ENDOGENOUS DDI BIOMARKERS

PBPK-QSP model of cholesterol and its CYP3A4 metabolite 4ß-OH cholesterol

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Intro

Drug-drug interactions (DDIs) can lead to adverse effects or therapeutic failure of a new drug candidate. Therefore, DDIs are a major concern in drug development and clinical practice, particularly with drugs that are metabolized by cytochrome P450 (CYP) enzymes. Preclinical *in vitro* data often overpredict the ability of small molecules to DDI through the induction of CYP3A4, and *in vivo* human data are required. Traditionally, the potency of new drug candidates to induce CYP-mediated metabolism and, by that, to be involved in DDIs with CYP-cleared drugs is assessed in clinical studies by co-administration of sensitive index substrates such as midazolam. This approach is time- and cost-intensive and involves additional exposure of test subjects to medications. 4β-OH cholesterol (4bOH) has been suggested as an alternative endogenous biomarker for CYP3A4 induction (1).

Objectives

To develop a PBPK model for cholesterol and its metabolite 4bOH and qualify it for evaluation and prediction of CYP3A4 induction potential of new drug candidates. The model should be used in an automated R-framework to assess CYP3A4 induction potency of a drug candidate from *in vitro* or *in vivo* data.

Methods

PBPK models of cholesterol and its metabolite 4bOH were developed with the Open Systems Pharmacology (OSP) Suite (2), version 11.2, and coupled with published inducer and victim models from the OSP CYP3A4-DDI network (3). The model was calibrated with published 4bOH data from perturbation scenarios with efavirenz and carbamazepine as CYP3A4 inducers. 23 DDI scenarios from the qualified database have been simulated, and area under the curve (AUC) ratios (AUCR) and concentration ratio (ConcR) reported for index substrates were compared with predicted 4bOH AUCR and concentration ratios.

Results

A schematic representation of the modeled processes is shown in **Figure 1**. The model includes endogenous production of cholesterol in the gut and liver, cholesterol conversion to 4bOH by CYP3A4, and liver plasma clearance. 4bOH is eliminated through liver plasma clearance. The framework integrates PBPK models of CYP3A4 inducers efavirenz, carbamazepine, and rifampicin.

The model accurately describes the observed increase in 4bOH concentrations after administrations of various CYP3A4 inducers. Exemplary simulations of DDI studies with administrations of rifampicin (panel a) and efavirenz (panel b) are shown in **Figure 2.**

23 DDI scenarios from the OSP model database with rifampicin and efavirenz as CYP3A4 inducers and midazolam and alprazolam as CYP3A4 victims have been simulated with the developed model to deduce a relationship between changes in 4bOH levels and the potency of CYP3A4 induction **(Figure 3).** The predicted median 4bOH ConcR (with induction / without induction) is 2.58, 1.82, 1.24, and 1.07 to discriminate among strong, moderate, mild, and no induction classifications (**Table 1**).

Conclusion

The developed PBPK-QSP model supports the idea of using 4bOH as a sensitive endogenous marker for CYP3A4 induction. The model can be used to a) predict induction potency of a drug candidate from *in vitro* data or b) to estimate induction parameters from clinically measured 4bOH data. A future regulatory acceptance of 4bOH as an important biomarker could bridge the gap between overpredicting CYP3A4 induction from *in vitro* data and the need for clinical DDI studies with midazolam. This could save unnecessary DDI trials, particularly in oncology or other fields, where exposure to the drug candidate should be kept to the minimum required.

