Mechanism-based PK-PD model of remoxipride with rat-to-human extrapolation: characterizing remoxipride CNS target site PK and positive systems homeostatic feedback

Jasper Stevens[1], Bart Ploeger[2], M. Hammarlund-Udenaes[3], Piet Hein van der Graaf[4], Meindert Danhof[1], Elizabeth C.M. de Lange[1]

[1] Division of Pharmacology, LACDR, Leiden, NL, [2] LAP&P Consultants, Leiden, NL, Uppsala University, SE [4]Pfizer Global R&D, Sandwich, Kent, UK

Introduction

Our ultimate **aim** is to develop a translational MB PKPD model for dopaminergic compounds, for the prediction of PKPD relationships following different routes of administration and animal-human extrapolation. To that end, information on drug specific- and biological system specific parameters is needed. Many dopaminergic compounds suffer from poor oral bioavailability and/or poor blood-brain barrier transport. Intranasal administration could offer an attractive alternative route of administration by enhancing the distribution to the brain. Here we present a translational PKPD model of prolactin (PRL) release following intravenous (IV) and intranasal (IN) administration of the dopamine D2-receptor antagonist remoxipride (REM) as model compound. The model allows translation between i) different routes of administration in rats, and ii) rat and human.

Methods

Animal experiments (as previously published[A]). Dataset 1; 0, 4, 8, or 16 mg/kg REM administration (30-min IV / 1-min IN infusion). Dataset 2; consecutive dosing of 3.8 mg/kg REM (30 min IV infusions, different time intervals).
Analytical procedures. REM concentrations were analyzed by online solid phase extraction coupled to LC-MS[B]. PRL was measured in plasma (ELISA).
Modeling. Modeling (NONMEM VI.2) was based on plasma- and brain$_{ECF}$ REM concentrations, and plasma PRL concentrations. PK was fixed during PD modeling.
Validation. Models were tested and evaluated (likelihood ratio test (p<0.05), goodness-of-fit, parameter estimate endpoints, and individual plots).
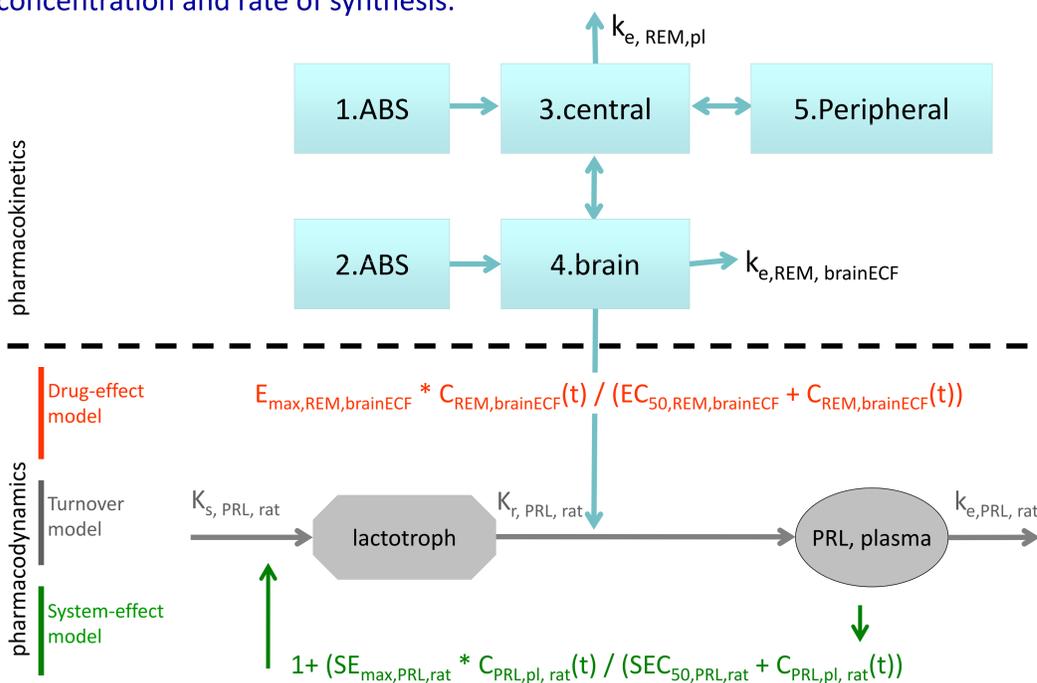**Rat-to-human translation**. Based on the animal PKPD model, human PKPD was simulated in Berkeley-Madonna and compared to a clinical dataset, kindly provided by M. Hammarlund-Udenaes[C]. Simulated human brain$_{ECF}$ concentration effect-relations were applied. Clinical PD parameters were obtained from literature when possible, otherwise allometric scaling was applied.

