In silico simulation study: A comparison of two population pharmacokinetic models of tamoxifen and its major metabolite endoxifen

L. Klopp-Schulze (1), M. Joerger (2), Z. P. Parra-Guillen (1), C. Kloft (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Germany,
(2) Dept. of Medical Oncology & Hematology, Cantonal Hospital St. Gallen, Switzerland

Background and Objectives

A high variability in the pharmacokinetics (PK) of **tamoxifen (TAM)** and its **major metabolite endoxifen (ENDX)** in oestrogen receptor-positive breast cancer patients has been associated with differences in clinical efficacy and treatment-related toxicity. Therefore, optimising TAM therapy by a personalised approach has been proposed [1, 2]. The aim of this study was to compare the characteristics of two recently published PK models of TAM and ENDX and their ability to reflect observed data [3].

Methods

- **Deterministic and stochastic simulations** (each n = 1000) were performed in Berkeley Madonna (8.3.18) using the published PK models "Model 1" [1] and "Model 2" [2] (Fig. 1).

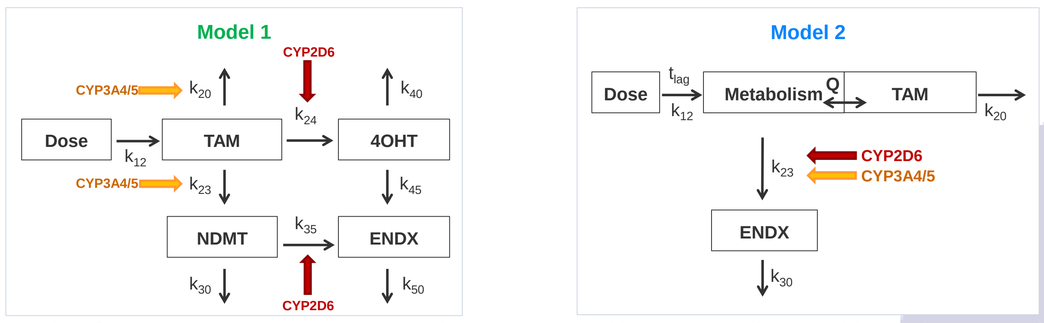

Figure 1. Schematic representation of the two PK models for TAM and metabolite(s). *Dose*: TAM dose; t_{lag}, lag time; k_{12}, absorption rate constant; k_{xy}, formation rate constant; k_{x0}, elimination rate constant; *Q,* inter-compartmental clearance; *NDMT,* N-desmethyltamoxifen; *4OHT,* 4-hydroxytamoxifen; *CYP3A4/5*, covariate CYP3A4/5; *CYP2D6,* covariate CYP2D6.

Table 1. Final parameter estimates from published PK models.

	Model 1		Model 2	
Parameter	**Estimates**	**RSE, %**	**Estimates**	**RSE, %**
t_{lag} [h]			0.455	10.4
k_{12} [1/h]	0.7 [a]	25	1.90	20.2
CL/F_{TAM} [L/h]	5.8	3	9.34	6.2
$\theta_{CYP3A4/5}$	0.16	41		
V/F_2 [L]	724	17	753	9
V/F_3 [L]	$= V_2$		400 [b]	
k_{20} [1/h]	0.00096 [c]		0.0124 [d]	
k_{23} [1/h]	0.007	14		
$\theta_{CYP3A4/5}$	0.07	38		
k_{24} [1/h]	0.000055	36		
$\theta_{CYP2D6\_PM/IM}$	-0.26	17		
k_{35} [1/h]	0.0003	70		
θ_{CYP2D6_PM}	-0.96	4		
θ_{CYP2D6_IM}	-0.56	12		
k_{45} [1/h]	0.015	72		
$k_{30/50}$ [1/h]	0.0086 [d]		0.0128 [d]	
CL/F_{NDMT} [L/h]	3.4	19		
CL/F_{4OHT} [L/h]	2.9	48		
CL/F_{ENDX} [L/h]	6.2	85	5.1 [b]	
CL/F_{MET} [L/h]			0.300	17
θ_{CYP2D6}			0.262	14
$\theta_{CYP3A4/5}$			0.157	72
Q/F [L/h]			61.8	65.4
ω CL/F_{TAM}, %CV	25	8	37.8	19.2
ω V/F_{TAM}, % CV			26.7	53.9
ω CL/F_{MET}, % CV			25.4	19.3
ω k_{23}, % CV	16	8		
ω k_{24}, % CV	26	12		
ω k_{35}, % CV	59	10		
ρ (CL/F_{TAM}, V/F_2), %			61.2	31.2
ρ (k_{24}, k_{45}), %	51	19		

a: Fixed to value from (1-CMT) TAM model without metabolites; b: Fixed to literature value (Ahmad et al. *Clin Pharmacol Ther* 2010); c: Calculated by CL_{TAM}/V-k_{23}-k_{24}; d: Calculated by CL/V; *CL/F,* relative clearance; *V/F,* relative volume of distribution; $\theta_{CYP3A4/5}$, CYP3A4/5 covariate effect; $\theta_{CYP2D6\_PM/IM}$, CYP2D6 covariate effect; *MET:* Endoxifen formation; *ω:* Inter-individual variability; *ρ:* Correlation coefficient;

