A Mechanism-Based Pharmacokinetic-Pharmacodynamic Model of the Time-Course of Prolactin following Antipsychotic Drug Treatment

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Objectives

Antipsychotic drugs interact with dopamine receptors and can cause release of prolactin into the circulation which may lead to unwanted side-effects.

The aim was to develop a pharmacokinetic-pharmacodynamic (PKPD) model characterizing the time-course of prolactin in healthy and schizophrenic subjects following administration of various doses and formulations of antipsychotic drugs.

Patients & Methods

- 1445 subjects from five Phase 1 studies (rich data) and four Phase 3 studies (sparse data) were included
  - 45 subjects were healthy males
  - 845 subjects were schizophrenic males
  - 555 subjects were schizophrenic females
- Antipsychotic drugs were administered as oral immediate release (IR), oral extended release (ER), i.m. injection (IM) or i.v. infusion (IV) as a single dose or as repeated once-daily dosing
- 9023 plasma prolactin concentrations were analyzed in NONMEM
- 2/3 of the data (index data set) was used for building the model. 1/3 (evaluation data set) was used for model evaluation
- Because of extensive run times, the PD model was driven by individual predicted drug concentrations added to the data set, and the FO method had to be used

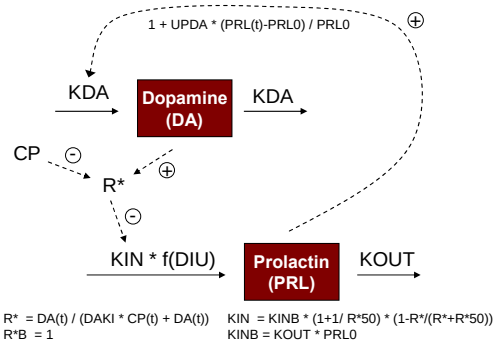

Fig 1. PKPD model of prolactin (PRL).
PRL0, baseline PRL concentration; f(DIU), diurnal rhythm function; KINB, KIN at baseline; DAKI, ratio between DA50 and KI; CP, antipsychotic drug concentration; R*, fraction of DA receptors blocked by DA; R*B, fraction of receptors blocked by DA at baseline; R*50, R* resulting in half of the maximum KIN

Table I. Parameter estimates from the final model when combining the index and evaluation data sets

Parameter	Typical estimate (% RSE)	IIV % (% RSE)
PRL0 (ng/mL)	Healthy males: 6.76 (7.0) Male patients: 13.7 (4.4) Female patients: 29.5 (4.2)	67 (3.7)
KOUT (h^{-1})	1.30 (11)	160 (25)
Diurnal rhythm		
Amplitude, 24 h period	0.387 (8.8)	51(29)
Amplitude,12 h period	-0.244 (10)	Not estimated
Phase, 24 h period (in relation to 8:00)	Healthy subjects: 19.8 (3.1) Patients: 18.3	Not estimated
Phase, 12 h period (in relation to 8:00)	Healthy subjects: 1.70 (4.4) Patients: 0.25	3.1 (19)
DAKI (mL/ng)	0.551 (13)	160 (25)
R*50	0.0423 (49)	Not estimated
KDA (h^{-1})	0.137 (8.5)	Not estimated
UPDA	1.71 (24)	Not estimated
Proportional error (%)	Healthy males: 29.5 (4.2) Male patients: 40.3 (4.2) Female patients: 55.5 (4.3)	-

References

[1] Bagli M et al. J Pharmacol Exp Ther; 1999; 291:547-54.
[2] Frantz AG. N Engl J Med; 1978; 298:201-7.
[3] Rao ML et al.Psychiatry Res; 1993; 47:187-203.
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[5] Movin Osswald G, Hammarlund Udenaes M. J Pharmacol Exp Ther; 1995; 274:921-7.