Model

REM PK-model. Following IN administration, total absorption of REM is defined by systemic uptake (1.ABS) and direct nose-to-brain transport (2.ABS). REM is distributed (blue arrows) in a central-, peripheral- and brain compartment, and eliminated from plasma ($k_{e,REM,pl}$) and brain ECF ($k_{e,REM,brainECF}$).
PK-PD model. An Emax model for relation between brain$_{ECF}$ REM concentrations and PRL release. A turnover model described PRL synthesis rate ($k_{s,PRL,rat}$), release of PRL from lactotrophs into plasma ($k_{r,PRL,rat}$), and PRL plasma elimination ($k_{e,PRL,rat}$)
System-feedback model. An Emax model for the relation between PRL plasma concentration and rate of synthesis.

$$E_{max,REM,brainECF} * C_{REM,brainECF}(t) / (EC_{50,REM,brainECF} + C_{REM,brainECF}(t))$$

$$1+ (SE_{max,PRL,rat} * C_{PRL,pl,rat}(t) / (SEC_{50,PRL,rat} + C_{PRL,pl,rat}(t))$$

Results Pharmacokinetics

Following IN administration total bioavailability was 89%. Brain distribution differs between administration routes. The brain ECF/plasma ratio improved for IN versus IV administration (28% vs. 19%). Brain$_{ECF}$ concentrations were slightly under-predicted, indicating more complex brain distribution (fig 1)
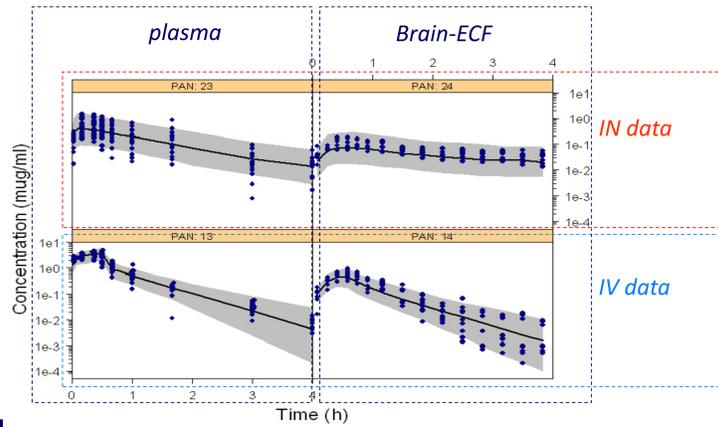
Results Pharmacokinetics cont.)

Fig 1. VPC for 1000 simulations, depicted per data set and per compartment. B lue dots; observed REM concentrations over time, black line; median of simulations, grey area's; 95% confidence intervals.

Results Pharmacodynamics

PRL profiles were accurately described following IV single as well as consecutive dosing (fig 2 & 3, respectively).
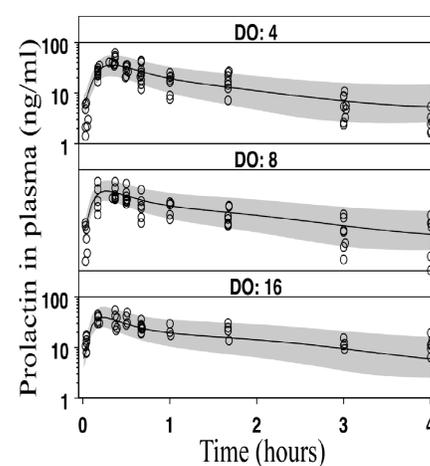

