Evaluation of a Mechanism-Based Pharmacokinetic-Pharmacodynamic Model for D_2 Receptor Occupancy of Olanzapine in Rats

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Introduction & Aim of the study

A mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) model was developed to predict the time course of dopamine receptor occupancy (D_2RO) in rat striatum following the administration of olanzapine, an atypical antipsychotic drug. This model aims at the separate characterization of association and dissociation rate constants (Kon and Koff) as the determinant of time delay between the brain concentration and D_2 receptor occupancy. This model also attempts to explain the effect of receptor binding on the free concentration of olanzapine in the brain.

The objectives of this study were to

(1) evaluate the model with alternative assumption, where receptor binding does not affect the free concentration of olanzapine.

(2) conduct a sensitivity analysis of this PK-PD model, ascertain the effect of parameter variations on model predictions, and identify influential model parameters.

Data

- 5 preclinical studies were included in the PK-PD analysis with different dose levels (0.03 to 30 mg/kg) administered by different routes (intraperitoneal, subcutaneous and intravenous). Only one PK-PD (plasma concentration, brain concentration, D_2 RO) information per animal.
- D_2RO information obtained from *in vivo* receptor binding studies.

PK-PD Model

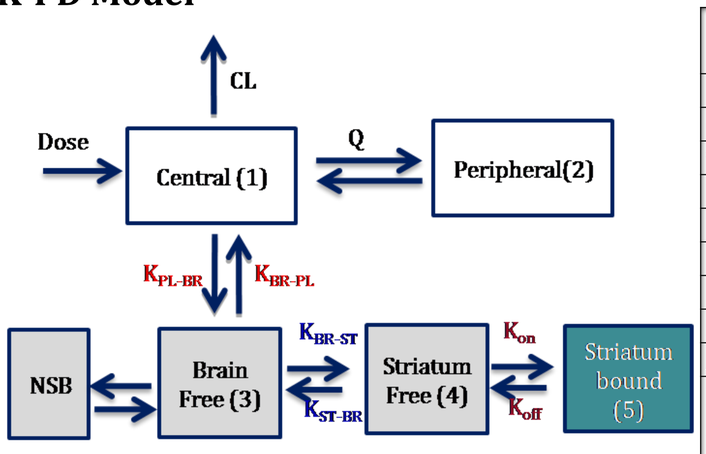

Fig 1. Schematic illustration of the PK-PD model

Population PK-PD Parameters	Estimate	%RSE
Structural model		
Cl_{brain} (L/hr/kg)	0.190	2
*KON ($nM^{-1}hr^{-1}$)	0.182	-
KOFF (hr^{1})	2.49	14
KD (nM)	13.7	6
Bmax (nM)	48 $_{fixed}$	-
Residual Variability		
PE - Brain Conc. (%)	46%	7
AE- D_2 RO	0.164	6
Derived as KON=KOFF/KD PE – Proportional Error AE – Additive Error		

A two-compartment pharmacokinetic model was used to explain the plasma pharmacokinetic (PK) profile. A binding model was developed to characterize the D_2 receptor binding in striatum, accounting for non-specific binding (NSB) and was fitted sequentially to the PK data. The PK-PD parameters were estimated using nonlinear mixed-effects modeling as implemented in the NONMEM VI, level 2.0. Brain and striatal volumes were fixed to the physiological values (4.6 and 0.2 ml/kg respectively)[1]. Fraction unbound in plasma (0.23) and brain (0.034), and Bmax (48 nM) were fixed to literature values.[2,3,4]

Assumption Testing

Model A, where receptor binding affect the free concentration of olanzapine

$$DADT(4)=K_{BR-ST}*FB*A(3)-K_{ST-BR}*FB*A(4)-K_{on}*A(4)*FB*(BMAX-CB)+K_{off}*A(5)$$

$$DADT(5)=K_{on}*A(4)*FB*(BMAX-CB)-K_{off}*A(5)$$ Where, CB= Concentration bound to receptor (in nM)

Model B, where receptor binding does not affect the free concentration

$$DADT(4)=K_{BR-ST}*FB*A(3)-K_{ST-BR}*FB*A(4)$$

$$DADT(5)=K_{on}*CSNM*FB*(1-RO)-K_{off}*RO$$ (Where, CSNM= Concentration (in nM)

1000 datasets were simulated using Model A and PK-PD parameters were estimated using Model A and Model B. Bias and RMSE in the parameter estimates were analyzed (Figures 2-3).

