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Data Article

Summary data of potency and parameter information from semi-mechanistic PKPD modeling of prolactin release following administration of the dopamine D_2 receptor antagonists risperidone, paliperidone and remoxipride in rats

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ABSTRACT

We provide the reader with relevant data related to our recently published paper, comparing two mathematical models to describe prolactin turnover in rats following one or two doses of the dopamine D_2 receptor antagonists risperidone, paliperidone and remoxipride, "A comparison of two semi-mechanistic models for prolactin release and prediction of receptor occupancy following administration of dopamine D_2 receptor antagonists in rats" (Taneja et al., 2016) [1]. All information is tabulated. Summary level data on the in vitro potencies and the physicochemical properties is presented in Table 1. Model parameters required to explore the precursor pool model are presented in Table 2. In Table 3, estimated parameter comparisons for both models are

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presented, when separate potencies are estimated for risperidone and paliperidone, as compared to a common potency for both drugs. In Table 4, parameter estimates are compared when the drug effect is parameterized in terms of drug concentration or receptor occupancy.

Specifications Table

Subject area	Pharmacology
More specific subject area	Neuropsychopharmacology
Type of data	Tables
How data was acquired	Experimental study in male wistar rats, as described below
Data format	Processed tabulated data
Experimental factors	Plasma samples were collected for bioanalysis of risperidone, paliperidone, and remoxipride using an on-line solid phase extraction with liquid chromatography – tandem mass spectrometry method. Serum prolactin levels were measured using an enzyme linked immunosorbent assay technique.
Experimental features	All animal procedures were performed at Leiden University, in accordance with Dutch laws governing animal experimentation. Male Wistar rats, received single intravenous doses of risperidone (2 mg/kg, $n=16$) or paliperidone (0.5 mg/kg, $n=21$). Plasma drug concentrations as well as plasma prolactin levels were measured at pre-dose and at serial intervals post-dose. In another study, remoxipride was administered to rats either as a single intravenous dose of 4, 8 or 16 mg/kg ($n=10$) remoxipride or two doses of 3.8 mg/kg at varying dosing intervals. Blood samples were serially collected. Plasma concentrations of the drugs as well as prolactin were assayed using validated analytical methods.
Data source location	Department of Pharmacology, Leiden Academic center for Drug Research, Leiden.
Data accessibility	The data is within this article.

Value of the data

Data can be used

- To compare experimental findings in literature with our model-based approach.
- As prior information, especially when the available data is scarce.
- For exploratory modeling.
- For translation from rat to humans.

1. Data

The information is presented in 4 tables. Table 1 presents the in vitro inhibition constant (*KI*) values in rat and humans and physicochemical characteristics of the antipsychotics risperidone, paliperidone and remoxipride. Table 2 presents the pharmacokinetic–pharmacodynamic model

Table 1
Overview of literature *KI* values and physicochemical characteristics of risperidone, paliperidone and remoxipride.

	Risperidone	Paliperidone	Remoxipride
***KI* values** (nM)			
Rat*	2.55	2.74	370.66
Human*	2.18	2.08	165.75
Human**	4.9 / 6	NA	243 / 125
Physicochemical characteristics			
Protein binding % (rat)*	88.2	74.7	20-30
Protein binding % (human)*	90	77.4	80
Molecular weight (g/mol)	410.48	426.48	371.26

* Data on file.
** Data from Richtand et al. [2]. Values depicted for D_2 and D_2 long receptor in vitro experimental *KI*.

Table 2
Model parameters used for the simulations in exploratory model analysis. Pharmacokinetic and pharmacodynamic parameters obtained from Kozielska et al. [3] and Stevens et al. [4], respectively.

