# A semi-mechanistic population pharmacokinetic model describing the time-dependent kinetics of Red Blood Cell (RBC) binding and partitioning of Drug X

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## Backgrounds:

- Drug X, a new chemical entity that possesses pharmacological activity on Platelet-Activating Factor (PAF). Drug X was approved into phase I evaluation for treatment of ischemic stroke in China. A nonlinear red blood cell (RBC) binding/partition was observed in clinical trial within PUMCH (Figure 2). The clinical observation of Drug X shows that both partitioning and kinetic of binding happens at the same time and it possibly has active transporters involved. In another term, Drug X has time-dependent kinetic binding process such that its ON rate to RBC is very rapid however the OFF rate to RBC is much slower.
- In this situation, *In Vitro* B/P experiment to determine the concentration dependent B/P relationship is not possible to predict the *In Vivo* B/P ratio. Furthermore, the semi-mechanistic binding model described by Hinderling [1,2] and Jusko [3] cannot fully represent the clinical data for both drug plasma and whole blood concentration.

## Objectives:

- A semi-mechanism population pharmacokinetic model with time-dependent kinetics of red blood cell binding and partitioning of Drug X was developed (Figure1). The model incorporated individual haematocrit level as a covariate and included the kinetics of Drug X in blood, erythrocytes and plasma (Equation 1).

$$\frac{B}{P} = \frac{C_{blood}}{C_{plasma}} = 1 + HCT * \left(\frac{C_{RBC}}{C_{plasma}} - 1\right)$$
$$CL_{blood} * C_{blood} = CL_{plasma} * C_{plasma} = CL_{unbound} * C_{unbound}$$

Equation1: blood (B), erythrocytes(RBC) and plasma (sys) relationship with haematocrit (HCT) as a covariate

- This model could predict the whole blood concentration from the measured plasma concentration data and predict plasma and blood concentration by knowing the individual haematocrit level or the distribution of haematocrit level of a patient population.

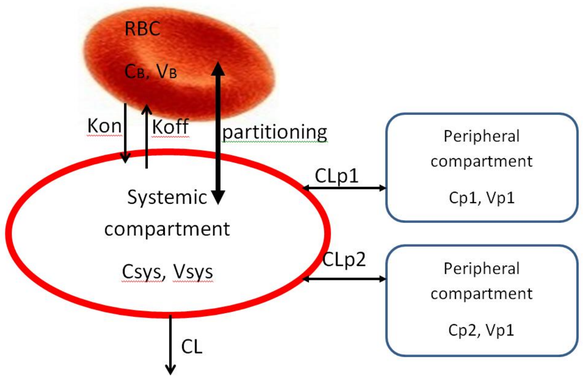


Figure 1: semi-mechanistic population pharmacokinetic model with the time-dependent kinetics of Red Blood Cell (RBC) binding and partitioning

## Methods:

- An *In Vitro* Drug X blood plasma partition assay was conducted with dosing solution 0.01 - 5 µM, respectively. The *In Vitro* assay included two sets of experiments:
- Time-profile experiment, with incubation for 5 min - 24 h.
- Equilibrium experiment
- This *In Vitro* assay is used to decided the concentration or time dependent B/P profile.
- Subsequently, a clinical trial which includes 7 escalation dose studies of Drug X (including 10mg, 20mg, 40mg, 60mg, 90mg, 120mg, 160mg) was performed in 54 healthy Chinese subjects.
- A semi-mechanistic RBC binding model (Equation 2) described by Hinderling [1,2] and Jusko [3] is used initially to build the model by using the PBPK model in the Simcyp® Simulator V13. The Bmax and KD can be obtained using B/P relationship from clinical study (Figure 3).

$$B/P = 1 - Hct + Hct \cdot fu \left(1 + \frac{B_{max}}{K_D + C_{p,t} \cdot fu}\right)$$

Equation2: Semi-mechanistic RBC binding model

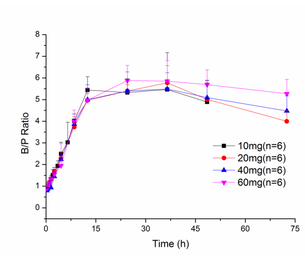


Figure 2: blood to plasma concentration ratio time profile Drug X

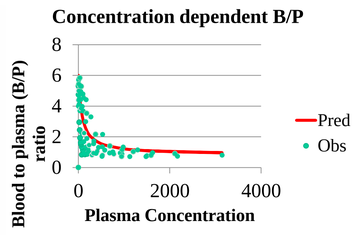


Figure 3: Concentration dependent B/P relationship

- Further, a sub-compartment of blood model is built in the software phoenix NLME (Pharsight Company, St. Louis, Missouri, USA). This sub-compartment blood model includes first-order kinetics of partitioning to RBC and ON/OFF rate binding process of RBC. A final two-compartmental pharmacokinetic model with this sub-compartment of blood model is developed for the pop-PK analysis of 7 escalation dose studies (Figure 1). The results for the full 54 healthy volunteers data is shown in Figure 5.

