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PK-PD modeling platform

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Predictive performance of two PK-PD models of D_2 receptor occupancy of the antipsychotics risperidone and paliperidone in rats

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Introduction & Aim of the study

The level of dopamine D_2 receptor occupancy is predictive of efficacy and safety in schizophrenia. Population PK-PD modelling has been used to link observed plasma and brain concentrations to receptor occupancy. In more mechanistic models receptor binding is assumed to influence brain distribution and brain concentration of a drug. In simpler models receptor occupancy is derived from brain concentration, but does not affect it.

The objective of this study was to compare the predictive performance of two structurally different PK-PD models for rats. Predicted brain concentration, brain to plasma ratio and D_2 receptor occupancy were compared.

Available data and plasma PK model

NONMEM VI was used to develop a population PK-PD model for receptor occupancy (RO) in rat. Data used for development of the models consisted mainly of studies where risperidone (RIS) was administrated and concentration of RIS was measured in plasma and brain together with the D_2 or 5-HT_{2A} receptor occupancy (not all the studies had all three measurements) at one time point per individual. Receptor occupancy measured using *in vivo* and *ex vivo* methods were treated in the same way in this analysis. Administrated doses ranged from 0.01-40 mg/kg by either subcutaneous or intraperitonial administration. Additionally one plasma PK study was available where paliperidone (PALI, the active metabolite of RIS) was administrated and another where RIS was administrated and plasma concentration of both RIS and PALI were measured.
First the plasma PK model was developed. A two-compartment model both for RIS and PALI with zero and first order absorption for SC administration fit the data best. For IP RIS administration data was not sufficient to describe absorption well and it was assumed that the dose was given directly to the central compartment. Plasma PK parameters were fixed in further PK-PD analysis.

D2 receptor occupancy models

Model I: PK-PD analysis showed that in order to properly describe available data binding to both D_2 and 5-HT_{2A} receptors has to be included in the model (both RIS and PALI show high binding affinity for both receptors) and this binding affects brain concentration and distribution (Fig. 1).

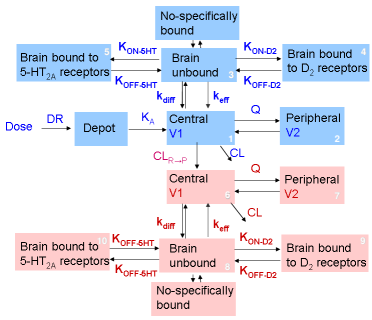

Fig. 1. Structure of Model I. RIS in blue, PALI in red.

$DADT(3) = A(1)/V1*K_{DIFF}*FU_{PI} - A(3)*K_{DIF}*FU_{Br} - A(3)*K_{EFF}*FU_{Br} - K_{ON\text{-}D2}*A(3)*FU_{Br}*(Bmax_{D2}\text{-}C4nM\text{-}C9nM) + K_{OFF\text{-}D2}*A(4) - K_{ON\text{-}5HT}*A(3)*FU_{Br}*(Bmax_{5HT}\text{-}C5nM\text{-}C10nM) + K_{OFF\text{-}5HT}*A(5)$

$DADT(4) = K_{ON\text{-}D2}*A(3)*FU_{Br}*(Bmax_{D2}\text{-}C4nM\text{-}C9nM) - K_{OFF\text{-}D2}*A(4)$

$DADT(5) = K_{ON\text{-}5HT}*A(3)*FU_{Br}*(Bmax_{5HT}\text{-}C5nM\text{-}C10nM) - K_{OFF\text{-}5HT}*A(5)$

$DADT(8) = A(6)/V6*K_{DIFF}*FU_{PI} - A(8)*K_{DIFF}*FU_{Br} - A(8)*K_{EFF}*FU_{Br} - K_{ON\text{-}D2}*A(8)*FU_{Br}*(Bmax_{D2}\text{-}C4nM\text{-}C9nM) + K_{OFF\text{-}D2}*A(9) - K_{ON\text{-}5HT}*A(8)*FU_{Br}*(Bmas_{5HT}\text{-}C5nM\text{-}C10nM) + K_{OFF\text{-}5HT}*A(10)$

$DADT(9) = K_{ON\text{-}D2}*A(8)*FU_{Br}*(Bmax_{SD2}\text{-}C4nM\text{-}C9nM) - K_{OFF\text{-}D2}*A(9)$

$DADT(10) = K_{ON\text{-}5HT}*A(8)*FU_{Br}*(Bmax_{5HT}\text{-}C5nM\text{-}C10nM) - K_{OFF\text{-}5HT}*A(10)$

FU – fraction unbound (Pl-plasma, Br-brain)
Bmax – receptor concentration
CxnM - concentration in compartment x in nM

Model II: Binding to D_2 receptor does not influence brain kinetics. Binding to 5-HT_{2A} receptors not included in the model.

