Exploring and explaining variability in tamoxifen and endoxifen pharmacokinetics in breast cancer patients: A pooled analysis

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Background and Objectives

To improve tamoxifen treatment, it is crucial to better understand the complex pharmacokinetics (PK) of tamoxifen and its major metabolite endoxifen, which is influenced by many internal (e.g. CYP polymorphisms) and external factors (e.g. drug-drug interactions).

By **combining data from different clinical studies** we enriched the single database for analysis, i.e. increased the power to detect covariate relationships. This study aimed to **explore and explain different levels of variability** in tamoxifen and endoxifen PK.

Methods

Database

- Plasma concentration data of tamoxifen and endoxifen from 468 breast cancer patients were pooled (Tab. 1):
  - → 2 large studies [1,2]: sparse sampling
  - → 4 smaller studies [3–6]: rich sampling
- A patient's CYP2D6 phenotype was predicted from genotype according to CPIC guidelines [7].

Table 1. Study characteristics of six pooled tamoxifen studies [1-6].

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Total
$N_{patients}$	247	128	40	7	15	31	468
$N_{samples/pts}$	≤4	1	≤9	≤18	≤18	≤27	-
$N_{occasion}$	≤4	1	1	≤3	≤3	≤3	-
20 mg QD, %pts	100	100	70	100	73	97	96
40 mg QD, %pts	0	0	30	0	27	3	4
Setting (%pts)			n.r. (5)		n.r. (33)	n.r. (3)	n.r. (2)
1: adjuvant		1 (100)	1 (65)	1 (100)	1 (67)	1 (97)	1 (43)
2: neo-adjuvant	2 (25)		3 (30)				2 (13)
3: metastatic	3 (75)						3 (42)
Age [years], median (range)	72 (48-95)	61 (41-80)	52 (25-70)	51 (29-60)	51 (38-65)	51 (27-68)	64 (25-95)
CYP2D6, %pts							
gUM	0	5	0	0	0	0	1
gNM	82	69	83	14	47	87	76
gIM	10	12	10	0	7	0	10
gPM	5	7	3	14	0	10	6
n.r.	3	8	4	72	47	3	7
SSRI, %pts	2.0	3.9	2.5	0	80	0	4.9
RIF, %pts	0	0	0	70	0	0	0.01

gUM, gNM, gIM, gPM: genotype-predicted ultrarapid, normal, intermediate and poor metaboliser; *n.r.*: not reported; *pts*: patients; *QD*: dosing once daily; *SSRI*: concomitant use of fluoxetine or paroxetine (Selective serotonin reuptake inhibitors); *RIF*: concomitant use of rifampicin.

Modelling approach

- A joint parent-metabolite model including key covariate relationships based on prior knowledge was developed (Fig. 1) using NONMEM (v. 7.3).
- To account for **interstudy variability (ISV)** three implementation strategies were investigated in NONMEM (**a:** as covariate, *CL20_STDY*; **b:** as variability nested into interindividual variability; **c:** as additional variability on *CL20/F*).
- To distinguish between and quantify **different levels of variability –interstudy (ISV), interindividual (IIV) and interoccasion variability (IOV)**– three models were compared:

Model 1: Without IOV, ISV and covariates.

Model 2: With IOV, ISV and without covariates.

Model 3: With IOV, ISV and covariates.

