Translational modelling of prolactin response following administration of D₂ antagonists in rats

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Introduction
Schizophrenia is a disorder of dopamine dysregulation, for which D₂ antagonists are the treatment of choice. Treatment with D₂ antagonists results in prolactin release, and thus prolactin is a biomarker of dopamine antagonism. We compare the performance of two semi-mechanistic PKPD models, the pool model and the agonist-antagonist interaction model, to describe prolactin release following administration of risperidone (RI), paliperidone (PA) and remoxipride (RE) in rats (1,2,3). The hypothesis that potency differences exist for RI and PA was evaluated and additionally, rat to human translations were conducted, for one compound, PA.

Methods
Data from 40 rats who received single IV doses (2 and 0.5 mg/kg) of RI or PA (n=20 each) and 50 rats who received multiple doses of REM (0, 3.8, 8, 16 mg/kg) were available for the analysis. Prolactin was measured hourly for 6-10 hours post-dose. The models were fitted to available data on the 3 paradigm compounds. The pool model was modified to estimate \( R_{50} \), the receptor occupancy at half-maximal effect, which is assumed to be a system specific parameter, using model predicted and observed Ki values. Population-predicted free plasma concentrations of the \( D_2 \) antagonist were considered as the driver of the pharmacodynamic (PD) response (4). Finally, we compared the predicted human time course of plasma prolactin, with either model, using an inter-species scaling approach, for PA. Deterministic simulations were performed to explore model structures prior to model fitting and subsequently to perform inter-species translations. We compared our findings with Ma et al, who compared the 2 models, in data from healthy volunteers, administered REM (5).

Results
Model Exploration: Single dose simulations with the pool model are shown in Figure 2 below, with RI as a paradigm. At the highest dose, a resetting of the baseline takes place, which is due to the use of the positive feedback (PF) function. Similar effects were seen with REM (data not shown). The pool model was modified by removing this function, while for the interaction model, the diurnal rhythm (DRI) function was removed, since no circadian rhythms were identifiable in rats.

Examination of 2 potencies: From Table 1 (left 3 columns) below, it can be seen that separate Ki’s for RI and PA did not significantly improve model fit.

Discussion
Both models were able to describe the data on all 3 compounds adequately (figure 3). No significant difference in potency between RI and PA was found. The same model structure could adequately describe single (RI/PA) or multiple dose (REM) data. The pool model can be extended to estimate \( R_{50} \), a system-specific parameter. Using an inter-species scaling approach, the pool model was able to predict the plasma prolactin response in humans following single doses of PA. Predicted lactotroph prolactin profiles were in agreement with those obtained by modeling of human data (1). However, it predicts tachyphylaxis following the first dose due to pool depletion (figure 5 lower panels). On the other hand, the interaction model reproduces prolactin response in humans at single doses and at steady state. No tachyphylaxis is seen with this model. Parameters for the pool model scale better between rat and man using allometric techniques, when compared to the interaction model (Table 2). Repeat dosing profiles could be predicted for REM, which has a \( t_1/2 \) of 4.5 hrs but not for PA (\( t_1/2 \) = 20 hrs).

Reference

Table 1: Comparison of parameter estimates with the interaction model for RI/PA, using free plasma concentrations (level 3 columns). Combined vs separate potency parameters for these compounds are compared. Pool estimates with the pool model are presented in the light 3 columns, using RO as the driving force for prolactin release.

![Image](https://via.placeholder.com/150)

Figure 1: The left panel shows time course of prolactin in 10 animals (pool) following single dose of RI, while the right panel shows the prolactin time course in plasma following single oral doses of 0.01, 0.05, 0.14, and 0.18 mg/kg. Similar effects are expected for PA.

Figure 2: Typical predicted human plasma prolactin profiles for the interaction model, following 5 daily doses of PA. Overlaid line are corresponding observed human plasma prolactin profiles. Left panel profiles are with relative constants while right panel profiles are with published human model estimated Ki’s.

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Figure 3: Typical predicted human plasma prolactin profiles for the interaction model, following 5 daily doses of REM, using parameter estimates Ma et al, with ours.

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Figure 4: Left: Simulated unbound plasma PA time course (oroid, delayed release formulation) and pool model predicted receptor occupancy in plasma following 5 daily doses of PA. The dotted line shows the observed receptor occupancy in humans at a clinically relevant dose (9 mg daily).

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Figure 5: Typical predicted human prolactin profiles, following 6 daily doses of PA, showing the effect of varying plasma prolactin concentrations (0.24-7.8 nM) in the upper and lower panels. Comparison results in data and green dashed line show observed human plasma prolactin profiles, respectively, at corresponding doses. Complete depletion of the pool following multiple doses is predicted.

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Figure 6: Typical predicted human plasma prolactin profiles for the interaction model, following 5 daily doses of REM, using parameter estimates Ma et al and ours.

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Figure 7: Typical predicted human plasma prolactin profiles for the interaction model, following 5 daily doses of REM, using parameter estimates Ma et al and ours.


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