Physiologically-Based Pharmacokinetic (PBPK) Models as Tools for the Prediction of Pharmacokinetics of Pemetrexed and Renal Transporter-Related DDI

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Purpose
The aim of this project was to predict the pharmacokinetics of the anti-cancer drug, pemetrexed, and to quantify the extent of interaction with a potential renal OAT3 inhibitor, ibuprofen, in humans using PBPK modeling. The renal excretion of pemetrexed involves active secretion in the kidney mediated by OAT3 and OAT4, which are expressed in the basolateral and apical membranes of proximal tubular cells, respectively.

Methods
The model was built using Simcyp® and included a mechanistic kidney model to predict the active secretion of pemetrexed. A new population of cancer patients was built into the model to better represent the physiological characteristics of the patients, including renal function, weight, height and age. In vitro parameters of pemetrexed and ibuprofen (Km, Vmax, Ki) were measured using HEK-OAT3 and 4 transfected and vector control cells. A sensitivity analysis indicated that the expression levels of the transporters in the kidney had a significant impact in the AUC0-inf of pemetrexed. Consequently, the in vivo Vmax values for both transporters were estimated using plasma concentration-time profiles from patients dosed with 500 mg/m² of pemetrexed and supplemented with folic acid and vitamin B12 to reduce toxicity. The model was validated using different data sets, including clinical studies with doses from 50 to 800 mg/m² and with a set of patients who received pemetrexed with ibuprofen.

Results
The predicted Cmax and AUC0-inf had an observed/predicted ratio of 0.99 and 1.01, respectively (Table 1). The model predicted a linear increase of these parameters with dose (Figure 1) which was also observed in the clinic. The observed/predicted increases in Cmax and AUC0-inf when ibuprofen was co-administered were 1.09 and 1.06. The percentage of dose excreted in urine after dosing was 100%, which is comparable to the 90% seen in vivo.

Conclusion
The PBPK model accurately reproduced pemetrexed kinetics in cancer patients. The PBPK model can be used to predict the changes in pharmacokinetics produced by variations in physiological parameters, changes in dose and infusion time, and by the concomitant administration of other substrates or inhibitors of OAT3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observed</th>
<th>Predicted</th>
<th>Observed/Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>102.1</td>
<td>103.2</td>
<td>0.99</td>
</tr>
<tr>
<td>AUC0-inf (µg/mL h)</td>
<td>164.7</td>
<td>163.3</td>
<td>1.01</td>
</tr>
<tr>
<td>CL plasma (L/h)</td>
<td>5.57</td>
<td>5.80</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Table 1

Figure 1