PBPK Modeling of Fluoxetine and its Metabolite Norfluoxetine: Prediction of the Extent of Their Involvement in Drug Interactions.

Grazyna Fraczkiewicz†, Viera Lukacova†, Neil Parrott‡, Michael B. Bolger†, John R. Crison†, Walter S. Woltosz†, & Thierry Lave‡

†Simulations Plus, Inc., 42505 10th Street West, Lancaster, CA 93534, USA

‡F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Pharma Research, Non-Clinical Development, Non-Clinical Drug Safety, Basel Switzerland.

Objectives

The aim of our study was to simulate the human pharmacokinetics of fluoxetine and its major metabolite, norfluoxetine, and predict the magnitude of their drug-drug interactions (DDIs) using physiologically based pharmacokinetics (PBPK).

Methods

GastroPlus™ (Simulations Plus, Inc.) was used to build PBPK models of fluoxetine and norfluoxetine in humans using plasma concentration-time (Cp-time) profiles for 20, 40, and 60 mg oral (PO) doses obtained from the literature[1, 2, 3]. Experimental postmortem human tissue:plasma partition coefficients (Kps) were used for drug partitioning into the following tissues: liver, lungs, kidney, spleen, brain, and heart[4]. Kps for all other tissues were calculated using a modified Rodgers and Rowland method based upon drug properties and tissue compositions. In vitro Km and Vmax values were used to describe the metabolic clearance of fluoxetine and formation of its major metabolite, norfluoxetine[5]. ADMET Predictor™ (Simulations Plus, Inc.) was used to predict human intestinal permeability for both compounds. DDIs were predicted using a test version of an upcoming DDI Module in GastroPlus using the steady-state option.

Results

PBPK models with experimental and predicted Kp values and in vitro metabolic clearance provided a very close fit to the experimental Cp-time profiles of fluoxetine and norfluoxetine after 20, 40, and 60 mg PO doses of fluoxetine. Volume of distribution, half-life, and fraction bioavailable were also predicted with high accuracy. DDI predictions (AUC ratios) for 7 substrates (alprazolam, desipramine, imipramine, amitriptyline, clozapine, tolterodine, and propafenone) were mostly within 20% of the observed in vivo values.

References

[1] Hamelin et al., Clin Pharmacol Ther **1996**, 60, 512-521.

[2] Zhi et al., J Clin Pharmacol **2003**, 43-4, 428.

[3] Fjordside et al., Pharmacogenetics **1999**, 9-1, 55-60.

[4] Johnson et al., J Anal Tox **2007**, 31-7, 409 - 414.

[5] Margolis et al., DMD **2000**, 28-10, 1187-1191.

[6] Greenblatt et al., Clin Pharmacol Ther **1992**, 52, 479-486.

[7] Heydari et al., Predicting Drug Interactions with SSRIs:

Impact of Non-specific Binding and Active Uptake ISSX **2006**.

[8] Calculated value based on the Ki(FLX)/Ki(NFLX) ratio observed in different reactions in

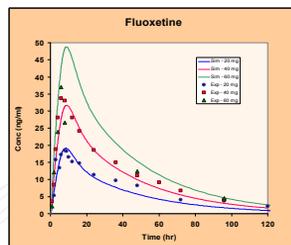Hemeryck et al, Current Drug Metabolism **2002**, 3, 13-37.

Fig 1. Experimental (dots) and GastroPlus simulated (lines) Cp-time profiles of fluoxetine after 20, 40, and 60 mg fluoxetine doses.
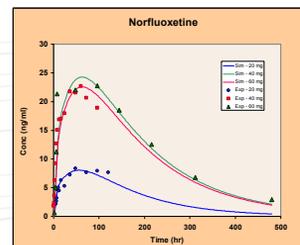

Fig 2. Experimental (dots) and GastroPlus simulated (lines) Cp-time profiles of norfluoxetine after 20, 40, and 60 mg fluoxetine doses.

Tissue	Human Kp
Lung	60
Adipose	2.83
Muscle	2.0
Liver	38
Spleen	20
Heart	10
Brain	15
Kidney	9
Skin	8.77
ReproOrg	33.05
RedMarrow	4.59
YellowMarrow	2.83
RestOfBody	20.94
Vss	571.805 (69 kg); 707.235 (85 kg)

Fig 4. Tissue:plasma partition coefficients (Kps) used in fluoxetine model. Blue color indicates experimental values. Black font indicates predicted values with a modified Rodgers method.