$DADT(3) = (A(1)/V1)*K_{DIFF}*FU_{PI} - A(3)*K_{DIF}*FU_{Br} - A(3)*K_{EFF}*FU_{Br}$ - RIS concentration in brain
$DADT(4) = K_{ON\text{-}D2}*C3nM*FU_{Br}*(1\text{-}A(4)\text{-}A(8)) - K_{OFF\text{-}D2}*A(4)$ - D_2 RO by RIS
$DADT(7) = (A(5)/V5)*K_{DIFF}*FU_{PI} - A(7)*K_{DIFF}*FU_{Br} - A(7)*K_{EFF}*FU_{Br}$ - PALI concentration in brain
$DADT(8) = K_{ON\text{-}D2}*C7nM*FU_{Br}*(1\text{-}A(4)\text{-}A(8)) - K_{OFF\text{-}D2}*A(8)$ - D_2 RO by PALI

Model III: As model II but developed for subset of data where dose was higher than 0.5 mg/kg.

It was not possible to achieve stable parameter estimates, when Model I was fitted to a subset of data where dose was higher than 0.5 mg/kg.

Simulations & Results

Based on typical value (THETAs) and inter-individual variability (ETAs) of parameters estimated by NONMEM, simulations of time course of brain concentration and D_2 receptor occupancy were done using R. Additionally, brain to plasma ratios were calculated. Results of the simulations were compared with observed values graphically.

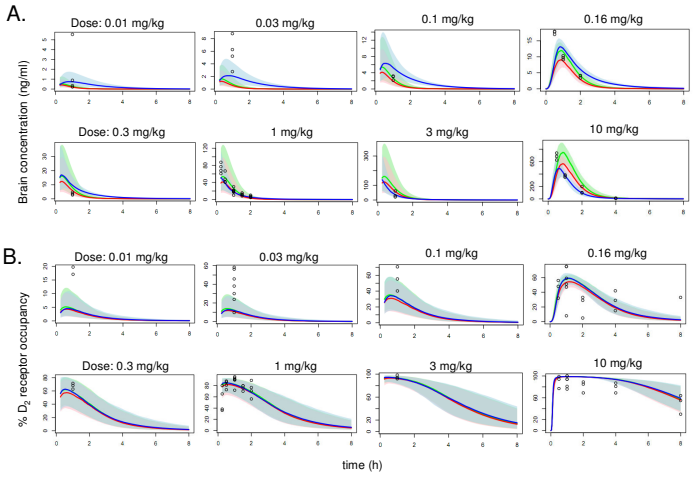

Fig. 2. Time course of brain concentration (A.) and D_2 receptor occupancy (B.) predicted by the three models: blue – Model I, green –Model II, red – Model III. Shaded areas represent 90% prediction interval based on 250 individual simulated profiles, solid line is a median. Black circles represent observed data.

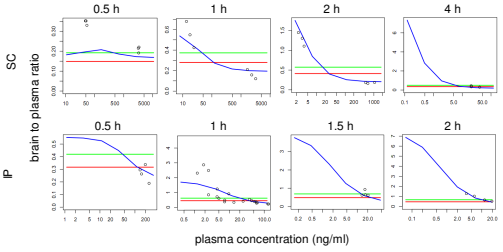

Fig. 3. Relationship between plasma concentration and brain to plasma ratio. Colours and symbols as on Fig. 2.

Model	Residual error	
	Brain	% D_2 RO
I	38.8 %	18.9
II	62.1 %	18.6
III	43.3 %	14.0

Table 1. Residual errors from model fit. Proportional error for brain concentration and additive for D_2 RO.

Predictions of brain concentrations of the three models differed, especially at lower doses, but no clear pattern in respect to fit to real data is seen (Fig. 2A). Model I showed lowest residual error, and Model II the highest (Table 1). Only Model I predicted accurately brain to plasma ratio pattern seen in real data (Fig 3).
D_2 RO predicted by all the models did not differ considerably (Fig. 2B).

Conclusions & Discussion

Only a more mechanistic model where binding to receptors influences brain kinetics can accurately predict brain to plasma ratio patterns seen in the dataset (high brain to plasma ratio at lower concentrations and relatively constant ratio at higher concentrations).
However, simpler models may be sufficient to accurately predict D_2 RO. Inclusion of binding to receptors in the brain kinetics may be especially important for the drugs with active efflux, where brain concentrations are relatively low and therefore drug bound to receptors can constitute relatively high proportion of total drug in brain. Brain to plasma ratio pattern may be informative of the importance of receptor binding. This is consistent with data for olanzapine, where brain to plasma ratio is relatively constant and simpler models can provide a good fit (data not shown).

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Partners in this project include:

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