

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 model 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 (REM) 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 RO₅₀, 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 D₂ antagonists 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).

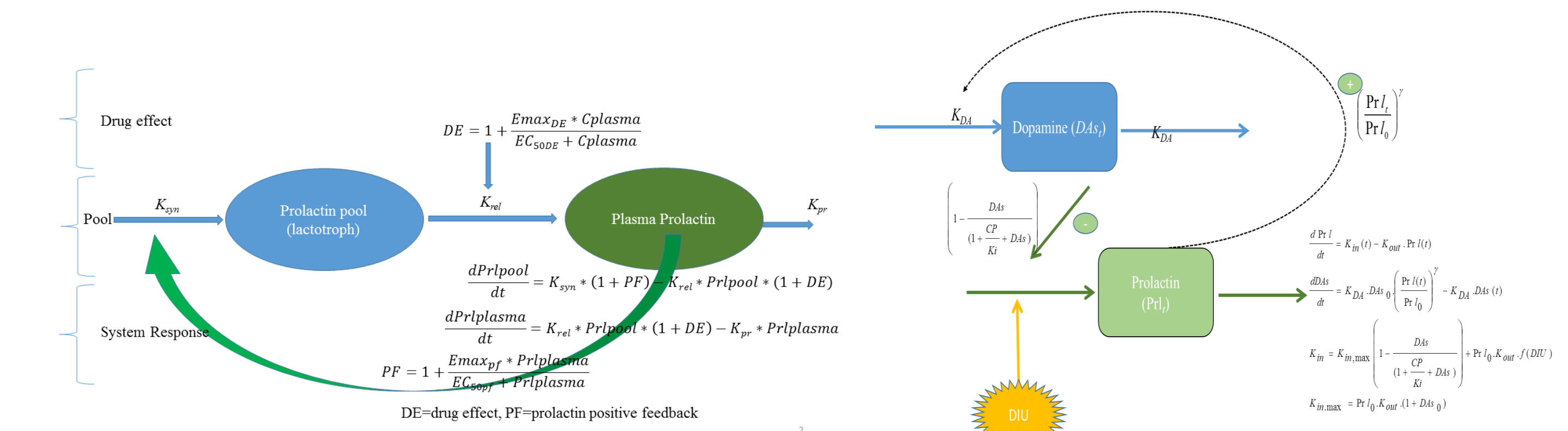


Figure 1: The pool (left panel) and interaction (right panel) models of prolactin response. K_{syn} , K_{rel} and K_{out} are the rate constants for prolactin synthesis, release from the pool and elimination from the plasma respectively. K_{di} , K_{in} and K_{out} are the rate constants for dopamine and prolactin turnover respectively.

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 (DIU) function was removed, since no circadian rhythms were identifiable in rats.

