 10 trials of 10 subjects
  - Single oral doses in fasted conditions

Discussion/Conclusion :

First elimination model needed physiological improvement with enzyme kinetics in order to be able to predict drug-drug interactions.
Issues were encountered with UGTs in SimCYP®:

- Not all UGTs were present: UGT1A3 is replaced by UGT1A4 and an additional liver and intestine clearance corresponding to UGT1A7, UGT1A8 and UGT1A10 clearances were entered.

- UGTs abundances are missing (some were found in literature) and rUGTs scalars factors neither (need to be adapted by sensitivity analysis).

In conclusion, this 2nd model described well the data but presents some weaknesses: the increase of $P_{t:p}$ muscle is arbitrary, UGTs abundances and UGTs scalars need to be validated by clinical data and fm (determined by sensitivity analysis) need to be validated by DDI clinical results.

Results

- 1st model: Validation of absorption and distribution

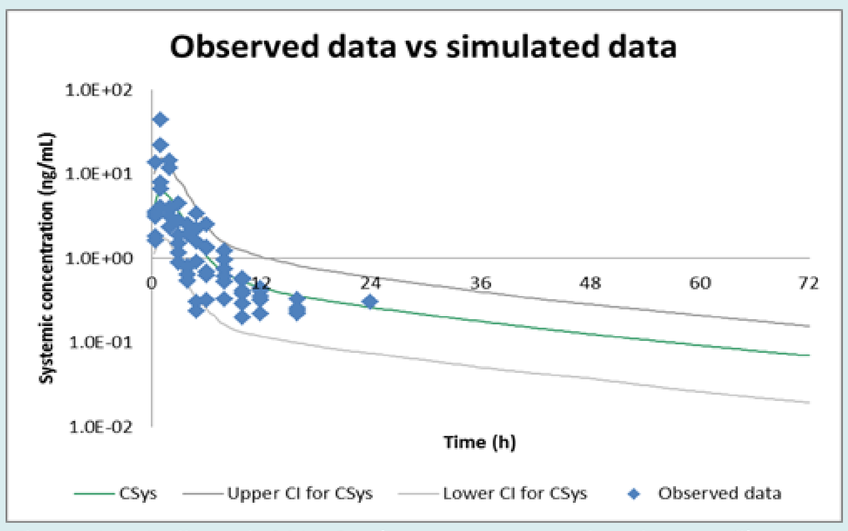

Figure 1 : Median +/- 90% CI plasma concentration-time profiles predicted by SimCYP (green line) vs. observed blood data (blue dots) after single oral administration of X mg of compounds S

- Observed data are well described by the model.
- Absorption is well described by the CAT model despite a slight underestimation of the observed C_{max}.
- Distribution is well described by the full PBPK model. The increase of $P_{t:p}$ muscle allows to better describe the sudden decrease of concentration after C_{max}.
- Elimination is well described by introducing CL_{po} from clinical data. There is no physiological basis.