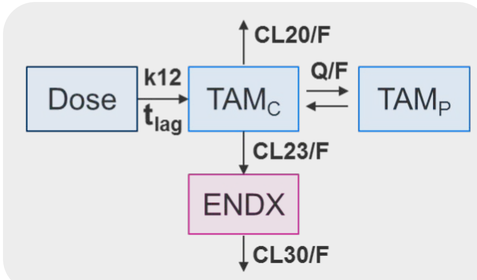


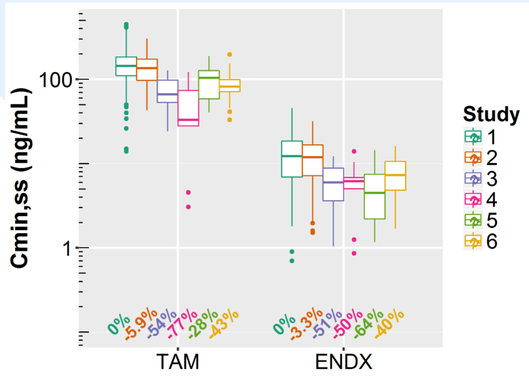
Figure 1. Schematic model representation. *CL20/F and CL30/F:* relative TAM and ENDX clearance; *Dose:* TAM dose; k_{12}*:* absorption rate constant; *CL23/F: relative* metabolic clearance of TAM to ENDX; *ENDX:* endoxifen compartment; *Q/F:* relative intercompartmental flow; t_{lag}*:* lag time; *TAMc/p*: tamoxifen central/peripheral compartment.

Results

Exploring and explaining several levels of variability

- ISV strategy (a) was superior over (b) and (c) (w.r.t. OFV reduction and model convergence) and thus taken forward for covariate analysis.
- ISV (Fig. 2), IIV and IOV were large with >25 CV% (Tab. 2, Model 2) and reduced upon covariate introduction (Tab. 3).
- Model predictions (Fig. 3) and predictive performance (Fig. 4) for Model 3 were considered good.

Figure 2. Interstudy variability. Minimum plasma concentrations of tamoxifen and endoxifen at steady-state (Cmin,ss) across 6 studies (20 mg dose group). %Difference to study 1 indicated below each box.



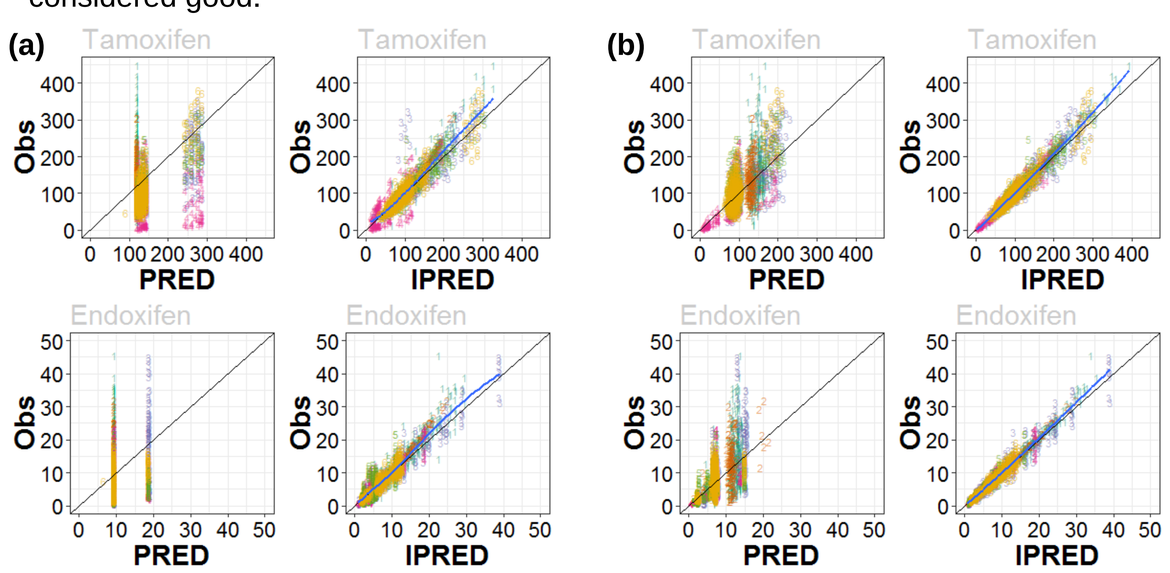


Figure 3. Goodness of fit plots **(a)** of Model 1 and **(b)** Model 3. *Obs*: observations; *IPRED*: individual predictions; *PRED*: population predictions; numbers & colours: respective study, see Tab 1; unit: ng/mL.

