

Simulations of the Drug-Drug Interaction Between Atomoxetine and Quinidine in Poor and Extensive CYP2D6 Metabolizers

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Introduction

Atomoxetine is indicated for attention-deficit hyperactivity disorder (ADHD) in children, adolescents and adults. It is metabolized to 4-hydroxy-atomoxetine primarily by CYP2D6, which is known to have polymorphic expression (poor vs. extensive metabolizers). CYP2D6 poor metabolizers account for approximately 7% of the population.

Quinidine is used to treat class I cardiac arrhythmias and is a potent inhibitor of CYP2D6. Inhibitions of CYP2D6 in patients undergoing treatment with atomoxetine may lead to drug overdose. In this study, the drug-drug interaction between atomoxetine and quinidine in poor and extensive CYP2D6 metabolizers was modeled using GastroPlus™ to assess the risk of coadministration of these two drugs.

Methods

Physiologically-based pharmacokinetic (PBPK) models were optimized for atomoxetine and quinidine based on literature data using GastroPlus v6.1 (Simulations Plus, Inc.). For atomoxetine, human tissue:plasma partition coefficients (Kps) were calculated using a modified Rodgers method^[1] based upon drug properties and tissue composition. For quinidine, human Kps for most tissues were converted from experimental values in rat^[2] except for red marrow, yellow marrow and "rest of body", which were calculated by the modified Rodgers method. *In vitro* Km and Vmax values were used as initial estimates to calculate metabolic clearances of atomoxetine^[3] and quinidine^[4]. The Vmax and Km values for CYP2D6 and 3A4 were fitted to match plasma concentration-time (Cp-time) profiles. For each compound, the same absorption/PBPK model accurately simulated Cp-time profiles after various single and multiple PO doses [atomoxetine (20-90 mg), quinidine (200-400 mg)] in different patient populations.

Substrate	Enzyme	Location	Vmax (mg/s)	Km (mg/L)
Atomoxetine	2C19	Liver	0.0084 ^[3]	0.23 ^[3]
Atomoxetine	2D6	Gut	0.017*	0.015*
Atomoxetine	2D6	Liver	0.017*	0.015*
Quinidine	3A4	Gut	0.008*	0.26 ^[4]
Quinidine	3A4	Liver	0.008*	0.26 ^[4]

Table 1. Km and Vmax values used in atomoxetine and quinidine PBPK models for extensive metabolizers. For CYP2D6 poor metabolizers, a fitted Km value 50 times higher than wild type was used.

* Fitted using Cp-time data from different doses

References:

- [1] Lukacova et al., General Approach to Calculation of Tissue:Plasma Partition Coefficients for Physiologically Based Pharmacokinetic (PBPK) Modeling, AAPS, 2008, Altanta, GA.
 [2] Harashima et al., *J Pharmacokinetic Biopharm* 1985, 13, 425-440.
 [3] Ring et al., *Drug Metabol Dispos* 2002, 30, 319-323.
 [4] Guengerich et al., *Mol Pharmacol* 1986, 30, 287-295.

The GastroPlus (Version 7.0 beta) Drug-Drug Interaction Module was used to predict the severity of drug-drug interactions based on steady state equations described by Lu et al.^[5] and Obach et al.^[6]

$$\frac{AUC^{inh}}{AUC} = \frac{1}{F_g + (1 - F_g) \left(\frac{fm_1^L}{1 + \frac{I_g}{K_{i1}}} + \frac{fm_2^L}{1 + \frac{I_g}{K_{i2}}} + \dots + \frac{fm_n^L}{1 + \frac{I_g}{K_{in}}} + fm_{inher}^L \right)} \times \frac{1}{\left(\frac{fm_1^L}{1 + \frac{I_L}{K_{i1}}} + \frac{fm_2^L}{1 + \frac{I_L}{K_{i2}}} + \dots + \frac{fm_n^L}{1 + \frac{I_L}{K_{in}}} \right) + fm_{inher}^L}$$

The inhibitor concentrations in gut (I_g) and liver (I_L), fraction of total clearance due to metabolism by individual enzymes (fm), and fraction of drug that escapes intestinal metabolism (F_g) were calculated by the simulation. K_i is the inhibition constant for individual enzymes. The severity of the drug interaction is classified by the FDA using the change in area under the curve (AUC) due to coadministration with the inhibitor (strong inhibitor > 5 fold, moderate inhibitor 2-5 fold, and weak inhibitor 1.25-2 fold increase in AUC).

