Using microdose-based activity measurement to individualise dosing of cytochrome P450 metabolised drugs: a case study with yohimbine and tamoxifen

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Background

- Clearance (CL) is an important driver of pharmacokinetic (PK) interindividual variability (IIV).
- **Genotype-derived phenotypes** can predict a patient's individual clearance (iCL) to a certain extent, but **have limitations**.
- **Direct estimation** of enzyme activity using a **microdosed probe** drug can be an option to derive iCL more reliably.
- A patient's iCL can be used for **model-informed precision dosing** (MIPD)[1].

Objective

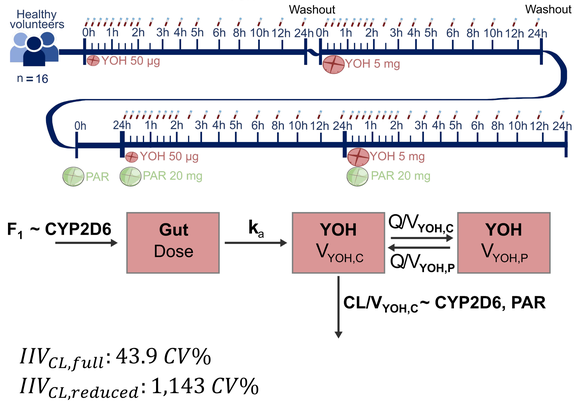
- Use the **CYP2D6 substrates** yohimbine (YOH as a microdosed probe drug and tamoxifen (TAM) as a **proof-of-concept** of a workflow to perform MIPD based on measured enzyme activity.
- Apply the workflow to predict the dose needed to reach the tamoxifen metabolite endoxifen (ENDX) target concentration of 5.97 ng/ml[2].

Conclusion

- Use of probe substrates and modelling and simulation to estimate iCL based on **only few samples** and performing **MIPD** based on this is **feasible** and overcomes many of the limitations of using the genotype-predicted phenotype.
- A **prospective clinical trial** could be performed to evaluate the proposed dosing adaptations. The developed workflow is **easily applicable to other compounds**.

WORKFLOW: Yohimbine model development

- **Model development** was performed based on a study investigating oral YOH as predictor for CYP2D6 activity[3] including microdose (50µg) and normal dose (5mg), the CYP2D6 genotype-derived phenotype and CYP2D6 interaction with paroxetine (PAR) using NONMEM v. 7.4.
- **Final PK model**: two-compartmental model with first-order absorption and linear elimination.
- **Model reduction**: the model was refitted to the uninhibited microdose data, blinded for the attributed CYP2D6 activity score to mimic the application where this data is not available, leading to a large increase in IIV_{CL}, indicating the significance of CYP2D6 activity on CL_{YOH}.



$$IIV_{CL,full}: 43.9\ CV\%$$
$$IIV_{CL,reduced}: 1{,}143\ CV\%$$

Figure 1: YOH model development: top: clinical study design, bottom: final PK model structure. YOH: yohimbine, PAR: paroxetine, F_1: bioavailability, k_a: first-order absorption rate constant, $V_{YOH,C}$: central volume of distribution, CL: clearance, $V_{YOH,P}$: peripheral volume of distribution, Q: intercomparmental clearance, IIV: interindividual variability.

Optimal experimental design

- **Optimal experimental design** for estimation of individual parameters based on varying amount (1-4) of samples at different time points (0.25 – 4h) using the popED package (v.0.5.0) in R/Rstudio (v.3.6.3/1.3.959).
- **Best setting**: 2 samples at 0.5 h and 2 h.
- **Design evaluation**: stochastic simulation of YOH concentrations for 1000 individuals, sample at the optimal times and compare maximum a posteriori (MAP) CL estimate to the iCL used in the simulations ("True CL") and the CL derived from the original PK dataset using non-compartmental analysis (CL_{NCA}).

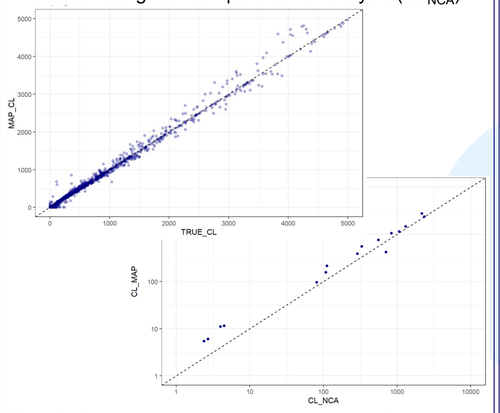
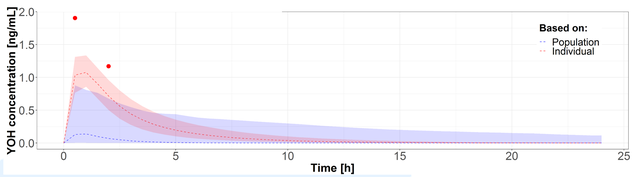


Figure 2: Evaluation of optimal experimental design. Top: Individual CL used in stochastic simulations vs MAP-estimated CL based on optimal time points, bottom: NCA-derived CI from model development dataset vs MAP-estimated CL based on optimal time points. Comparison to the original dataset is shown on log-log scale. Dashed line: line of identity.