Results cont.

- IIV, IOV and ISV were partly explained by the investigated covariates (Tab. 3):

Drug-drug interactions

CL20/F ↑↑: Rifampicin (potent *CYP3A4 inducer; RIF*) caused 569% increase.

CL23/F ↓: Fluoxetine and paroxetine (Strong *CYP2D6 inhibitors;* SSRI) responsible for 64.6% reduction.

Table 2. Parameter estimates of model 1-3.

Parameter		Model 1		Model 2		Model 3	
	OFV	-3471		-6511		-7087	
	ΔOFV to model 1	0		-3039		-3616	
		Estimate	**RSE**	**Estimate**	**RSE**	**Estimate**	**RSE**
Structural	CL20/F (L/h)	5.98	2.60%	5.13	2.20%	5.49	3.90%
	V2/F (L)	285	13.1%	286	15.5%	282	15.1%
	CL23/F (L/h)	0.363	2.90%	0.361	3%	0.414	3.50%
	k12 (1/h)	0.225	(FIX)	0.225	(FIX)	0.225	(FIX)
	t_{lag} (h)	0.295	(FIX)	0.295	(FIX)	0.295	(FIX)
	Q/F (L/h)	71.1	(FIX)	71.1	(FIX)	71.1	(FIX)
	CL30/F (L/h)	5.10	(FIX)	5.10	(FIX)	5.10	(FIX)
Covariate	CL20_RIF					5.87	8.80%
	CL20_STDY			0.873	11.9%	0.569	17.2%
	CL23_PM					-0.675	4.30%
	CL23_IM					-0.433	16.9%
	CL23_UM					0.764	26.3%
	CL23_SSRI					-0.646	7.60%
	CL20_AGE					-0.461	28.4%
	CL23_RIF					1.25	38.4%
Variability	IIV CL20, CV	46.8%	5.20%	35.2%	7.30%	35.2%	6.20%
	IIV CL23, CV	58.4%	3.80%	56.9%	4.30%	47.6%	7.20%
	IOV CL20, CV			26.9%	14.5%	14.8%	20.6%
	IOV CL23, CV			25.8%	10.8%	17.0%	16.6%
	RUV TAM, CV	30.6%	16.3%	15.6%	5.50%	15.7%	5.20%
	RUV ENDX, CV	33.8%	11.1%	16.1%	3.80%	16.2%	3.80%

CV: Coefficient of variation; *FIX:* Fixed based on model development using rich data only; *IIV* interindividual variability; *IOV:* interoccasion variability; *OFV*: Objective function value; *RUV:* Residual unexplained variability; *RSE*: relative standard error; for abbreviations see Tab 1.; for parameter names see Fig. 1.