Sensitivity Analysis

A local sensitivity analysis, with one parameter perturbation at a time, was performed. D_2RO time profiles were simulated using Model A for perturbations in *Bmax, Kon, Koff* at the 3 mg/kg dose level. The values were perturbed 5- and 10-fold at the higher and lower ends of the nominal value. Profiles of D_2 RO with respect to each parameter were analyzed. (Figure 4)

Results

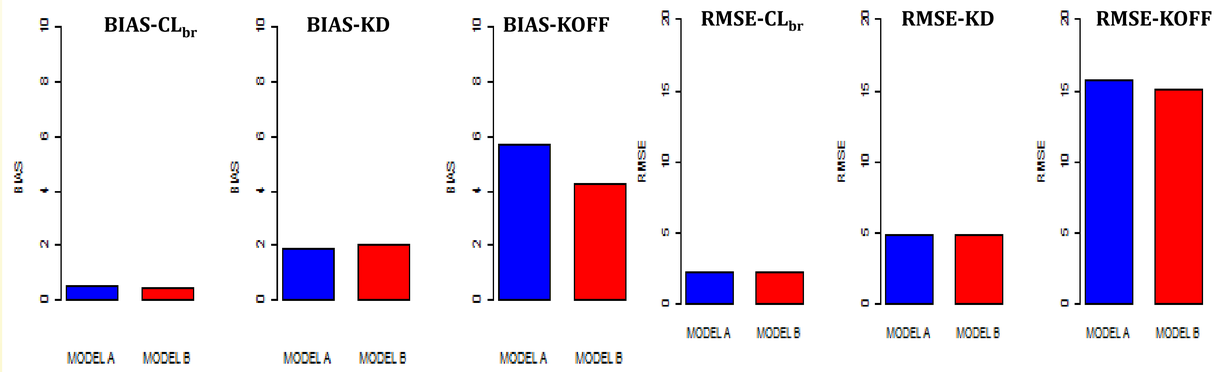

Fig 2. Accuracy of parameter estimates obtained from 1000 simulated datasets

Fig 3. Precision of parameter estimates obtained from 1000 simulated datasets

- ✓ Acceptable bias and precision in the parameter estimates.
- ✓ No difference observed between Model A and Model B in parameter estimates .

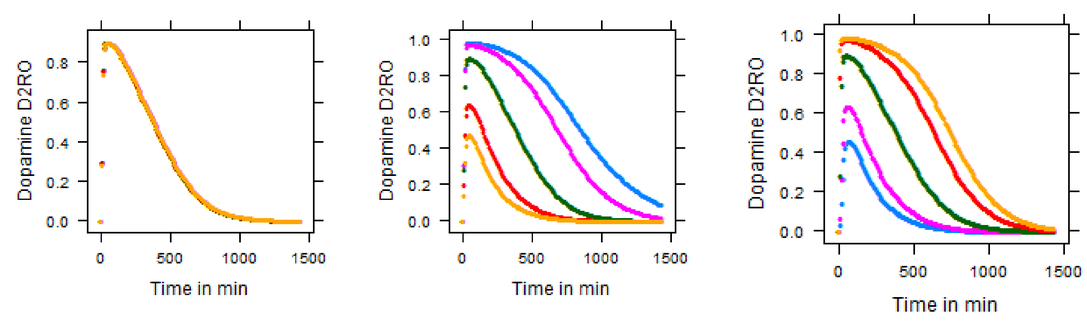

Fig 4. Simulated D_2RO profiles after perturbation of different parameters.

- ✓ Bmax did not influence the model outcome when perturbed to different values, whereas Kon and Koff showed large influence.

10 times lower than nominal
5 times lower than nominal
Nominal
5 times higher than nominal
10 times higher than nominal

Discussion

- Little or no influence of Bmax on the model output (D_2 RO) justifies its removal from the model and model simplification.
- The lack of influence of Bmax on the model output (D_2 RO) may be explained by the high free concentration in the receptor vicinity.
- Further, to utilize this model in a system dependent interspecies translational framework, Bmax can be estimated from other D_2 receptor antagonists.

Conclusion

- A simpler model (Model B) could predict the D_2 RO time course and reduced the need for Bmax which is difficult to identify from the available data.
- Moreover, this modeling framework can be utilized to scale the *in vitro* and preclinical information to clinical receptor occupancy.

References :

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Partners in this project include:

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