Fluoxetine (Prozac) → Norfluoxetine
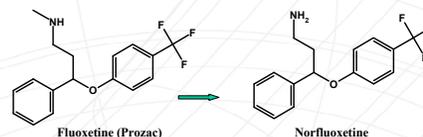
Enzyme	Location	Vmax (mg/s)	Km (ug/ml)
2C9	Liver	0.79	9.496
2D6	Liver	0.017	0.68
2D6	Gut	0.017	0.68
3A4	Liver	0.327	5.97
3A4/5	Gut	0.2205	27.65

Fig 5. The in vitro Km and Vmax values[5] were used to describe the metabolic clearance of fluoxetine and formation of its major metabolite, norfluoxetine.

Substrate	Ki Fluoxetine	Ki Norfluoxetine	AUC Ratio Fluoxetine	AUC Ratio Norfluoxetine	AUC Ratio Total	AUC Ratio Observed
Alprazolam	83.3 (α-OH) [6] 47.2 (4-OH) [6]	11.1 (α-OH) [6] 8.8 (4-OH) [6]	1.03	1.05	1.06	1.09 [6]
Desipramine	0.099 [7]	0.125 [8]	2.63	5.6	6.8	5.3 - 7.4 [10]
Imipramine	0.099 [7]	0.125 [8]	1.41	1.65	1.7	3.33 [10]
Amitriptyline	0.099 [7]	0.125 [8]	1.5	1.55	1.65	1.8 [11]
Clozapine	0.099 [7]	0.125 [8]	1.17	1.25	1.31	1.58 [12]
Tolterodine	0.099 [7]	0.125 [8]	1.44	3.16	3.63	4.84 [13]
Propafenone	0.33 [9]	0.55 [9]	1.21	1.27	1.43	1.5 [9]

Fig 6. Observed and predicted AUC ratios for DDI interactions between fluoxetine/norfluoxetine and different substrates under steady-state conditions.
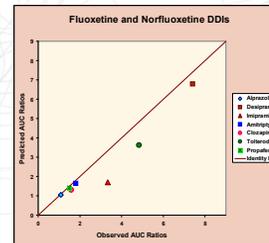

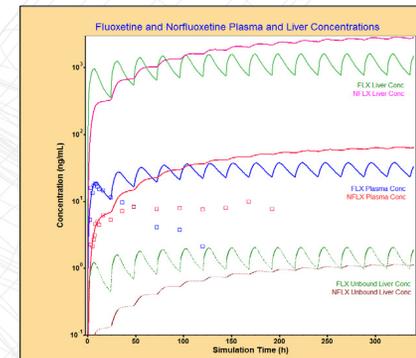Fig 7. DDI predictions for fluoxetine and its metabolite.

Fig 3. Simulated fluoxetine 20 mg dose given once daily for 2 weeks. The dots represent the experimental plasma concentrations of fluoxetine and norfluoxetine after a single 20 mg dose.

Conclusions

Experimental Kps for the major human organs were essential for modeling fluoxetine and norfluoxetine. In silico methods for predicting Kps were also investigated; however, they significantly underpredicted Kps for organs where lysosomal trapping contributes to the drug's partitioning (lungs, liver, and kidney). Accurate prediction of the fluoxetine and norfluoxetine unbound liver concentrations was of particular importance in explaining and predicting drug-drug interactions, showing that the major portion of them was caused by the metabolite when the drug is dosed over longer periods. All predicted AUC ratios were within 2-fold of the observed values, with the majority being within 20% of the in vivo values.

[9] Cai et al., Clin Pharmacol Ther **1999**, 66, 516-521.

[10] Bergstrom et al., Clin Pharmacol Ther **1992**, 51, 239-248.

[11] El-Yazigi at al, J Clin Pharmacol **1995**, 35, 17.

[12] Spina et al., Int Clin Psychopharmacol **1998**, 13, 141-145.

[13] Brynne et al., Br J Clin Pharmacol **1999**, 48, 553–563.

Roche
Pharmaceuticals

simulations plus, inc.