Fig 2; VPC of PRL plasma profiles after single IV REM, per dose (DO, in mg/kg). (O) observed PK (black line); median of simulations, (grey area) and 95% confidence interv.als)
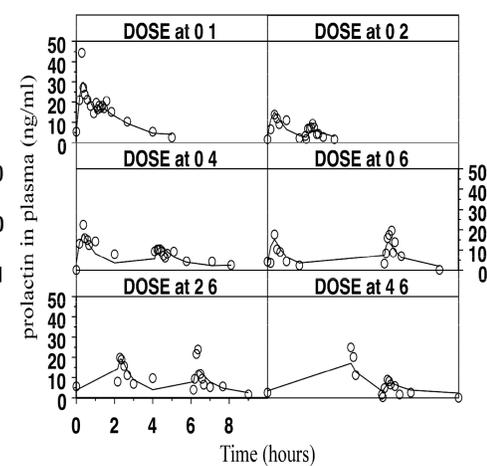
Fig 3; typical individual predictions (black line) and observed PRL plasma PK O) after consecutive dosing of REM, per dosing regiment (DOSE, hours)

Results Translation

The translational properties for IN REM indicate slight under-prediction of measurements (fig 4), attributed to larger variability in the IN dataset and more complex brain distribution. The model showed accurate translational properties in reduction of human PKPD (Fig 5, PK not shown)
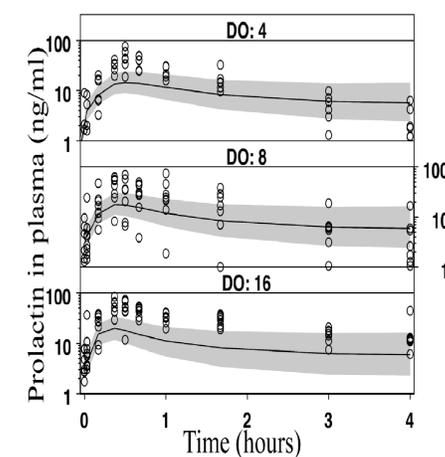

Fig 4 (up); translation to intranasal administration. VPC showing the median simulated PRL concentrations (black line) with the 95% confidence interval, and the experimental data (open symbols)
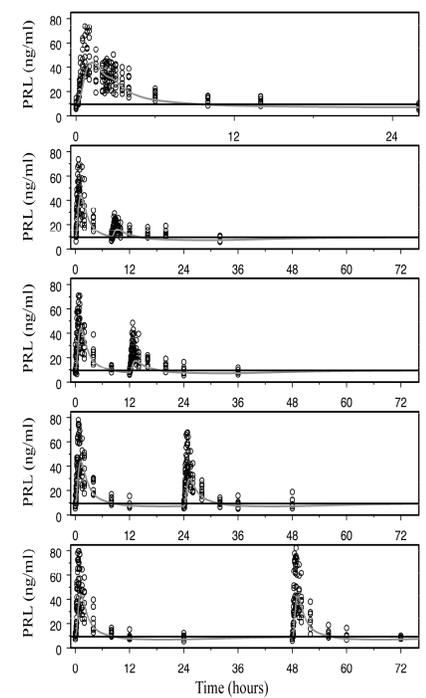
Fig 5 (right); translation to human PD. Based on estimated human brainECF PK the predicted PRL PK (grey line) are in accordance with the clinical data (O)

Conclusions and perspectives

The preclinical PKPD model provides, for the1[st] time, **quantification** of direct nose-to-brain transport in terms of rate and extent following IN administration. It also indicates a **positive feedback** of PRL plasma concentrations on PRL synthesis. Finally it provides a useful approach for **rat-to-human translation** of PKPD relationships of dopaminergic drugs.

A. Stevens et al., Pharm.Res,2009,26(8);1911-1917
B. Stevens et al., J. Chromatogr. B Analyt Technol. Biomed. Life Sci., 2010, 878; 969-975
C. Movin-Osswald et al., J.Pharmacol.Exp.Ther.,1995, 274:921-927
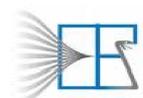
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