An application of PBPK-PD model to identify the target site of prolactin response induced by D2 receptor antagonists – which is the target site, brain or plasma? -

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Objectives: On inhibition of the D2 receptor, prolactin is released from anterior pituitary, which is one of the brain endocrine glands, but can be distinct from the other brain regions due to the lack of blood-brain barrier (BBB). A semi-mechanistic PBPK-PD model was applied to assess the target site of prolactin response induced by D2 receptor antagonists in rats.

Methods: Risperidone (RIS) and its active metabolite paliperidone (PAL) were used as a model D2 receptor antagonist. A 12-compartmental semi-mechanistic PBPK model, including metabolic conversion of RIS to PAL, was constructed to describe PK profiles in brain, CSF, and plasma. A microdialysis study in rats was performed to obtain detailed brain (brain extracellular fluid), CSF, and plasma drug concentrations. In order to examine the target site of prolactin response, a pool model was used with a PK driver set on plasma or brain. Model developments were performed using NMEM implemented in NONMEM VII. Pirana and R 3.0.0 were also used for model-building management, data processing, and plots.

Results: The semi-mechanistic PBPK model was successfully developed, providing accurate description of PK profiles of RIS and PAL in brain, CSF, and plasma. The prolactin response was nicely described by the pool model with PK driver on plasma (Figure 1) while the analysis failed with PK driver on brain.

Conclusions: Not brain but plasma exposure was suggested to be a driver to induce prolactin response after administration of RIS and PAL in rats. It is shown that semi-mechanistic PBPK-PD modeling can be used to delineate the target site of drugs specifically by examining whether an exposure driver can be set on plasma or brain.


Figure 1. Pool model (A) and resulting VPC (B) for prolactin response. A: Prolactin is synthesized in pool compartment (k_{synthesis}) and then released into plasma (k_{release}). Released prolactin in plasma is eliminated (k_{elimination}) out of the body. Drug exposure stimulates k_{release} either through plasma or brain PK. B: Prolactin VPC result after administration of D2 receptor antagonists (RIS and PAL). Black dotted: 90% confident interval, Red: median of simulations, Light green: median of observations.