Physiologically-Based Pharmacokinetic Modeling of Rilpivirine During Pregnancy

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• A physiologically-based pharmacokinetic (PBPK) modeling approach may be used to assess the effect of pregnancy on drug pharmacokinetics (PK).
• We developed a PBPK model for rilpivirine (RPV) using Simcyp® v16.1 with physicochemical, in vitro, and clinical PK parameters from literature.
Methods

• The model built in the nonpregnant state was verified with PK data from clinical trials in healthy volunteers and adults living with HIV.

• The RPV model was then modified to account for the progressive physiological changes of pregnancy, including changes in:
  ▪ albumin
  ▪ CYP3A4 activity
  ▪ glomerular filtration rate

• Predictions were verified from 3 clinicals trials in pregnant women living with HIV.
Results from the Nonpregnant State

- Predictions for RPV PK fell within a 2-fold range of observed clinical values.
Results from 2\textsuperscript{nd} Trimester

- Predictions for RPV PK fell within ± 50% of the mean observed clinical values.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Predicted</th>
<th>Observed</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>140</td>
<td>142</td>
<td>0.99</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>2369</td>
<td>2090</td>
<td>1.13</td>
</tr>
</tbody>
</table>
Results from 3rd Trimester

- Predictions for RPV PK fell within ± 50% of the mean observed clinical values.

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Observed</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>139</td>
<td>124</td>
<td>1.12</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>2387</td>
<td>1700</td>
<td>1.40</td>
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</table>
Conclusion

• Progressive physiological changes during pregnancy incorporated in the model lead to:
  ▪ Increase in the fraction of drug unbound in plasma (16 – 30%)
  ▪ Increase in the volume of distribution (50 – 60%)
  ▪ Increase in clearance (50%)
• Our PBPK model for RPV captured the effects of pregnancy on maternal exposure, with a predicted decrease in exposure of approximately 30% for AUC and $C_{\text{min}}$ when compared with non-pregnant adults.
• Future work will investigate the effects of modifying the Simcyp® pregnant population using laboratory values collected from pregnant women living with HIV in the P1026s database.
• Additional antiretroviral compound models will be built to continue assessment of predictive performance of the pregnancy PBPK model.
Acknowledgments

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References


