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Quantification of Pharmacokinetic Interactions: MDDI-Calculator of the Scholz-Datenbank vs. Physio-logically-Based Pharmacokinetic Modeling (PBPK)

Introduction

Nowadays, polymedication plays an immense role in both clinical and ambulatory care. Patients are treated with drugs, which are influencing each other, so their plasma concentrations may increase or decrease. Especially the inhibition of liver enzymes like cytochrome P450 oxidases (CYP) provokes a higher risk for side effects. So, there is a great relevance to predict the possible extent of a pharmacokinetic interaction e.g. if a dose reduction is useful when those drugs are combined.

Methods

With their agreement, fourteen (5 male, 9 female) inpatients at Alexianer Hospital in Münster [Table 1], who are treated with the combination of both the antidepressants mirtazapine and venlafaxine, were recruited. In the context of therapeutic drug monitoring, samples were taken via Dried-blood-spot method.

Table 1: Summary statistics of the recruited subjects

Variable	Min	Max	Arithmetic mean (±Standard deviation)
Age [years]	60	86	71 (± 8,73)
Weight [kg]	64	85,2	71,51 (± 6,39)
Height [cm]	156	177	166 (± 7,00)
Dose (D) of Mirtazapine [mg/d]	15	45	23,57 (± 9,34)
Dose of Venlafaxine [mg/d]	37,5	225	120,54 (± 58,75)
Concentration (C) of Mirtazapine [µg/L]	12,5	118,1	38,04 (± 26,51)
C/D of Mirtazapine	0,83	3,94	1,59 (± 0,74)

Afterwards, the plasma concentrations of mirtazapine were determined by LC-MS. The MDDI Calculator of the Scholz-Datenbank allows the prediction to what extent an inhibitoric drug influences the area under the curve (AUC/exposition) of another drug. Venlafaxine`s potential weak inhibitoric effect on CYP 2D6 and the limited extent mirtazapine's metabolism is processed through the same enzyme are illustrated in Table 2 as well as relative changes of AUC and dose are displayed.

Table 2: Pharmacokinetic interaction between mirtazapine and venlafaxine, calculated by MDDI-module of the Scholz-Datenbank

	Drug	Drug Type	CYP2D6
Enzymes/ Transporter, Metabolism and elimination	Mirtazapine	Substrate	Minor
	Venlafaxine	Inhibitor	Minor
	Parameter	**Relative Value**	**Relative Change**
Pharmacokinetic data-based estimated values	AUC	108%	8%
	Dose	93%	-7%

To evaluate the predict-tion ability of this soft-ware for the described pharmacokinetic inter-action, PBPK-modeling via PK-Sim® is used [Table 3]. For the single substance models a young population was chosen. The interaction model was extrapolated to an elderly population [Table 4].

Table 3:
Biochemical and Pharmacokinetic values, which are applied for the single substance models in PK-Sim®. Data in squared brackets represent literature values; CYP: Cytochrome P450 enzymes; Km: Michaelis-Menten constante; Ki: inhibitoric constante; Kcat: Turnover frequency; *parametrized with PK-Sim®; **calculated by PK-Sim®.

Variable		Mirtazapine	Venlafaxine
Dose [mg]		1 (Dose corrected)	75
Form of Release		immediate	extended
CYP 2D6	Km [µmol/L]	136 [136 ± 44]	26 [26 ± 7,26][1]
	kcat [min^{-1}]	207* [46]**	27,5* [18,5]**
	Ki [µM]		41 [41 ± 9,5][2]
CYP 3A4	Km [µmol/L]	242 [242 ± 34]	405,89 [405,89][3]
	kcat [min^{-1}]	62,1* [13,8]**	31* [86,11]**
CYP 1A2	Km [µmol/L]	570 [570 ± 281]	
	kcat [min^{-1}]	63,99* [14,22]**	
Renal elimination [min^{-1}]		0,52** [unchanged <4%]	0,23** [unchanged 5%]
Partition coefficents		Schmitt	Poulin and Theil
Cellular permeability		PK-Sim® Standard	PK-Sim® Standard

Table 4:
Characterization of populations and doses of venlafaxine and mirtazapineused in PK-Sim®; BMI: Body Mass Index, *: calculated by PK-Sim®.

Variable	Number of patients [percentage of females]	Range of age [years]	Range of Weight [kg]	Range of Height [cm]	BMI [kg/m²]	Dose [mg/d]	
						Mirtazapine	Venlafaxine
Substance models	1000 [50%]	20-30	50-95	150-195	20-30	1	15
Interaction model	1000 [50%]	65-85	*	*	23-34	75	150

Results

The created models of dose-corrected immediate release (IR) mirtazapine [Figure 1] and of 75 mg extended release (ER) venlafaxine [Figure 2] show in the goodness-of-fit (GOF) plot a good predictive capability.