Results

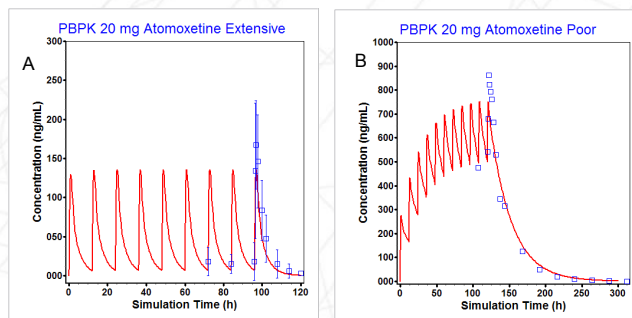


Figure 1. Experimental (squares) and GastroPlus simulated (lines) Cp-time profiles of atomoxetine for CYP2D6 extensive metabolizers (A) and poor metabolizers (B). 20 mg of atomoxetine was administered PO twice daily for 5 days. Experimental data came from Belle et al.^[7] and Sauer et al.^[8]

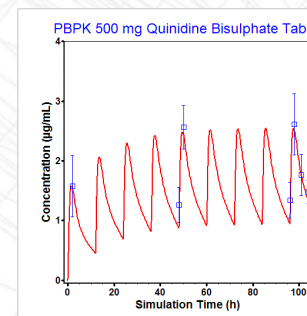


Figure 2. Experimental (squares) and GastroPlus simulated (lines) Cp-time profiles of quinidine. 500 mg of quinidine bisulphate was administered PO twice daily for 4 days. Experimental data came from Henning et al.^[9]

Subject	Ki (µM)	AUC Ratio	Classification
Extensive	0.16 ^[10]	9.8	Strong
Poor	0.16 ^[10]	1.5	Weak

Figure 2. Predicted AUC ratios for DDI between atomoxetine and quinidine under steady-state conditions. 100 mg of quinidine sulphate was administered PO once daily for 3 days and atomoxetine was administered 12 h after quinidine on day 3.

The predicted quinidine inhibition of atomoxetine metabolism was strong for extensive metabolizers and weak for poor metabolizers. According to the Strattera® (atomoxetine HCl) package insert^[11], in extensive metabolizers inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to poor metabolizers. In extensive metabolizers treated with paroxetine or fluoxetine, the AUC of atomoxetine increased approximately 6-8-fold. The package insert also states that *in vitro* studies suggest that coadministration of CYP2D6 inhibitors to poor metabolizers will not increase the plasma concentrations of atomoxetine.

Conclusions

- Pharmacokinetic models incorporating accurate simulations of inhibitor concentrations are essential for predicting drug-drug interactions.
- The predicted severity of inhibition by quinidine in CYP2D6 extensive and poor metabolizers was in agreement with the data reported in the Strattera package insert.

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- [5] Lu et al., *Drug Metabol Dispos* 2007, 35, 79-85.
 [6] Obach et al., *J Pharmacol Exp* 2006, 316-336.
 [7] Belle et al., *J Clin Pharmacol* 2002, 42, 1219-1227.
 [8] Sauer et al., *J Clin Pharmacol Kinet* 2005, 44, 571-590.
 [9] Henning et al., *Eur J Clin Pharmacol* 1973, 6, 239-244.
 [10] Moltke et al., *J Pharm Sci* 2000, 87, 1184-1189.
 [11] Strattera [package insert], Indianapolis, IN: Eli Lilly and Company, 2009.