Yohimbine individual clearance prediction

- **Implementation**: the model and MAP estimation procedure were implemented in an easy-to-use RShiny-based application, shown here for an example patient.
- **iCL prediction**: MAP estimation of individual PK parameters based on dosing and sampling information + a posterior prediction of the concentration-time profile is provided.
- **iCL_{YOH} application:** conversion of iCL_{YOH} to an activity score and corresponding phenotype, based on the iCL_{YOH} and the CYP2D6 activity score of the patients in the YOH model development dataset.



Population and individual parameter estimates

Parameter	Individual	Population
Clearance [L/h]	14.03	168
Central volume of distribution [L]	12.35	42.2
Absorption rate constant [1/h]	1.029	1.02

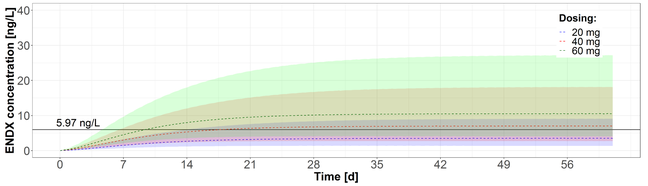
Translating individual yohimbine clearance into CYP2D6 Phenotype

Yohimbine clearance estimate [L/h]	Activity score	Phenotype
14.03	0	PM

Figure 3: Snapshot from the iCL_{YOH} prediction implemented in RShiny for an example female patient (29 y, 58 kg) from the original model development dataset. Two samples at 0.5 and 2 h after 50 µg of YOH were compared to the population prior prediction (blue) and then used for MAP estimation of the individual parameters, resulting in the individual posterior prediction (red.) Red dots: observations, dashed line: median prediction, shaded area: 90% prediction interval, PM: poor metabolizer (iCL_{YOH} < 20 L/h)

Proof-of-concept: model-informed precision dosing of tamoxifen

- **Proof-of-concept**: link **iCL_{YOH}** to a published parent-metabolite TAM PK model[4]. As this model is parameterised using the activity score, the converted CYP2D6 scores based on estimated iCL were implemented as covariates in the TAM model (same example patient). Ideally, estimated probe drug iCL would be used directly in the target drug PK model, which could be then based on a clinical study involving both drugs.
- **Dosing simulation**: ENDX exposure was stochastically simulated (n=1000) after 20, 40 and 60 mg daily doses. The percentages of virtual patients reaching the target ENDX minimum steady state concentration of 5.97 ng/mL were calculated.
- **Dose selection:** lowest dose resulting in >90% ≥ target ➔ 40 mg for example patient.



Dose [mg]	Median Cmin,ss [ng/ml]
20	3.496
40	6.993
60	10.49

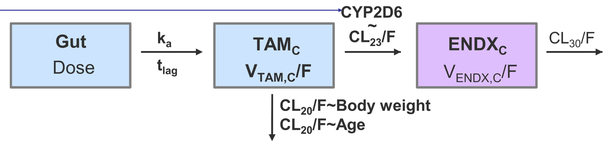


Figure 4: Snapshot from the TAM dosing simulation implemented in RShiny for the same example female patient (29 y, 58 kg) from the original model development dataset. Endoxifen steady state concentrations are shown after 20, 40 and 60 mg daily TAM dose. Simulations are based on the PK model depicted on the bottom. Dashed lines: median prediction, shaded area: 90% prediction interval, F: bioavailability, k_a: first-order absorption rate constant, t_{lag}: absorption lag time, $V_{TAM,C}$: central volume of distribution for TAM, CL_{20}: TAM clearance, CL_{23}: TAM metabolic CL to ENDX, $V_{ENDX,C}$: volume of distribution of ENDX, CL_{30}: ENDX clearance.

References:
[1] F Kluwe et. al. Clin Pharmacol Ther. 109: 29-36 (2021)
[2] L Madlensky et. al. Clin Pharmacol Ther. 89: 718-25 (2011)
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