Physiologically-based model for fluvoxamine disposition and prediction of drug-drug interactions

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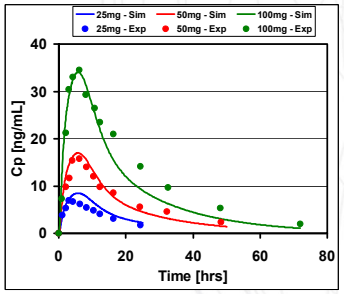
Abstract:

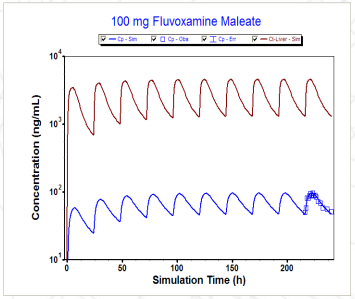
Fluvoxamine absorption and pharmacokinetics were simulated using GastroPlus™ 6.0 (Simulations Plus, Inc.). The program's Advanced Compartmental and Transit model described the absorption; pharmacokinetics was simulated with a physiologically-based pharmacokinetics model. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related Physiology™ module. Where available, human tissue/plasma partition coefficients (Kps) were approximated with experimental human Kps for a similar drug, fluoxetine. Remaining Kps were predicted in GastroPlus from drug properties and tissue composition using a modified version of a method based on equations published by Rodgers & Rowland. Clearance was fitted to plasma concentration-time profiles of fluvoxamine after oral dosing reported in literature. The final model accurately reproduced *in vivo* plasma concentration-time profiles in human for solution and solid oral doses over the range of 25-100 mg. Simulated plasma and liver concentrations were used in predictions of drug-drug interactions using steady-state models. Experimental values for *in vitro* and *in vivo* inhibition constants were reported in literature for CYP 1A2 and 2C19, suggesting higher inhibition potency of fluvoxamine *in vivo* than *in vitro* against both enzymes. However, when these Kis were combined with the relevant simulated concentrations (*in vitro* Ki with liver concentration and *in vivo* Ki with plasma concentration), both were able to predict fluvoxamine inhibition effect on CYP 1A2 and 2C19 substrates.

Pharmacokinetics:

- None of the published methods for Kp prediction currently accounts for possible accumulation of compound in tissue lysosomes (Daniel 1997), so for tissues where this lysozomal accumulation is expected to have high impact, the Kps were approximated by experimental Kps for fluoxetine (Johnson 2007).
- Clearance was fitted across three single oral doses (25–100 mg) within GastroPlus. To describe the steady-state plasma concentration after multiple oral doses, the clearance was further decreased by ~50%. This required decrease may be due to different populations used in the two studies (the dominant metabolizing enzyme, CYP2D6, is known for polymorphic expression), and/or inhibition of metabolism after multiple dosing.



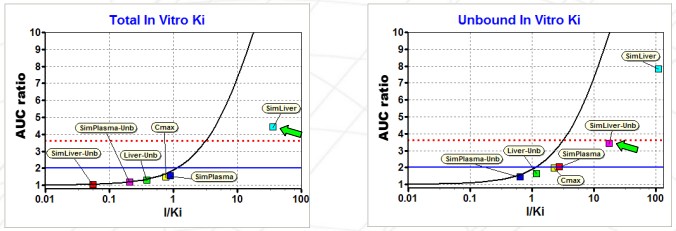
Single-dose plasma concentration-time profiles of fluvoxamine after oral doses of 25 mg, 50 mg and 100 mg of fluvoxamine maleate. *In vivo* data were obtained from literature (De Vries 1993).



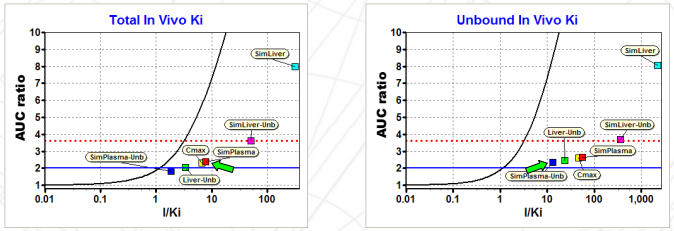
Multi-dose concentration-time profiles of fluvoxamine in plasma and liver after oral dose of 100 mg of fluvoxamine maleate. *In vivo* data (squares) were obtained from literature (Luvox CR). Simulated total concentrations (lines) are shown on the plot. Unbound concentrations used to estimate DDIs were calculated from the total concentrations using reported fractions unbound in plasma and hepatocytes.