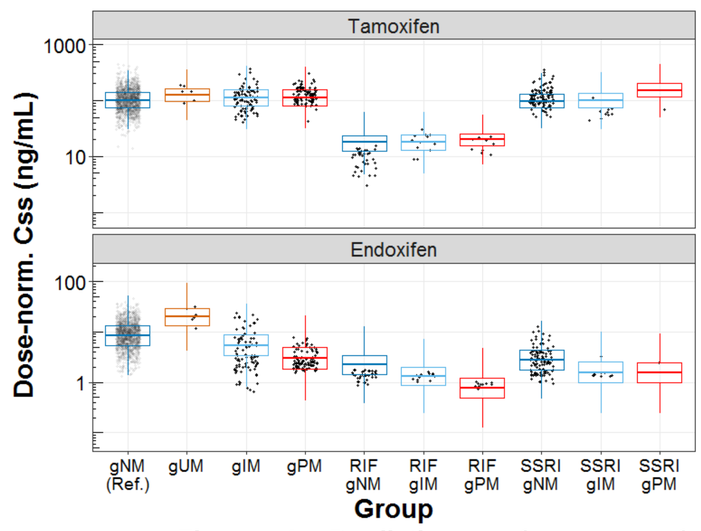


Figure 4. Predictive performance of Model 3. Predicted (boxes) and observed (dots) minimum concentrations at steady-state (Css) of tamoxifen (top) and endoxifen (bottom) dose-normalised and stratified by 10 subgroups. *Boxes:* simulations ($n_{samples}$=1000); *dots:* observations (Study 1-6). *gNM (Ref.), gUM, gIM, gPM:* genotype-predicted normal (reference, darkblue box), ultrarapid (orange box), intermediate (lightblue box) and poor metaboliser (red box); *RIF gX, SSRI_gX:* rifampicin or paroxetine/fluoxetine concomitant use by respective CYP2D6 phenotype.

CYP2D6 phenotype

CL23/F ↓: Poor and intermediate metabolisers showed 67.5% and 43.3% reduction, respectively (reference group: normal metabolisers).

CL23/F ↑: ultrarapid metabolisers showed 76.4% increase.

→ All covariates (but age) had a substantial impact on CL20/F and CL23/F (Fig. 5).

→ Unexplained variability remained in IOV (≤17%), IIV (>35%) and ISV (>50%).

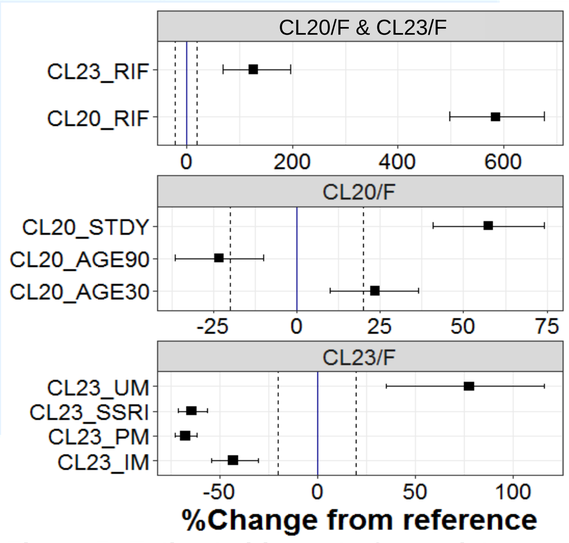


Figure 5: Estimated impact of covariates on tamoxifen clearance (CL20/F) and endoxifen formation (CL23/F) parameters. *CLx_y* (y-axis)*:* Covariate y on parameter x, see Tab. 1 for abbreviations. Reference patient: CYP2D6 normal metaboliser, 60 years, study 1-2, no concomitant rifampicin (RIF) or CYP2D6 inhibitor (SSRI). Error bars: median and 95th confidence interval derived by sampling importance resampling method; Vertical dashed lines: -20% and 20% change from reference.

Table 3. Reduction of unexplained variability after covariate inclusion.

Variability	Parameter	Reduction in variability[a], %
ISV[b]	CL20/F	34.8
IIV	CL20/F	0.00
	CL23/F	16.3
IOV	CL20/F	45.0
	CL23/F	34.1

a: Comparing estimates from model 2 and 3 (Tab. 2).
b: *CL20_STDY*, using strategy (a) with study 1-2 as reference.

Discussion & Conclusion

- Although the **database was heterogeneous and unbalanced** (representing "real world data")
  - ✓ Nonlinear mixed-effects approach was able to differentiate and quantify several levels of variability;
  - ✓ Influential factors were strong and reliably identified.
- However, **unexpectedly large differences between** the pooled **studies** were observed (remaining unexplained ISV):
  - → Study design, bioanalytical methods or factors that had not been reported, such as adherence or tamoxifen formulation, might cause these differences [8].
- To avoid subtherapeutic concentrations we need to identify and control these factors **by investigating high-quality clinical studies** which will inform PK models and thus dose individualisation strategies such as model-based therapeutic drug monitoring.

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