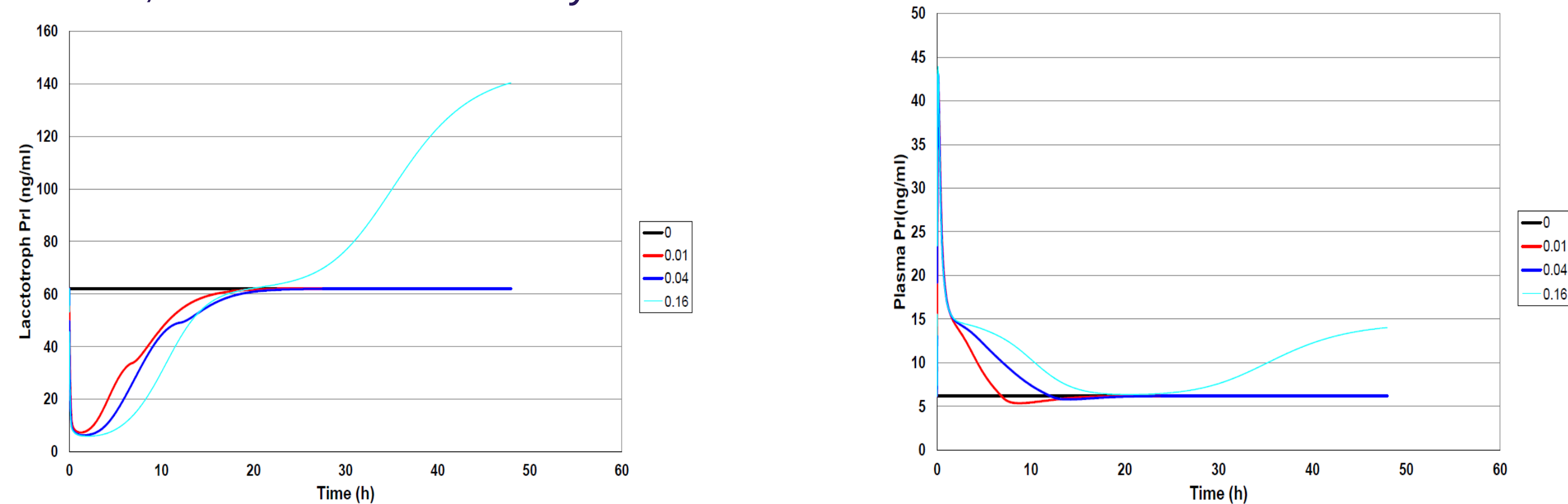


Figure 2: The left panel shows time course of prolactin in lactotroph (pool) following single doses of RI while the right panel shows the prolactin time course in plasma following single oral doses of 0, 0.01, 0.04, and 0.16 mg/kg. Similar results are expected for PA.

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

Parameter	Interaction model Estimates (RSE%)		Parameter	Pool model model Estimates RSE%
	Single KI for RI and PA	Separate KIs for RI and PA		
Kin (ng/ml.h)	23.80 (6)	23.81 (6)	Ksyn (ng/ml.h)	49.8 (10)
Kout (/h)	3.34 (9)	3.35 (10)	Krel (/h)	0.23 (11)
DA (dimensionless)	1000 FIX	1000 FIX	Kpr (/h)	6.96 (12)
Kda (/h)	5.51 (21)	5.12 (19)	Emax (dimensionless)	3.33 FIX
KI_PA (nM)	35.7 (12)	34.1 (14)	RO50 (%)	28.7 (27)
KI_RI (nM)		47.7 (20)		
KI_REM (nM)	360 (11)	370 (11)	RE(%)	37 (8)
IIV-BSL (%)	19 (12)	22 (12)	IIV-Kpr(/h)	17.9 (18)
Residual error (%)	11 (4)	12 (4)	Additive Residual error(ng/ml)	2.68
Min	++	++	Minimization	++
Cov	++	++	Covariance	++
OFV	3727.802	3726.086	OFV	3430.775

Table 1: Comparison of parameter estimates with the interaction model for RI, PA, using free plasma concentrations (left 3 columns). Combined vs 2 separate potency parameters for these compounds are compared. Final estimates with the pool model are presented in the right 2 columns, using RO as the driving force for prolactin release

