Translational pharmacology of dopamine receptor agonists and antagonists : prolactin and oxytocin as biomarkers

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1

Background, objectives and outline

The dopaminergic system organizes many behavioral mechanisms in the brain. Dysfunctions of the dopaminergic system can result in disease states like e.g. schizophrenia, Parkinson's disease and sexual disorders (Marsden, 2006). Dopamine receptor antagonists have been developed to block hallucinations and delusions that occur in schizophrenic patients, whereas dopamine receptor agonists are effective in alleviating the hypokinesia of Parkinson's disease. However, blockade of dopamine receptors can induce extrapyramidal effects similar to those resulting from dopamine depletion in Parkinson's disease, and high doses of dopamine agonists can cause psychoses. Also, the occurrence of sexual dysfunctions is high in Parkinson's disease patients, but dopamine replacement therapy can cause hyper sexuality and aberrant sexual behavior (Meco, et al., 2008). The therapies of disorders resulting from dopamine imbalances are thus associated with severe side effects.

To develop treatments with improved safety and efficacy, one of the scientific challenges is to understand the biological mechanisms underlying the pharmacokinetic- and pharmacodynamic (PK–PD) relationships of (partial) dopamine agonists and antagonists. PK–PD modeling is the gold standard to investigate such complex mechanisms. Often, these models include plasma drug concentration–effect relationships. However, for dopaminergic compounds, the target site is the brain extracellular fluid (ECF) that surrounds the dopamine receptors. Consequently, a more mechanistic approach should be aimed at understanding the drug concentrations at the target site (De Lange, et al., 2005; Danhof, et al., 2007; Ploeger, et al., 2009).

Also, to achieve a more rapid onset of action and an increased therapeutic window for compounds that have high clearance and/or low oral bioavailability characteristics, alternative routes of administration are developed. Intranasal administration of dopaminergic compounds avoids gastrointestinal- and hepatic first-pass elimination and is hypothesized to circumvent the blood-brain barrier by direct nose–to–brain transport (Dhuria, et al., 2009). This administration route is therefore anticipated to improve the time to onset- and/or the selectivity of action, specifically for drugs acting on the central nervous system.
This thesis addresses different aspects of the PK–PD correlations of dopaminergic drugs following intravenous and intranasal administration.

Chapter 2 reviews how detailed preclinical investigations in combination with mechanistic PK–PD modeling may provide a scientific basis for the translational pharmacology of dopaminergic drugs to man, following systemic and intranasal administration.

Chapter 3 of this thesis reports on the development and validation of a new 'minimum-stress' animal model that allows intranasal- and, for comparative purposes, intravenous drug administration. In this preclinical model, PK–PD parameters can be obtained over time in blood- and brain ECF samples in freely moving animals. A staining study was performed to confirm the selectivity of intranasal administration and corticosterone concentrations were determined over time to exclude stress-related experimental influences. Subsequently, acetaminophen was administered intravenously and intranasal as a model compound to test the animal model.

To investigate dopaminergic PK–PD relationships, the weak but selective dopamine D2-receptor antagonist remoxipride was chosen as a paradigm compound. To detect low remoxipride concentrations in small plasma-, brain ECF- and brain homogenate samples, novel analytical methods were required. *Chapter 4* reports on the development, optimization and validation of these methods, for which online solid phase extraction and liquid chromatography-tandem mass spectrometry techniques were used.

Following intranasal administration, compounds can enter the brain by direct nose–to–brain transport or via systemic absorption followed by blood-brain barrier transport. Comparison to intravenous administration provides insight on intranasal bioavailability. Using the newly developed animal model and analytical methods, we can obtain serial datapoints in plasma and close to, if not at, the target site following intravenous and intranasal administration of remoxipride. In *chapter 5*, nonlinear mixed effect modeling (Beal and Sheiner, 1992) was applied to quantitate the PK of remoxipride in plasma and brain ECF following intranasal and intravenous administration. This approach provides, for the first time, quantitation of direct nose–to–brain transport of remoxipride.

The next step was to develop a mechanism-based PK–PD model on data obtained in rats, which could be used to predict the PK–PD relationship in different situations and systems, including the biological system response in humans. To that end, the effects of brain ECF remoxipride concentrations on prolactin concentrations, as translational biomarker for dopaminergic system activity, were assessed following intravenous administration of remoxipride.

We report in *chapter 6* on the development and validation of a novel mechanism-based PK–PD model containing:

- a PK model for remoxipride concentrations in plasma and brain ECF after intravenous remoxipride administration
- a pool model incorporating the rate of synthesis of prolactin in lactotrophs, and the rate constants for prolactin release into- and elimination from plasma
- a biological system response model for homeostatic feedback
- a drug concentration–effect model for prolactin release in response to brain ECF remoxipride concentrations.

The dataset obtained following intranasal administration of remoxipride was used to challenge the predictive value of the model for alternative routes of administration. Finally, a first step towards translation from rat to humans was performed and compared to clinical data, to investigate if the structural model can be applied for both species.

In *chapter 7* the conclusions and general discussion of this scientific basis for the translational pharmacology of dopaminergic drugs following systemic and intranasal administration are discussed.

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