→ a 2nd model is needed for a more physiological description of the elimination

- 2nd model: Elimination with enzyme clearances

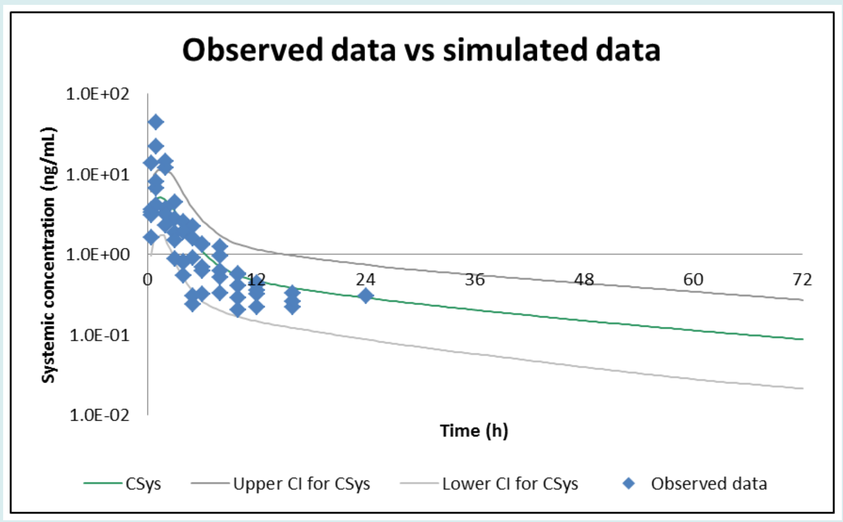

Figure 2 : Median +/- 90% CI plasma concentration-time profiles predicted by SimCYP (green line) vs. observed blood data (blue dots) after single oral administration of X mg of compounds S

PK parameters	Simulation 2nd model Dose = X mg (n=100)	Observed data Dose = X mg (n=6)
AUC (ng/mL.h)	34 (29)	36 (23)
C_{max} (ng/mL)	5.2 (4.7)	15 (7.3)
t_{max} (h)	1.30	1.00
CL_{po} (L/h)	14977 (12526)	16065 (14310)

Table 1 : Comparison of AUC, C_{max}, t_{max} and CL_{po}. Data expressed as mean (median) except tmax as median.

- CYPs: CYP1A2, CYP2C8, CYP2C9, CYP3A4 CL_{int} were entered.
- UGTs: Compound S is metabolized by UGT1A1, UGT1A3, UGT1A7, UGT1A8 UGT1A9 and UGT1A10

Issue : UGT1A3, UGT1A7, UGT1A8 and UGT1A10 are not available in SimCYP®.

↳ UGT1A3 and UGT1A4 have a high nucleic acid sequence homology. UGT1A4 used instead of UGT1A3.

↳ Additional clearance in liver and intestine corresponding to UGT1A7, UGT1A8 and UGT1A10 clearances were added.

Issue : liver UGT abundance are not available in SimCYP®

↳ Liver abundance of UGT1A1, UGT1A9, UGT1A4 were found in literature[1].

→ Observed data are well described by the model. Enzyme kinetics function well captured the elimination model.

- Model evaluation : repeated doses

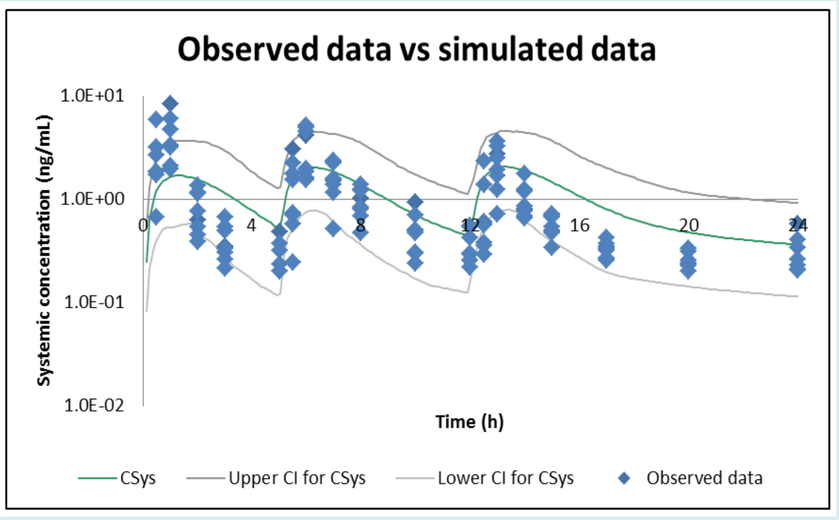

Figure 3 : Median +/- 90% CI plasma concentration-time profiles predicted by SimCYP (green line) vs. observed blood data (blue dots) after repeated oral administration of X mg of compounds S

- Observed data are well described by the model after repeated oral doses.
- A slight underestimation of the 1st C_{max} is observed.

1. Harbourt et al. Quantification of human uridine-diphosphate glucuronosyl transferase 1A isoforms in liver, intestine and kidney using nanobore liquid chromatography – tandem mass spectrometry. Anal.Chem 2012,84:98-105