- Simulations were investigated for multiple dosing of TAM (20 mg/day p.o.) and typical population PK estimates including clinically discussed covariates (CYP2D6, CYP3A4/5) on PK (Tab. 1).
- **Stochastic and covariate models** were implemented as described [1, 2].
- Continuous covariates were simulated from a log-normal distribution and categorical covariates from a discrete probability distribution (resulting in the same CYP2D6 phenotype frequency for both models).
- Simulated concentrations were compared to (i) steady-state concentrations (C_{ss}) reported in [3] and to (ii) a proposed **threshold concentration of ENDX ($C_{TH,ENDX}$)** of 5.97 ng/mL associated with therapeutic success [4].
- The **probability of target attainment** (PTA) defined as percentage of patients with $C_{ss,min}$ of ENDX > $C_{TH,ENDX}$ was calculated for each virtual population (R 3.2.0).

Results & Discussion

- PK profiles of TAM and ENDX showed **higher C_{ss} and $t_{97\%Css}$** (time to 97% of steady-state) in **Model 1** than in the Model 2 (Fig. 2) .
- $C_{ss,TAM}$ were ~10-fold higher than $C_{ss,ENDX}$ in both models.
- C_{ENDX} increased more steeply in Model 2 comparing to the Model 1.

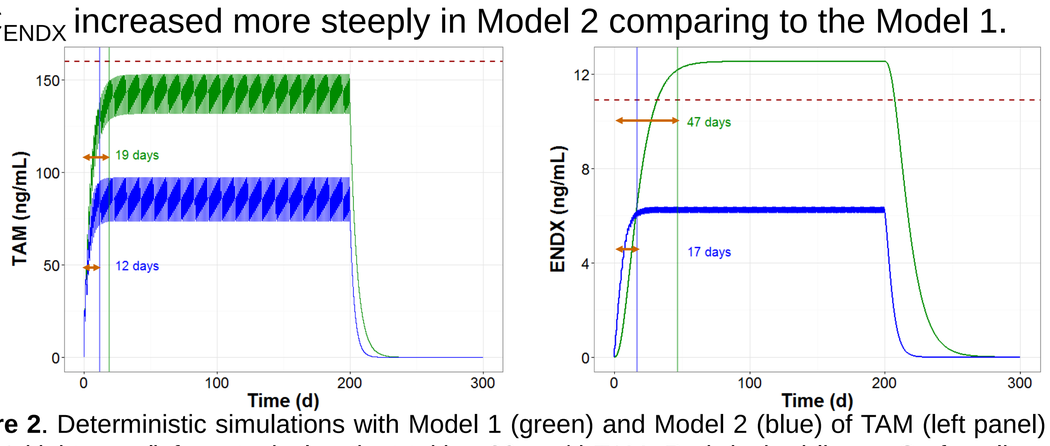

Figure 2. Deterministic simulations with Model 1 (green) and Model 2 (blue) of TAM (left panel) and ENDX (right panel) for a typical patient taking 20 mg/d TAM. Red dashed lines: C_{ss} from literature reference [3]. Orange arrows: $t_{97\%Css}$.

Results & Discussion

- Simulations of typical populations (incl. covariates and IIV) using Model 1 and Model 2 resulted in median **$C_{ss,min}$ TAM** of 126.5 and 73.1 ng/mL and median **$C_{ss,min}$ ENDX** of 8.6 and 6.3 ng/mL, respectively (Fig.3).
- Hence, data from literature [3] seems to be better reflected by Model 1.

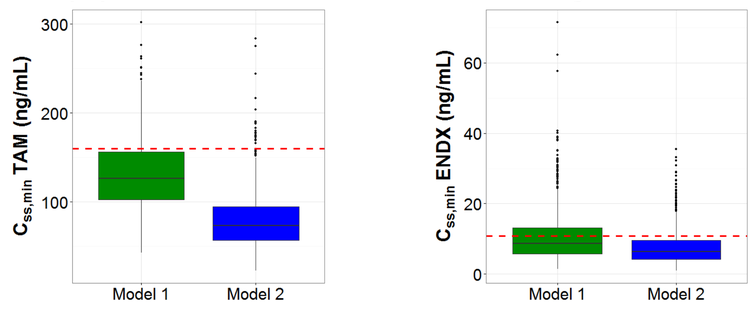

Figure 3. Simulated $C_{ss,min}$ of TAM (left panel) and ENDX (right panel) after 6 months of 20 mg/day TAM (n = 1000). Red dashed line: C_{ss} from literature reference [3].

