

A Translational Pharmacokinetics Model Platform for Delivery of Enzymes and Proteins Utilizing a Brain-Penetrant Transport Vehicle

Mahdiar Sadeghi, Cinthia V Pastuskovas, Annie Arguello, Cathal Mahon, Kapil Gadkar, Mohammad Jafarnejad

ACoP14 (2023), poster T-068 / PMX609 · 2023

The effective delivery of therapeutics to the brain is a significant challenge when treating central nervous system (CNS) disorders. One possible approach to overcome this challenge is to utilize human transferrin receptor (TfR) to deliver biotherapeutic agents such as enzymes and proteins across the blood-brain barrier (BBB) to the CNS. Transport vehicle (TV) platform consists of an anti-human TfR binding domain engineered in the Fc region that is designed to enable BBB crossing after intravenous (IV) administration.

In this study, we developed translational pharmacokinetic (PK) models for TV molecules that are designed to deliver enzymes and proteins across the BBB, e.g., iduronate-2-sulfatase (IDS). The PK model employs a mathematical formalism to gain insights into the mechanisms impacting systemic PK and uptake of these molecules into the brain and identify appropriate approaches for translation of PK from nonclinical species to human.

The model is calibrated to serum and brain PK data from nonclinical studies in mice and monkeys, and serum PK from participants in our ongoing clinical studies where available. The serum PK component of this mechanistic model includes a standard two-compartment representation with a non-specific clearance, non-linear TfR-mediated clearance, and a non-linear mechanism to account for other receptor-mediated clearance in serum. The brain PK component of this model includes terms representing non-specific uptake as well as TfR-mediated uptake across the BBB, and a linear term to represent the loss of biotherapeutic agent in the brain via cellular uptake and other clearance mechanisms. This model allows for the translation of PK data of a given molecule from mice and cynomolgus monkeys to humans. Using the model, we identified the appropriate translational approach for each parameter based on three categories of parameters: 1) molecule-independent and species specific, 2) molecule specific and allometrically scaled across species, and 3) molecule-independent and allometrically scaled across species. The data not used for model calibration is used to test and confirm the translation of the clearance mechanisms across the three species. In addition, we conducted local and global sensitivity analysis of the calibrated model parameters to ensure a robust identifiable model structure for the data.

Overall, the presented PK model plays a critical role in understanding the processes impacting PK and distribution of therapeutics to the brain and optimizing the design of preclinical studies for development of future therapeutic candidates for central nervous system disorders. Furthermore, the model can inform the clinical development and first-in-human (FIH) dose selection for current and future TV-enabled molecules for delivery of enzymes and proteins.

Reference

https://fliphtml5.com/gbngh/wata/ACoP14_Abtracts/193/