Drug-Drug Interactions:

- Fluvoxamine is a strong inhibitor of 1A2 and 2C19. Although CYP 2D6 is the dominant metabolizing enzyme, it is a weak inhibitor of 2D6 and 3A4.
- CYP 2D6, 1A2 and 2C19 contribute to metabolism of imipramine
- Total and unbound *in vitro* and *in vivo* Kis of fluvoxamine for CYP 1A2 (Yao 2001) and 2C19 (Yao 2003) were obtained from literature; only *in vitro* values (total and unbound) were available for CYP 2D6 (Crewe 1992 & Brown 2006)
- All types of Kis predicted significant fluvoxamine-imipramine DDI (AUC ratio > 2) when combined with the relevant concentrations (total *in vitro* Ki & total liver conc; unbound *in vitro* Ki & unbound liver conc; total *in vivo* Ki & total plasma conc; unbound *in vivo* Ki & unbound plasma conc)
- Both types of *in vitro* Kis predicted AUC ratios close to observed values (5.5% and 20% error in prediction)
- Both types of *in vivo* Kis underpredicted AUC ratio by ~35% (due to the unavailability of *in vivo* Ki for CYP 2D6, the *in vitro* Ki value was used for this isoform).
- Calculated[1] systemic C_{max} gave similar DDI predictions as simulated plasma concentrations
- Calculated[1] unbound liver inlet concentration (Liver-Unb) consistently underpredicted DDI, because the simple equation used to estimate this concentration does not account for drug accumulation in liver



Fluvoxamine-Imipramine DDI prediction using different types of simulated and calculated fluvoxamine concentrations combined with total or unbound *in vitro* Kis for CYP 2D6, 1A2 and 2C19.



Fluvoxamine-Imipramine DDI prediction using different types of simulated and calculated fluvoxamine concentrations combined with total or unbound *in vivo* Kis for CYP 1A2 and 2C19 and unbound *in vitro* Ki for CYP 2D6 (*in vivo* value for this enzyme is not available).

In all graphs: The concentration type which matches the type of Ki used, and would therefore be expected to give good DDI predictions, is marked by a green arrow; the blue solid line marks the standard cutoff of AUC ratio = 2 for significant DDI; the red dotted line marks experimentally observed AUC ratio = 3.63 (Ito 2004) for effect of fluvoxamine on imipramine pharmacokinetics; the solid black line represent the theoretical AUC ratio based on [I]/Ki.

[1]Equations for calculated systemic C_{max} ($[I]_{max}$) and unbound liver inlet (Liver-Unb; $[I]_{in}$) concentration of fluvoxamine (Ito 2004):

$$[I]_{max} = \frac{[I]_{in} k_a \tau}{1 - e^{-k_a \tau}} \qquad [I]_{in} = [I]_{av} + \frac{k_a \times FDp \times D}{Q_h}$$

Summary of Fluvoxamine Ki values used in the DDI predictions

	Ki [uM]				
	Total *in vitro*	Unbound *in vitro*	Total *in vivo*	Unbound *in vivo*	References
2D6	8.2	2.47	NA	NA	Crewe 1992, Brown 2006
2C19	0.235	0.076	0.0135	0.0019	Yao 2003
1A2	0.115	0.038	0.0253	0.0036	Yao 2001

- Using *in vivo* Kis for CYP 1A2 and 2C19 and *in vitro* Ki for 2D6, combined with corresponding total or unbound plasma concentration of fluvoxamine underpredicted the AUC ratio
- The effect of CYP 2D6, for which *in vivo* Ki is not available, was explored

Simulated concentration type & Ki type for CYP 1A2 and 2C19 used in DDI prediction (*in vitro* Ki for CYP 2D6 used in all cases)	Predicted AUC ratio	
	Including inhibition of 2D6 by fluvoxamine	Not including inhibition of 2D6 by fluvoxamine
Total liver conc & Total *in vitro* Ki	4.43	2.43
Unbound liver conc & unbound *in vitro* Ki	3.43	2.37
Total plasma conc & Total *in vivo* Ki	2.4	2.24
Unbound plasma conc & unbound *in vivo* Ki	2.37	2.33

- Disregarding the contribution of weak inhibition of CYP 2D6 by fluvoxamine in the calculation using *in vitro* Kis and corresponding total or unbound liver concentration resulted in 45 and 30% decrease in predicted AUC ratio
- The *in vivo* Kis for CYP 1A2 and 2C19 were 10-40-fold lower than corresponding *in vitro* Kis. Assuming that a similar shift between *in vitro* and *in vivo* Ki can be expected also for 2D6, the underprediction of AUC ratio from plasma concentrations is likely a consequence of underpredicted contribution of 2D6 due to mismatched Ki value for this CYP isoform.

References:

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