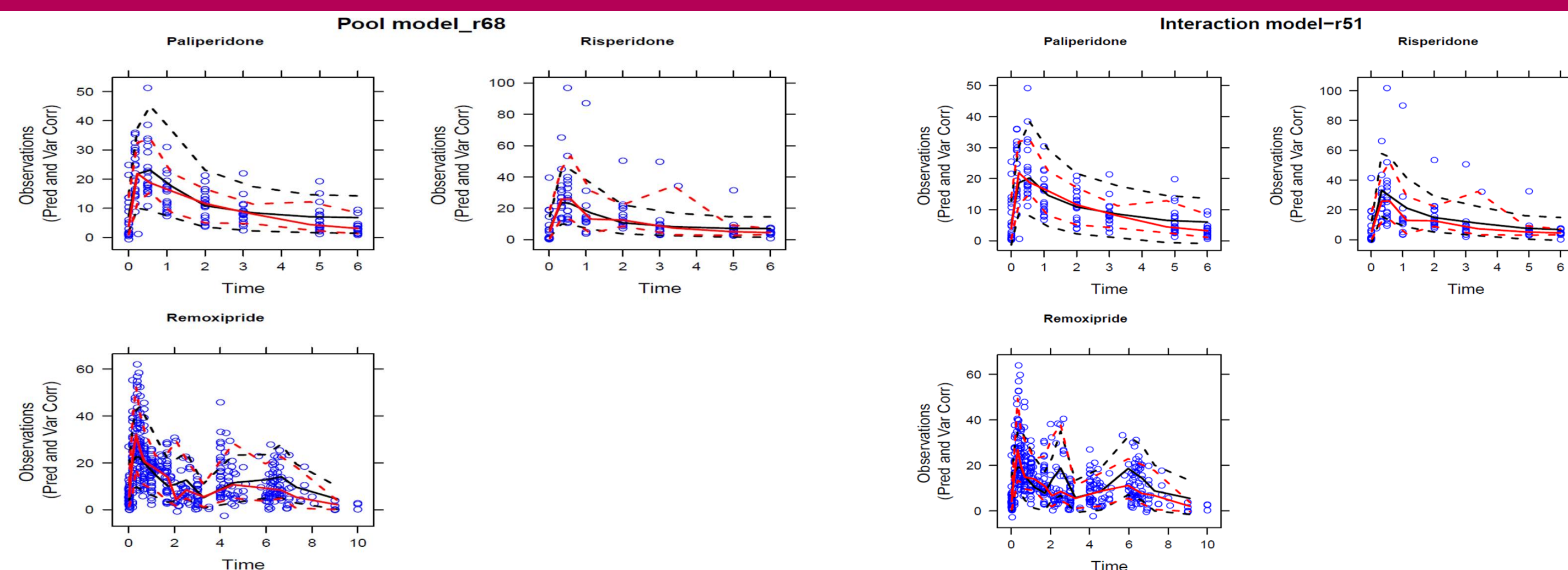


Fig 3: VPCs with the final pool and interaction models, depicted per compound. The black and red solid and dotted lines are the median, 10 and 90% prediction intervals of the observed and simulated data respectively while the blue circles are the observations

Rat to human translations for both models are shown for PA in figures 4 and 5.

Standard allometry was used to scale rate constants with $b = -0.25$.