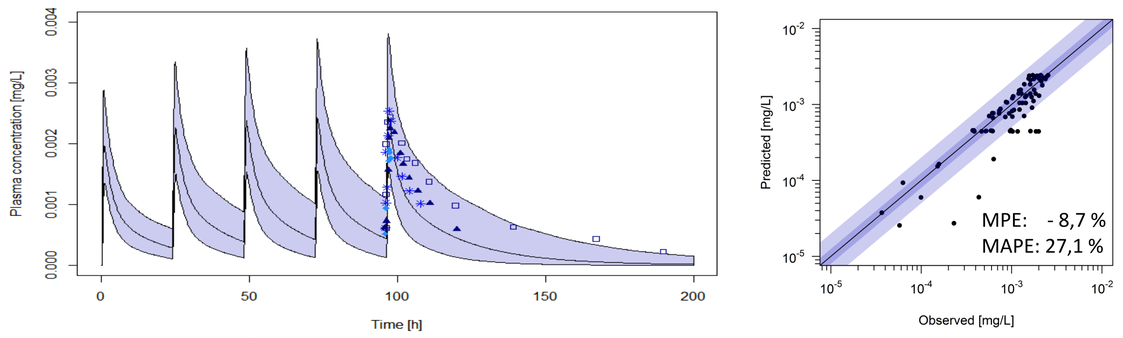

Figure 1: PBPK-model of dose-corrected IR mirtazapine with its GOF-plot, the blue painted areas represent the 5 and 95% range, the points are literature values[4]; MPE: Mean prediction error, MAPE: mean absolute prediction error.

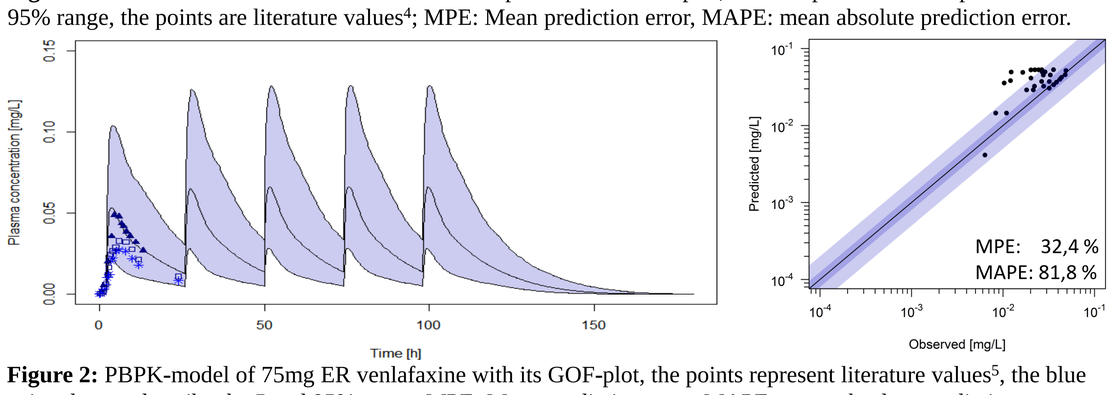

Figure 2: PBPK-model of 75mg ER venlafaxine with its GOF-plot, the points represent literature values[5], the blue painted areas describe the 5 and 95% range; MPE: Mean prediction error, MAPE: mean absolute prediction error.

For the interaction model, the most given dosage combination (3 of 14 patients) was used [Figure 3]. In the elderly population, there is no significant difference in the AUC of mirtazapine, irrespective of given with or without venlafaxine (2,1 vs. 2,25 mg*h/L).

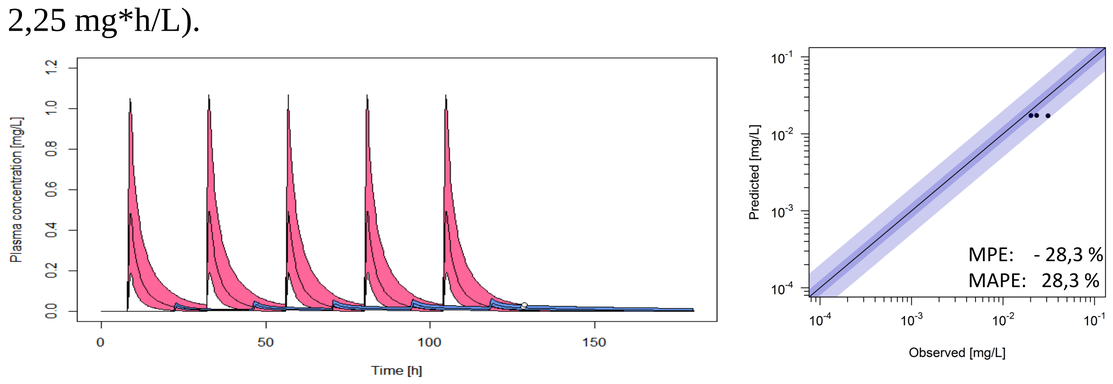

Figure 3: Interaction PBPK-model of venlafaxine and mirtazapine with its GOF-plot, red surrounded curve re-present the venlafaxine plasma concentration, blue surrounded curve the mirtazapine plasma concentration with its respective 5 and 95% range, white filled circles describe the trough levels of mirtazapine, stated by 3 inpatients; MPE: Mean prediction error, MAPE: mean absolute prediction error.

The MDDI-Calculator of the Scholz-Datenbank computes a small increase of mirtazapine's AUC of 8% which is clinically not relevant due to the therapeutic index of the substrate [Table 2]. This effect caused by the weak inhibitor venlafaxine is, however, consistent with clinical data measured in scenarios with CYP2D6 Poor Metabolizers mimicking drug drug interactions through strong CYP2D6 enzyme inhibitors.

Conclusions

The PBPK model does not show any impact on the metabolism of mirtazapine by venlafaxine in contrast to the MDDI Calculator of SCHOLZ Databank. To evaluate the model's clinical relevance more clinical research and comparison is needed including other CYP2D6 substrates, inhibitors and pharmacogenomics.

Literature/References

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