PBPK model describes **4ß-OH cholesterol increase** during **CYP3A4 induction**

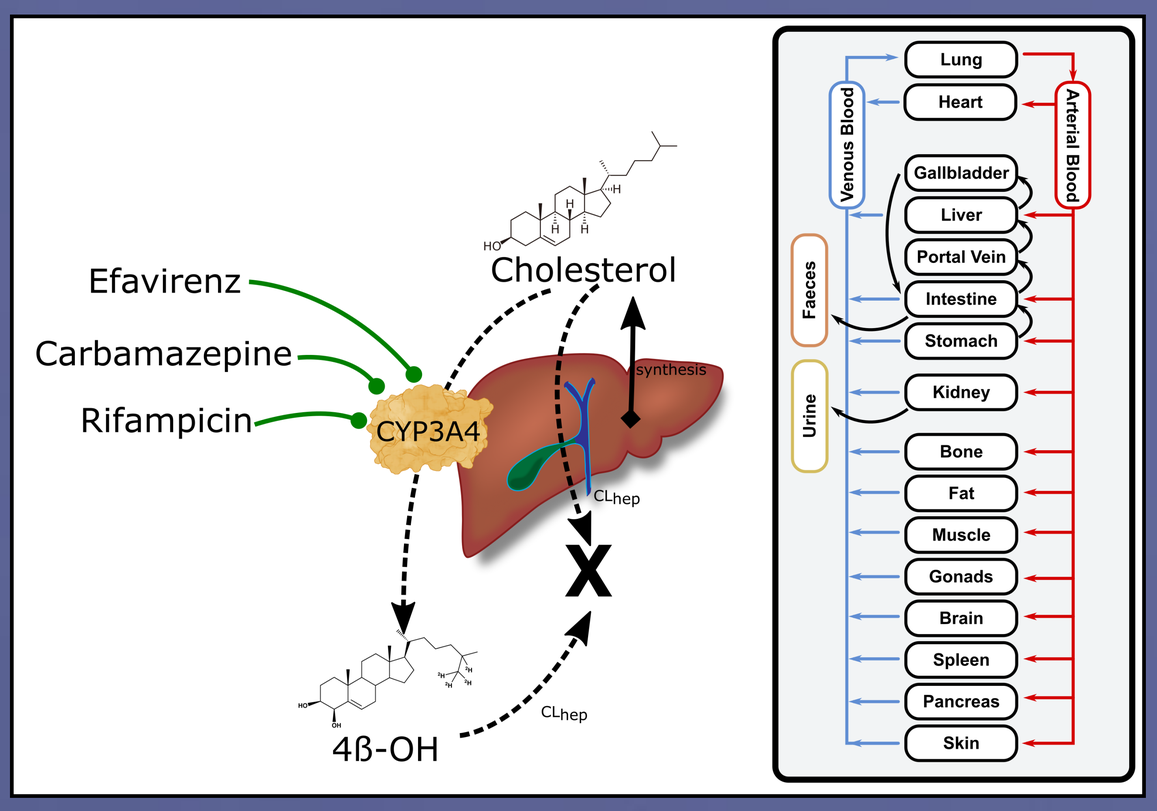


Figure 1: Simplified schema of modeled processes. CLhep: Unspecific hepatic clearance. 4ß-OH: 4-ß hydroxycholesterol. The right part shows the organs considered in the PBPK structure.

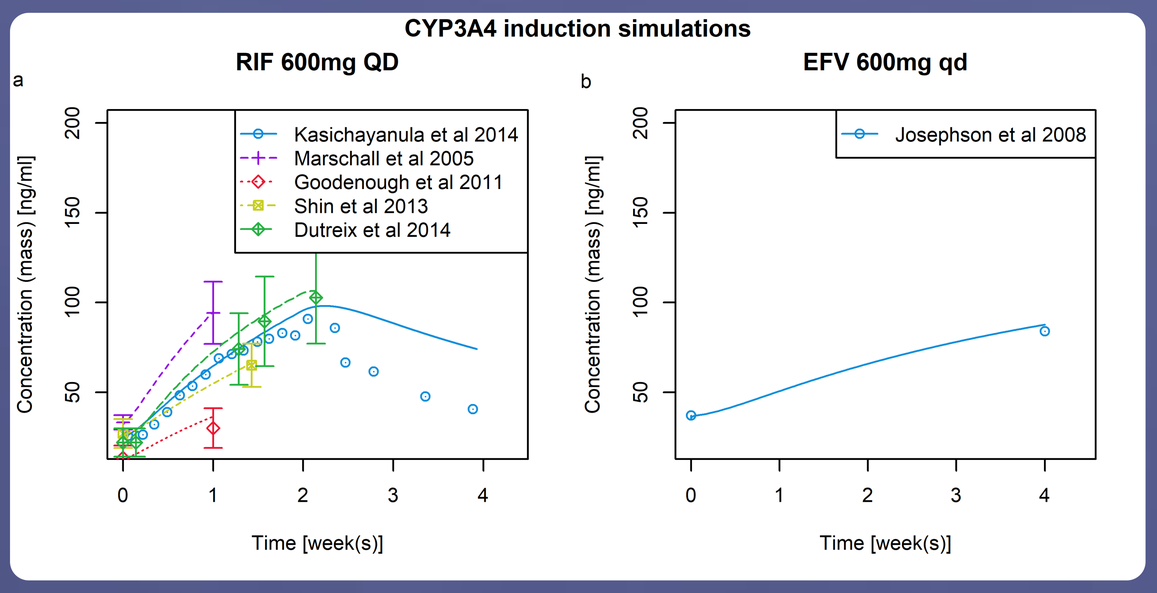
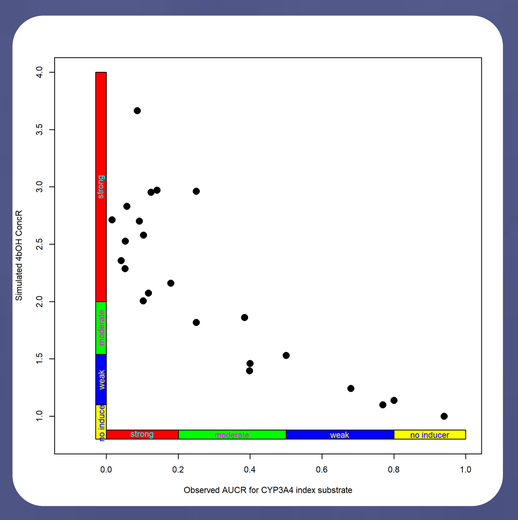


Figure 2: DDI studies simulations. Simulated (lines) and observed (symbols) plasma concentrations of 4bOH during treatment with CYP3A4 inducers. Panel a: 600 mg rifampicin QD. Panel b: 600 mg efavirenz QD.



Index AUCR	4bOH ConcR
<0.2 (strong inducer)	> 2
>=0.2; <0.5 (moderate inducer)	>1.45 and <= 2
>=0.5; <0.8 (weak inducer)	>1.1 and <=1.45
>=0.8 (no inducer)	<=1.1

Figure 4: Observed AUCR for reference index substrates vs. predicted 4bOH concentration ratios (ConcR).
Table 1: Proposed 4bOH concentration ranges for classification of inducer potency.

References

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[2] www.open-systems-pharmacology.org

[3] Frechen, S et al. CPT Pharmacomet Syst Pharmacol. 2021, DOI: 10.1002/psp4.12636

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