$$\frac{K_{hum}}{K_{rat}} = \left(\frac{BW_{hum}}{BW_{rat}} \right)^b$$

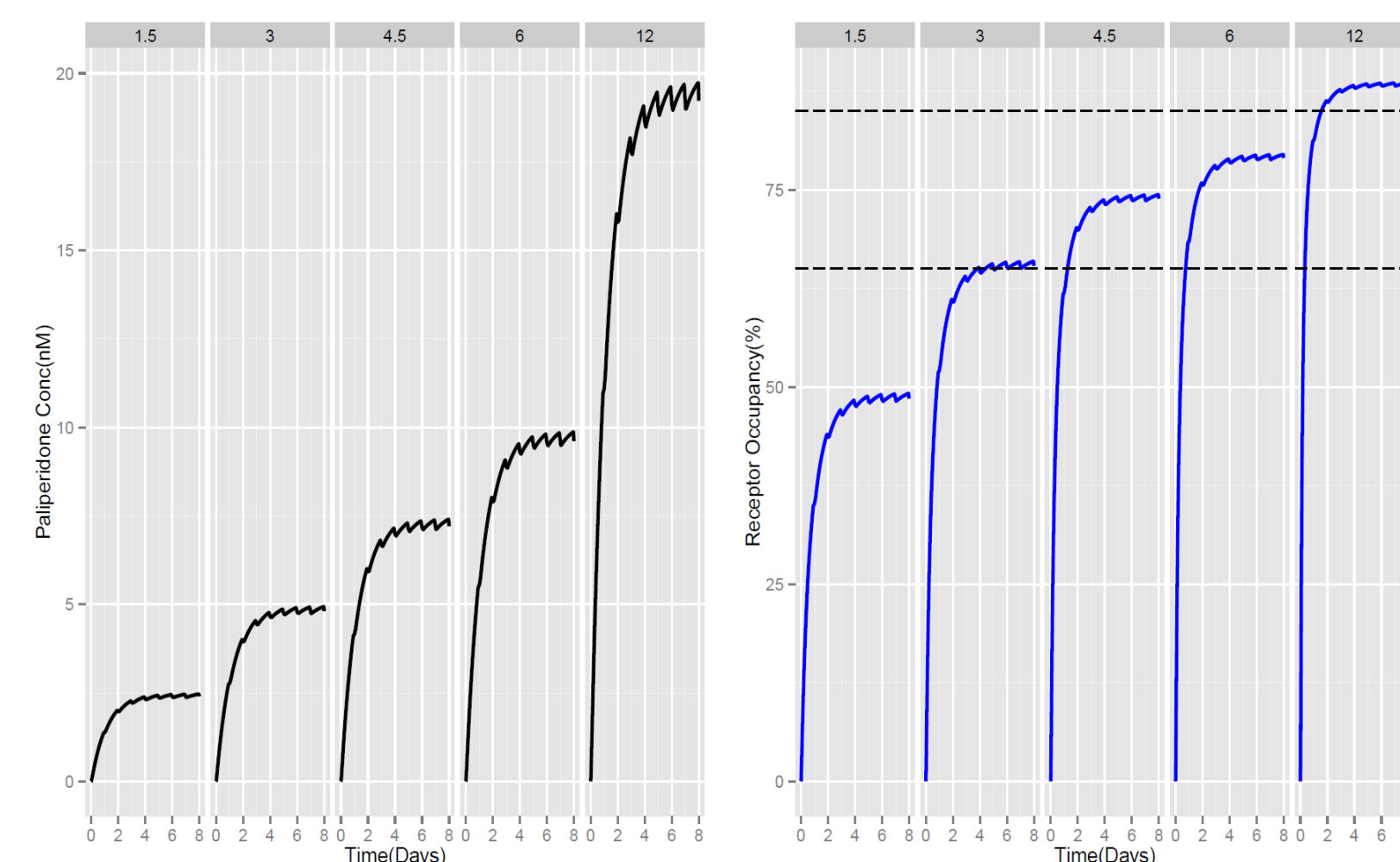


Fig 4 (left): Simulated unbound plasma PA time course (OROS, delayed release formulation) and pool model predicted receptor occupancy in humans, for x 8 doses at a dosing interval of 24 hours. The dotted lines show the zone of observed receptor occupancy in humans at a clinically relevant dose (9 mg daily).

Table 2 (below left): Parameter estimates from the original pool model are compared with those of Ma et al, and with our findings, obtained by inter-species scaling. Ma et al improved the original pool model by conserving mass balance in the modelling (5). A similar comparison is done for the interaction model, where we compared the parameter estimates of Ma et al, with ours.

Parameter	Pool model (IIV%) (Movin-Osswald et al, 1995)	Pool model Estimates (IIV%) (Ma et al, 2010)	Our findings translation from rat to human
Baseline Prolactin pool conc (ng/ml)	97.5 (53)	246	250.4
Baseline Prolactin plasma conc (ng/ml)	9.88 (28)	12.7 (23)	7.60
Ksyn (ng/ml.h)	13.5 (34)	26.5	12.52
Krel (/h)	0.11(34)	0.11	0.05
Kpr (/h)	1 (18)	2.09	1.65
		Interaction model (Ma et al, 2010)	
Baseline Prolactin plasma conc (ng/ml)		9.13 (5.5)	5.15
Kout(/h)		0.803	0.89
Kda(/h)		0.134	1.24
KI_REM (nM)		129 (21.3)	165

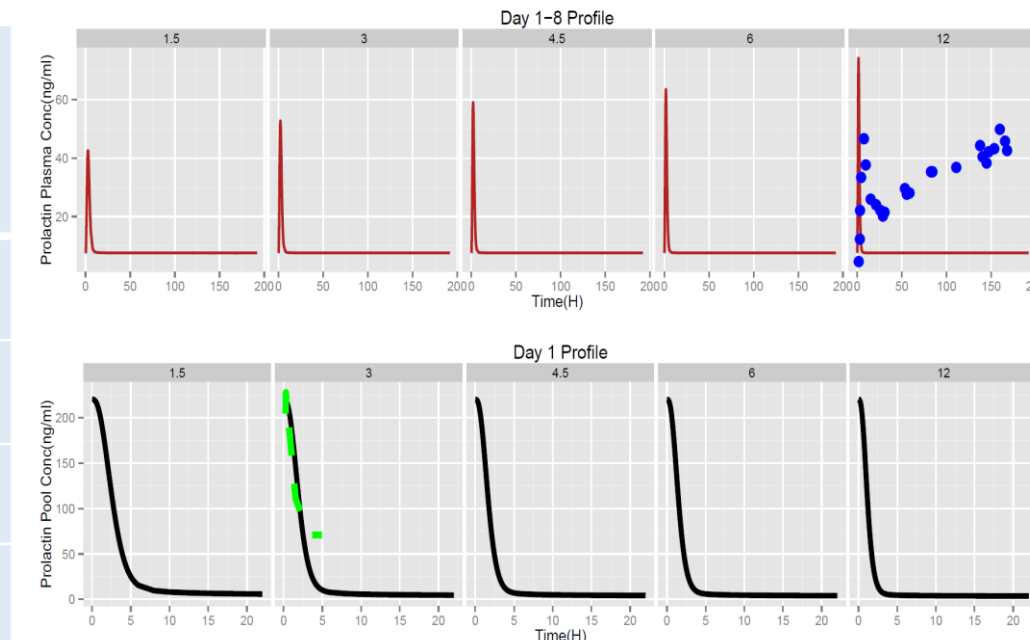


Fig 5: Typical predicted human prolactin profiles, following 8 daily doses of PA. Plasma (0-200 h) and lactotroph concentrations (0-24 h) in the upper and lower panels respectively. Overlaid blue dots and green dashed line are observed human plasma prolactin profiles and predicted lactotroph prolactin profiles respectively, at corresponding doses. Complete depletion of the pool following multiple doses is predicted.

