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

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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, 9]. 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[3]. 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.

Conclusions
Experimental Kps for the major human organs were essential for modeling fluoxetine and norfluoxetine. In vitro 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.