Parameter	Estimate
CL ($l \cdot h^{-1}$)	1.62
$V1$ (l)	1.29
Q ($l \cdot h^{-1}$)	0.0882
$V2$ (l)	0.169
F	1
Ka (h^{-1})	2.84
$C_{prl,0}$ ($ng \cdot ml^{-1}$)	6.2
R_{form} ($ng \cdot ml^{-1} \cdot h^{-1}$)	35.3*
K_{base} (h^{-1})	0.57
K_{out} (h^{-1})	5.7
E_{max}	25
EC_{50} ($ng \cdot ml^{-1}$)	0.08
γ	1
E_{max_pf}	3.5
EC_{50_pf} ($ng \cdot ml^{-1}$)	12.4

CL = clearance from the central compartment, $V1$ = volume of the central compartment, Q = intercompartmental clearance, $V2$ = volume of the peripheral compartment, F = bioavailability, Ka = absorption constant, $C_{prl,0}$ = plasma concentration of prolactin in the absence of antipsychotic drug, R_{form} = zero-order rate constant for prolactin synthesis, K_{base} = first-order rate constant of prolactin release from the pool, K_{out} = first-order rate constant of elimination of prolactin from plasma, E_{max} = maximum increase in the prolactin release from the pool, EC_{50} = drug concentration at half-maximal effect, γ = slope parameter, E_{max_pf} = maximum prolactin feedback, EC_{50_pf} = plasma prolactin concentration at half-maximal effect.

* R_{form} is calculated as the product of $C_{prl,0}$. K_{out} (equation (5) of Taneja et al. [1]).

Table 3
Parameter comparison (relative standard error in %) of the pool model with different ECu_{50} for risperidone and paliperidone vs. single ECu_{50} and the interaction model with different *KI* for risperidone and paliperidone vs single *KI*.

	Estimates	
	Different ECu_{50}	Single ECu_{50}
Pool Model		
R_{form} ($ng.ml^{-1} \times h^{-1}$)	52.1 (12)	48.7 (12)
K_{base} (h^{-1})	0.251 (12)	0.250 (12)
K_{out} (h^{-1})	6.96 (14)	6.57 (12)
E_{max}	3.5 FIXED	3.5 FIXED
ECu_{50} paliperidone (nM)	38.2 (52)	35.1 (51)
ECu_{50} risperidone (nM)	39.6 (142)	
ECu_{50} remoxipride (nM)	95.2 (41)	94.8 (31)
γ	1 FIXED	1 FIXED
IIV R_{form} (%)	40 (18)	40 (18)
Residual error (%)	50 (7)	50 (7)
Minimization	++	++
Covariance	++	++
Objective Function Value	3454.764	3455.775
Interaction Model		
$K_{in,0}$ ($ng.ml^{-1} \times h^{-1}$)	23.8 (6)	23.8 (6)
K_{out} (h^{-1})	3.35 (10)	3.34 (9)
K_{DA} (h^{-1})	5.12 (19)	5.51 (21)
DAs_0 (dimensionless)	1000 FIXED	1000 FIXED
KI paliperidone (nM)	34.1 (11)	35.7 (12)
KI risperidone (nM)	47.7 (20)	
KI remoxipride (nM)	370 (11)	360 (11)
γ	1 FIXED	1 FIXED
IIV $K_{in,0}$ (%)	40 (22)	40 (22)
Residual error (%)	56 (12)	56 (12)
Minimization	++	++
Covariance	++	++
Objective Function Value	3727.802	3726.086

R_{form} = zero-order rate constant for prolactin synthesis, K_{base} = first-order rate constant of prolactin release from the pool, K_{out} = first-order rate constant of elimination of prolactin from plasma, E_{max} = maximum increase in the prolactin release from the pool, EC_{u50} = unbound drug concentration at half-maximal effect, γ = slope parameter, IIV = inter-individual variability, $K_{in,0}$ = basal prolactin release rate, K_{DA} = first-order turnover constant for hypothetical dopamine, DAs_0 = hypothetical scaled dopamine concentration at baseline, *KI* = drug potency parameter.

parameters used to perform exploratory model simulations of the precursor pool model, as referred to in Section 3.2, Fig. 5 of Taneja et al. [1]. Table 3 presents the model parameters assuming equal or different potency of risperidone and paliperidone. Table 4 presents the model parameters obtained with different parameterizations, assuming either unbound drug concentration or dopamine D_2 receptor occupancy as the driving force for drug effect.

2. Experimental design, materials and methods

Details of the experimental procedures have been described previously [1,5,6].

Table 4
Pool model: Comparison of parameter estimates with parameterization of drug effects as ECu_{50} as compared to RO_{50} (relative standard error in %).