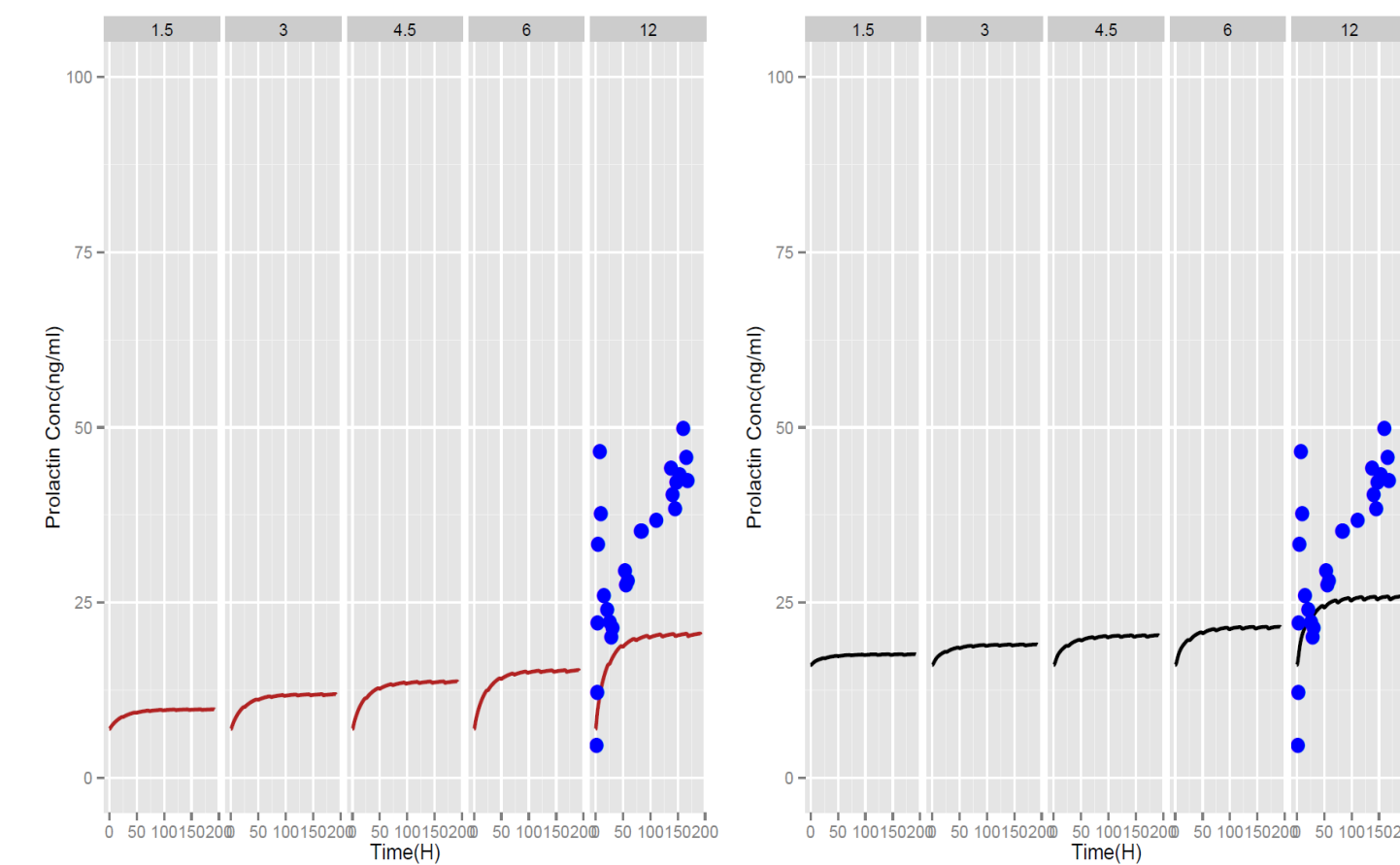


Fig 6: Typical predicted human plasma prolactin profiles for the interaction model, following 8 daily doses of PA. Overlaid blue dots are corresponding observed human plasma prolactin profiles. Left panel profiles are with scaled rate constants while right panel profiles are with published human rate constants and scaled KI.

