Predictive performance of two PK-PD models of D2 receptor occupancy of the antipsychotics risperidone and paliperidone in rats

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Introduction & Aim of the study

The level of dopamine D2 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 D2 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 D2 or 5-HT2A 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. Administered doses ranged from 0.01-40 mg/kg by either subcutaneous or intraperitoneal administration. Additionally one plasma PK study was available where paliperidone (PALI), the active metabolite of RIS was administrated and where risperidone 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 D2 and 5-HT2A 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).

Model II: Binding to D2 receptor does not influence brain kinetics. Binding to 5-HT2A receptors not included in the model.

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 D2 receptor occupancy were done using R. Additionally, brain to plasma ratios were calculated. Results of the simulations were compared with observed values graphically.

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 D2 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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