Predicting whole blood concentrations of zonisamide in human using a physiologically based pharmacokinetic model combined with nonlinear red blood cell (RBC) binding

Xin Zheng1,3, Kairui Feng2, Pei Hu1, Jun Shi2, Ji Jiang1
1. Peking Union Medical College Hospital 41 Damucang Hutong, Xicheng, Beijing, 100032, China
2. Simcyp Ltd, John Street, Sheffield, S2 4SU, UK; 3. Roche-PUMCH fellows; 4. Roche pRED

Backgrounds:
- Concentration dependent Blood to plasma ratio (B/P) of zonisamide (ZNS) was observed in clinical trial, which requires measuring both plasma concentration and whole blood concentration for clinical observation.
- B/P is one of the important parameters which are required by physiologically based pharmacokinetic (PBPK) models, in conjunction with other ADMET and physicochemical properties, for predicting whole body pharmacokinetics. A compound concentration-dependent B/P may due to not only passive diffusion into RBC, but also binding to RBC membrane or active transporters in the RBC[1]. In this situation, the parameters determined using plasma data may be misleading and the prediction of whole blood concentration is required a more mechanistic model.

![Figure 1. Relationship between serum and erythrocyte concentrations of zonisamide and the binding parameters to erythrocytes. (Bmax and Kd indicates the maximum binding capacity and dissociation binding constant)](image)

Objectives:
- To predict the whole blood concentration of ZNS in Chinese population using PBPK model combined with nonlinear blood to plasma ratio model in the Simcyp® Simulator V13.

Methods:
- Prior knowledge of in vitro physicochemical and in vivo pharmacokinetics parameters of zonisamide were collected from the literatures[2].

![Table 1. Zonisamide Physicochemical and pharmacokinetic Parameters](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
<td>212.23</td>
</tr>
<tr>
<td>logP</td>
<td>0.5</td>
</tr>
<tr>
<td>pKa</td>
<td>10.2</td>
</tr>
<tr>
<td>fu</td>
<td>0.55</td>
</tr>
<tr>
<td>Plasma Binding Components</td>
<td>HSA</td>
</tr>
<tr>
<td>fa</td>
<td>1</td>
</tr>
<tr>
<td>ka</td>
<td>2.1/h</td>
</tr>
<tr>
<td>Vss</td>
<td>1.45(L/kg)</td>
</tr>
<tr>
<td>CLpo</td>
<td>1.14(L/h)</td>
</tr>
<tr>
<td>GFR</td>
<td>0.21(L/h)</td>
</tr>
</tbody>
</table>

- Subsequently, the Simcyp® retrograde model was used to calculate intrinsic clearance values from oral clearance (CLPo) for ZNS metabolism by CYP3A4.
- The concentration-dependent B/P profile was gained from the average blood and plasma concentration data of 10 subjects who received 300 mg zonisamide single dose.

![Figure 2. The concentration-dependent B/P profile input in the Simcyp® Version 13](image)

- The observed data of 20 healthy Chinese subjects administrated 100 mg or 300 mg single dose ZNS were acquired from a phase I clinical trial and the concentrations of 9 Japanese patients undergoing brain surgery were extracted from a literature report[2].
- The verification model is used to predict the whole blood concentrations of ZNS in Chinese healthy subjects using nonlinear B/P ratio model in the Simcyp Simulator.

![Figure 4. The predict result of plasma and whole blood time profile for Chinese population (100 mg)](image)

Conclusions:
- A physiologically based pharmacokinetic model successfully predicted the concentration of ZNS in whole blood using the modeling process that combined the Top-Down and Bottom-Up approaches.
- The PBPK model combined with Nonlinear RBC binding predicts both plasma and whole blood ZNS concentration across different ethnic groups including Chinese and Japanese population.
- The prediction values are within 2 folds of observed values. This verified compound data and PBPK model are potentially useful for predicting drug-drug interactions of ZNS in human such as literature 4 and further clinical trial design.

References:

Acknowledgements:
- The authors thank Dr. Bob Powel and Prof. Amin Rostami for their great help in the project design. Thank Dr. Paavan Vajhah for his support in SimCYP simulation. Thank Dr. Ao Peng for his work in the bioassay.