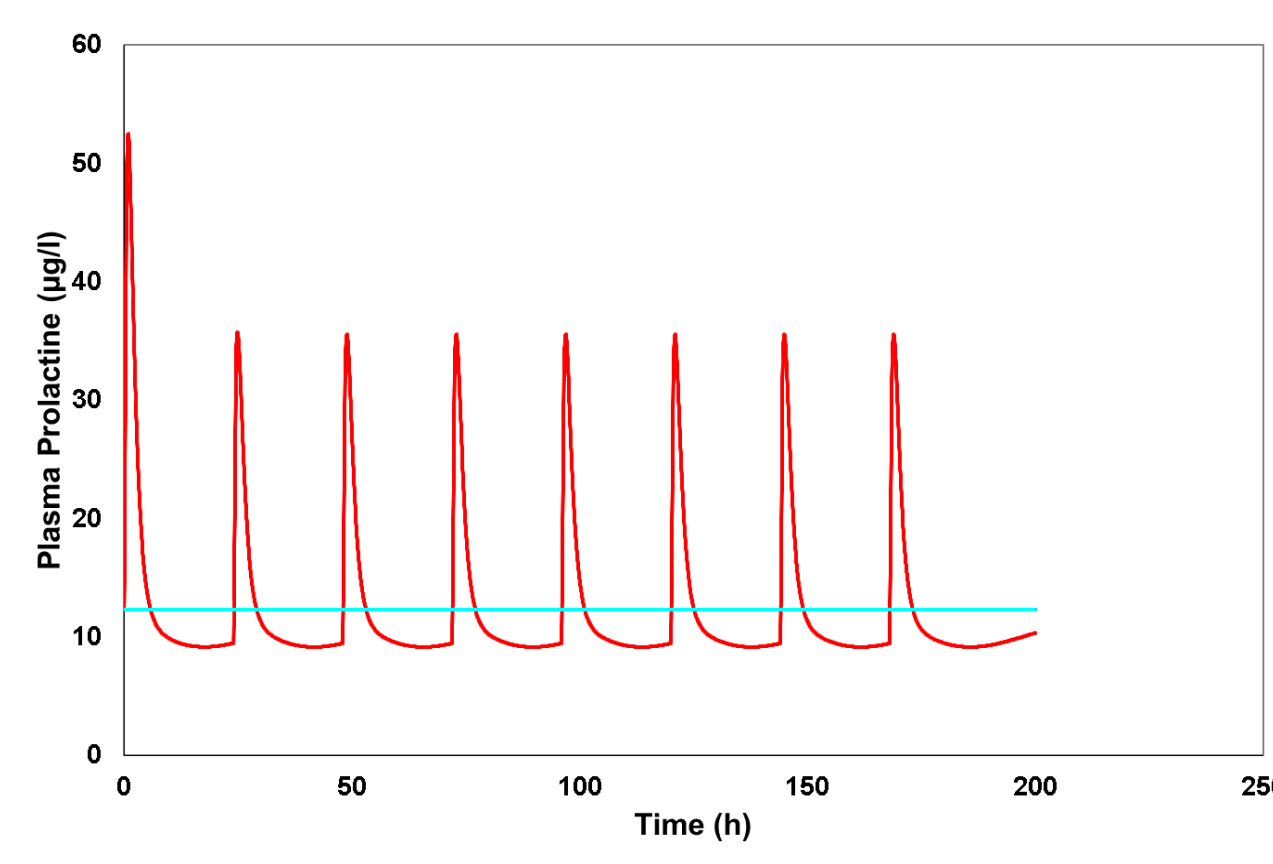


Fig 7: Typical predicted human plasma prolactin profiles for the pool model, following 8 daily doses of REM, using parameters from (1), see Table (2). Peaks with repeat dosing indicate partial recovery of the pool. Blue line is the basal level.

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 the RO₅₀, a system-specific parameter. Using an interspecies 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 modelling 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 underpredicts prolactin response in humans at single doses and at steady state. No tachyphylaxis is seen with this model. 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).

References

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