Results

- In the final model (Fig 1 & 2, Table I)
  - a spare-receptor model mimicked the tonic inhibition of peripheral dopamine receptors by dopamine
  - an agonist-antagonist interaction model illustrated the competition between the drug and hypothetical dopamine concentrations for the receptors [1]
  - tolerance development was characterized by allowing prolactin to stimulate dopamine production
  - two cosine functions described the diurnal rhythm of prolactin release (f(DIU)), resulting in a similar pattern of plasma prolactin concentrations after placebo administration as previously described [2] (Fig 3, upper middle panel), including a phase-shift in patients of –1.45 h [3] (Table I)
  - the typical baseline value of prolactin was significantly higher in women than in men and higher in patients than in healthy subjects (Table I, Fig 3)
  - $t_{1/2}$ of circulating prolactin was estimated to 32 min, in line with literature [4]
  - IIV in PRL0 was correlated (-0.86) with IIV in DAKI (drug potency relative to dopamine potency) indicating a smaller response in subjects with a high baseline
- The evaluation data set was well predicted by the model (Fig 2, right panel)
- The pool model [5], in which the tolerance to prolactin release following antipsychotic drug treatment is assumed to be caused by drainage of a prolactin pool, resulted in poor population predictions (ΔOFV > 2000 units). The model presented here can also predict a tolerance to a second infusion (Fig. 3, upper left panel) as was seen in the data from which the pool model was developed

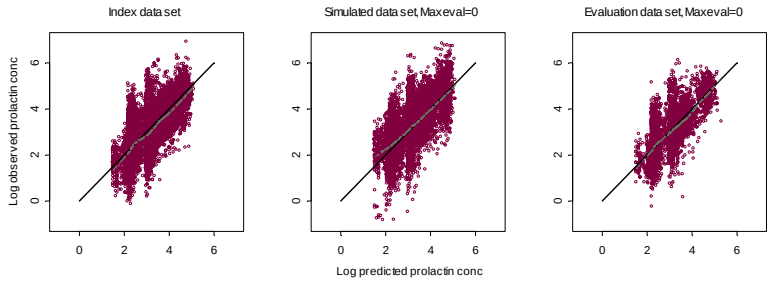

Fig 2. Observations versus population predictions for the index data set (left), a data set simulated from the final model (middle) and for the evaluation data set (right) when using parameter estimates from the index data set. Included are lines of identity (—) and a smooth through the data (—)

Conclusions

The developed model accurately described the prolactin concentrations after different forms of administration and was based on known mechanisms of antipsychotic drug, dopamine and prolactin interaction with parameter estimates of prolactin kinetics close to literature values.

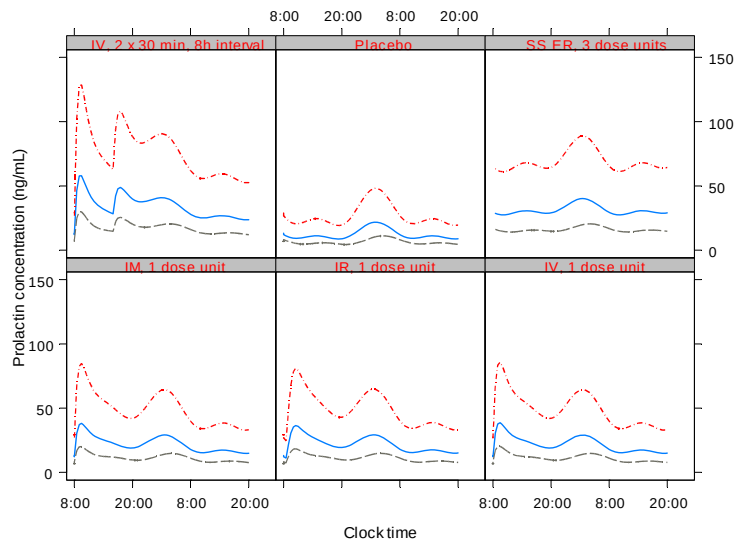

Fig 3. Typical predicted profiles for various schedules of administration for male (—) and female patients (-·-) and for healthy males (—) . Doses are administered at 8:00 on the first day (and at 16:00 for the hypothetical double infusion schedule). The ER formulation is assumed to be at steady-state (SS).