## Results:

- *In Vitro* B/P partition assay result indicated that the B/P ratio of Drug X is close to 1 and is independent from concentration and incubation time. The PBPK model using semi-mechanistic RBC binding model in Simcyp proved that it cannot fully present the clinical plasma and whole blood concentration data (Figure 4).

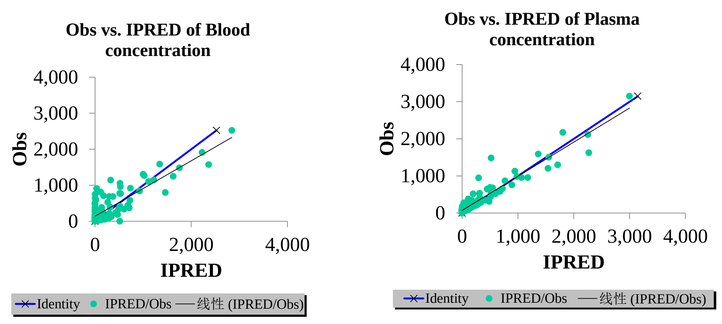


Figure 4: DV vs IPRED of average blood and plasma concentration of 7 escalation dose using Simcyp® Simulator V13

- A two compartment pharmacokinetic model with a parallel RBC partitioning and kinetic RBC receptor binding (Figure 1) could describe both Drug X plasma and whole blood concentration data (Figure 5). The population prediction (Figure 5&6) indicated that the haematocrit level significantly improved the prediction for both plasma and blood concentration.

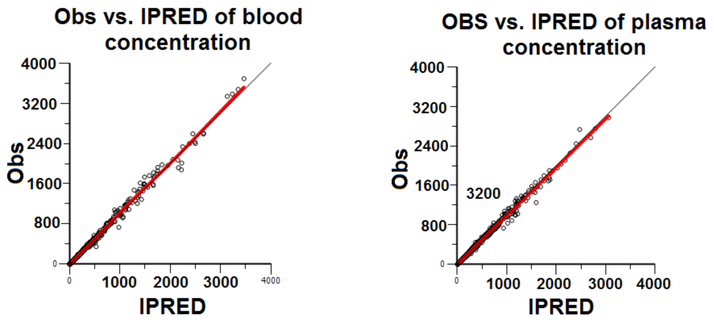


Figure 5: DV vs IPRED of blood and plasma concentration of all subjects in all 7 escalation dose using Phoenix NLME

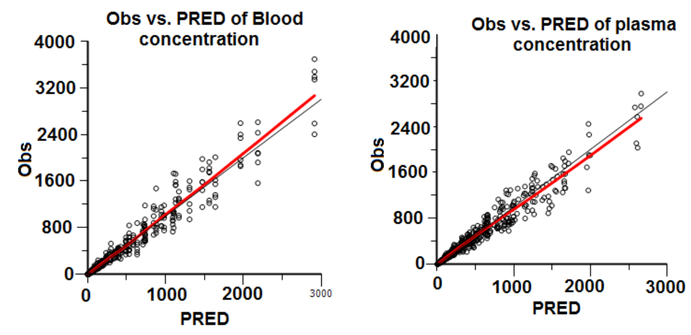


Figure 6: DV vs PRED of blood and plasma concentration of all subjects in all 7 escalation dose using Phoenix NLME

## Conclusions:

- The RBC distribution of Drug X involved two parallel processes and *In Vitro* B/P experiment is not possible to provide the *In Vivo* time-dependent kinetic of RBC binding and partitioning. Unless some more advanced *In Vitro* B/P experiment is used such as BIOCORE using surface plasmon resonance (SPR).
- A simple semi-mechanistic blood compartment cannot predict the time-dependent kinetic of RBC binding and partitioning. This is due to a rapid ON rate and a slow OFF rate to the RBC. The true mechanism is still unknown because of the complexity of red blood cell structure.
- The developed semi-mechanistic population PK model incorporated individual haematocrit level best described plasma and whole blood profiles of Drug X in Chinese subjects and using the individual haematocrit level can predict the whole blood concentration from the measured plasma concentration data and hence potentially to save the clinical trial.

## References:

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