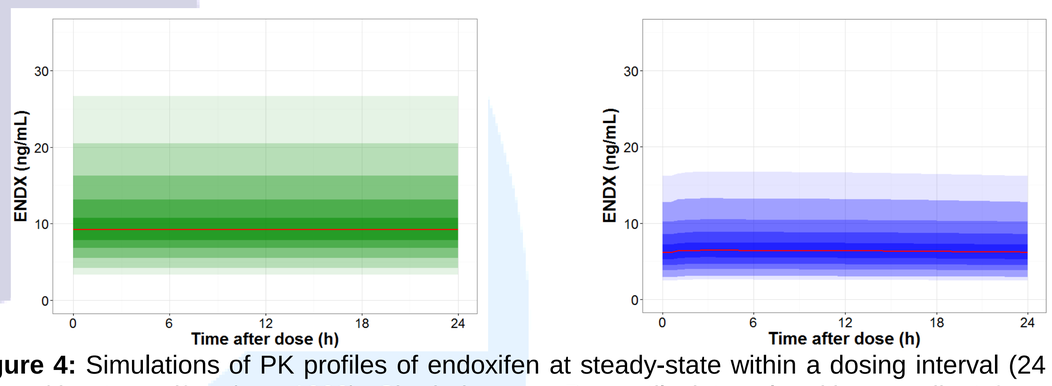

Figure 4: Simulations of PK profiles of endoxifen at steady-state within a dosing interval (24 h) of 20 mg/day tamoxifen (n = 1000). Shaded areas: Percentile intervals with a gradient from 90% percentile interval (lightest) to 20% percentile interval (darkest). Red lines: Respective median.

- **$C_{ss,ENDX}$ showed low fluctuations** within a dosing interval for both models (Fig. 4).
- The **PTA for the simulated populations** (n = 1000, replicates = 100) using **Model 1** was **76%** (95% CI: 73% - 78%) and **52%** (95% CI: 50% - 55%) when using **Model 2**.
- Stratification by CYP2D6 activity identified patients at highest **risk for subtherapeutic $C_{ss,ENDX}$** i.e. poor metaboliser (PM) with a PTA < 3% in both models (Fig. 5).
- However, patients with higher CYP2D6 activity showed highly variable **percentages of risk** (< $C_{TH,ENDX}$) between Model 1 and Model 2 (*IM,* Intermediate metaboliser: 41% vs. 73%; *EM,* Extensive metaboliser: 7.1% vs. 24%).

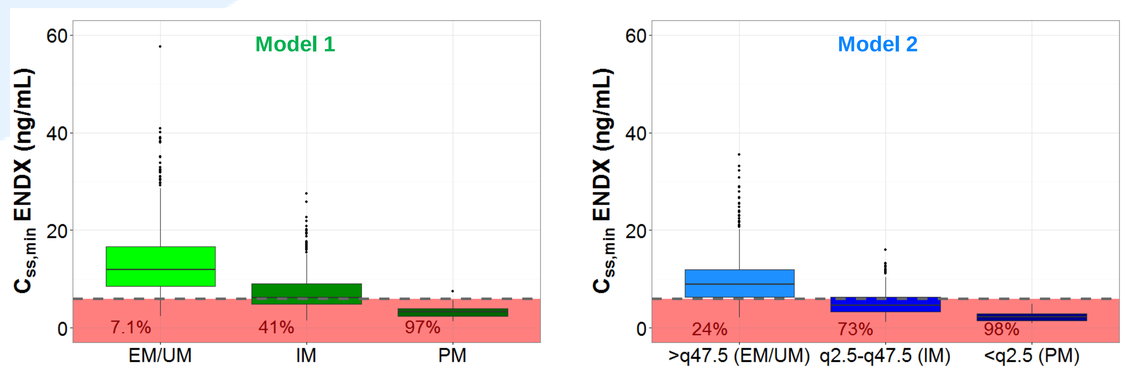

Figure 5. Simulated $C_{ss,min}$ of ENDX after 6 months of 20 mg/day TAM stratified based on covariate CYP2D6 (n = 1000). Left panel: Virtual population of Model 1 stratified by metaboliser category (EM, incl. 2.5% ultra-rapid metaboliser, IM, PM). Right panel: Virtual population of Model 2 divided into quantiles based on CYP2D6 activity. Grey dashed line represents proposed therapeutic threshold [4]. Red numbers show percentage of patients at risk (< $C_{TH,ENDX}$).

Conclusions

- This simulation study of TAM and ENDX displayed substantial differences between the investigated PK models.
- Also for anticipated exposure-response relationship, as indicated by the proposed threshold concentration, the two PK models resulted in a **profoundly different probability of target attainment**.
- External validation (with clinical trial data) with respect to the predictive performance of the PK models is currently ongoing and shall eventually contribute to a more comprehensive understanding of TAM/ENDX PK.

References:

[1] Dahmane EBA. *Thèse de doctorat: Univ. Genève* (2013) no. Sc. 4617.
[2] Ter Heine R et al. *Brit J Clin Pharmacol* (2014) 78(3): 572–86.
[3] Mürdter TE et al. *Clin Pharmacol Ther* (2011) 89(5): 708–17.
[4] Madlensky L et al. *Clin Pharmacol Ther* (2011) 89(5): 718–25.

For additional information, please contact:
Lena Klopp-Schulze
Email: lena.klopp-schulze@fu-berlin.de

CLINICAL PHARMACY