Parameter	Estimates using ECu_{50}	Estimates using RO_{50}
R_{form} ($ng.ml^{-1} \times h^{-1}$)	45.7 (10)	49.8 (10)
K_{base} (h^{-1})	0.25 (10)	0.226 (11)
K_{out} (h^{-1})	6.06 (12)	6.96 (13)
E_{max}	3.5 FIXED	3.5 FIXED
ECu_{50} risperidone/paliperidone (nM)	35.1 (51)	*
ECu_{50} remoxipride (nM)	94.8 (31)	*
RO_{50} (%)	NA	28.7 (27)
γ	1 FIXED	1 FIXED
IIV K_{out} (%)	42.1 (18)	42.3 (18)
Residual error - proportional (%)	47.2 (4)	37.4 (8)
Residual error - additive ($ng \cdot ml^{-1}$)	NE	2.68 (29)
Minimization	++	++
Covariance step	++	++
Objective Function Value	3434.44	3430.56

R_{form} = zero-order rate constant for prolactin synthesis, K_{base} = first-order rate constant of prolactin release from the pool, K_{out} = first-order rate constant of elimination of prolactin from plasma, E_{max} = maximum increase in the prolactin release from the pool, EC_{u50} = unbound drug concentration at half-maximal effect, RO_{50} = receptor occupancy at half-maximal effect, γ = slope parameter, IIV = inter-individual variability.
NA = not applicable.
NE = not estimated.
* *KI* risperidone/paliperidone = 2.55 nM, *KI* remoxipride = 370.66 nM (fixed to in vitro experimental values).

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References

[1] A. Taneja, A. Vermeulen, D.R.H. Huntjens, M. Danhof, E.C.M. De Lange, J.H. Proost, A comparison of two semi-mechanistic models for prolactin release and prediction of receptor occupancy following administration of dopamine D_2 receptor antagonists in rats, Eur. J. Pharmacol. 789 (2016) 202–214. http://dx.doi.org/10.1016/j.ejphar.2016.07.005.
[2] N.M. Richtand, J.A. Welge, A.D. Logue, P.E. Keck Jr., S.M. Strakowski, R.K. McNamara, Dopamine and serotonin receptor binding and antipsychotic efficacy, Neuropsychopharmacology 32 (8) (2007) 1715–1726. http://dx.doi.org/10.1038/sj.npp.1301305.
[3] M. Kozielska, M. Johnson, V. Pilla Reddy, A. Vermeulen, C. Li, S. Grimwood, R. de Greef, G.M. Groothuis, M. Danhof, J. H. Proost, Pharmacokinetic-pharmacodynamic modeling of the D(2) and 5-HT(2A) receptor occupancy of risperidone and paliperidone in rats, Pharm. Res. 29 (7) (2012) 1932–1948. http://dx.doi.org/10.1007/s11095-012-0722-8.
[4] J. Stevens, B.A. Ploeger, M. Hammarlund-Udenaes, G. Osswald, P.H. van der Graaf, M. Danhof, E.C. de Lange, Mechanism-based PK-PD model for the prolactin biological system response following an acute dopamine inhibition challenge: quantitative extrapolation to humans, J. Pharmacokinet. Pharmacodyn. 39 (5) (2012) 463–477. http://dx.doi.org/10.1007/s10928-012-9262-4.
[5] J. Stevens, D.J. van den Berg, S. de Ridder, H.A. Niederlander, P.H. van der Graaf, M. Danhof, E.C. de Lange, Online solid phase extraction with liquid chromatography-tandem mass spectrometry to analyze remoxipride in small plasma-, brain homogenate-, and brain microdialysate samples, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 878 (13–14) (2010) 969–975. http://dx.doi.org/10.1016/j.jchromb.2010.02.024.
[6] J. Stevens, B.A. Ploeger, P.H. van der Graaf, M. Danhof, E.C. de Lange, Systemic and direct nose-to-brain transport pharmacokinetic model for remoxipride after intravenous and intranasal administration, Drug Metab. Dispos. 39 (12) (2011) 2275–2282. http://dx.doi.org/10.1124/dmd.111.040782.