PBPK/PD Modeling and Simulations to Guide Dose Recommendation of Amlodipine with Viekirax or Viekira Pak

Dwaipayan Mukherjee, Ph.D.
Jiu Hong Zha, Ph.D.
Rajeev Menon, Ph.D.
Mohamad Shebley, Ph.D.

Clinical Pharmacology & Pharmacometrics

Presented at the International Workshop for Clinical Pharmacology in HIV and Hepatitis, 2016, Washington D.C.

** AbbVie contributed to the research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.
Overview

• Amlodipine is a commonly prescribed anti-hypertensive drug
  - Substrate for CYP3A4 and CYP3A5 (only 10% contribution from CYP3A5)

• Co-administration with Viekira Pak increases single-dose amlodipine $C_{\text{max}}$ to 1.3 fold and AUC to 2.6 fold
  - Due to CYP3A4 inhibition by ritonavir (RTV), the PK booster in Viekira Pak

• Current recommendation for concomitant use with amlodipine is:
  - Viekira Pak USPI: “Decrease the dose of the calcium channel blocker. The dose of amlodipine should be decreased by at least 50%.”
  - Viekirax SmPC: “Decrease amlodipine dose by 50% and monitor patients for clinical effects”
  - Viekirax JPI: “… caution should be exercised, such as use with reduced doses of calcium channel blockers …”

• PBPK Modeling was utilized to evaluate dosing adjustments
  - Amlodipine PBPK model is not available in the literature
  - RTV PBPK model was developed previously in Simcyp® (Shebley et al., Clinical Pharmacology & Therapeutics, 99, S1, 2016)
Objectives

**Model development**
- Develop a PBPK model for amlodipine using data from literature
- Quantitatively capture the CYP3A contribution
- Apply “top-down” approach for model optimization:
  - Link PBPK model to pharmacodynamic (PD) model to capture effect on systolic BP

**Model validation**
- Validate amlodipine PBPK model using published clinical data
- Validate model predicted DDI with RTV using clinical DDI data

**Model application**
- Simulate multiple-dose PK of amlodipine when co-administered with ritonavir-containing Viekira Pak
- Evaluate various amlodipine dosing scenarios after the last dose of Viekira Pak/Viekirax
- Analyze changes in systolic blood pressure due to various dosing strategies using pharmacodynamic (PD) model
Amlodipine PBPK Model Development
# Amlodipine Physiochemical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>408.88</td>
<td><a href="http://www.drugbank.ca">www.drugbank.ca</a></td>
</tr>
<tr>
<td>Fraction unbound in plasma</td>
<td>0.025</td>
<td>Norvasc labeling (Pfizer.com)</td>
</tr>
<tr>
<td>logP (n-octanol:water)</td>
<td>2.96</td>
<td>Caron et al., 2004</td>
</tr>
<tr>
<td>Solubility (mg/mL)</td>
<td>0.774</td>
<td>McDaid &amp; Deasy, 1996</td>
</tr>
<tr>
<td>B:P</td>
<td>0.596</td>
<td>Simcyp® prediction toolbox</td>
</tr>
<tr>
<td>pKa (base)</td>
<td>9.1</td>
<td>Caron et al., 2004</td>
</tr>
</tbody>
</table>
# Amlodipine ADME/PK properties

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>1.75 × 10⁻⁶ cm/s (Caco2, pH 6.5:7.4)</td>
<td>Rausl et al., 2006</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>$V_d$ (IV) = 21.4 L/kg</td>
<td>Faulkner et al., 1986</td>
</tr>
<tr>
<td></td>
<td>$V_{SAC} = 6.38$ L/kg; $Q_{SAC} = 102$ L/h</td>
<td>Park et al., 2012</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP3A4 (CYP3A5 10%)</td>
<td>Zhu et al., 2013</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>6% renal clearance</td>
<td>Beresford et al., 1988</td>
</tr>
<tr>
<td></td>
<td>33.9 L/h (IV clearance)</td>
<td>Faulkner et al., 1986</td>
</tr>
<tr>
<td></td>
<td>Enterohepatic recirculation</td>
<td>Rausl et al., 2006</td>
</tr>
</tbody>
</table>
## Summary of amlodipine clinical PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV and oral PK study</td>
<td>12 healthy subjects</td>
<td>PK parameters estimated</td>
<td>Faulkner et al., 1986</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>27 renally impaired subjects</td>
<td>No significant changes</td>
<td>Laher et al., 1988</td>
</tr>
<tr>
<td>IV and oral $^{14}$C study</td>
<td>2 healthy subjects</td>
<td>6% renal clearance</td>
<td>Beresford et al., 1988</td>
</tr>
<tr>
<td>DDI study with Indinavir + RTV</td>
<td>18 healthy HIV-negative subjects</td>
<td>AUC ratio = 1.8 Cmax ratio = 1.77</td>
<td>Glesby et al., 2005</td>
</tr>
<tr>
<td>SAD PK study with 2.5 mg, 5 mg, &amp; 10 mg Amlodipine</td>
<td>12 healthy subjects</td>
<td>Time &amp; dose proportional</td>
<td>Williams &amp; Cubeddu, 1988</td>
</tr>
<tr>
<td>Food effect study with 10 mg dose of Amlodipine</td>
<td>6 healthy subjects</td>
<td>No food effect observed</td>
<td>Faulkner et al., 1989</td>
</tr>
<tr>
<td>DDI study with Viekira Pak</td>
<td>14 healthy subjects</td>
<td>AUC ratio = 2.57 Cmax ratio = 1.36</td>
<td>Menon et al., 2015</td>
</tr>
</tbody>
</table>
Verification of PBPK model for Amlodipine (IV dose)

Simcyp® model predictions of plasma concentration agree reasonably well with clinical data for 10 mg IV infusion

(Clinical data and observed PK parameters from Faulkner et al., 1986; Mean of data from 12 healthy male volunteers)
Model optimization for Amlodipine oral dose

Simcyp model predictions of plasma concentration for 10 mg oral dose agree well with clinical data within prediction 12% error

(data points and observed PK parameters from Faulkner et al., 1986 for 12 subjects)
PBPK model simulation of 5 mg daily dosing of Amlodipine

Simcyp model predictions for amlodipine oral dosage of 5 mg QD over 20 days. Model predicted time to reach steady-state is consistent with reported observations (Meredith & Elliott, 1992).
Amlodipine PBPK Model Validation
Model validation across multi-study clinical data

Clinical measurements across multiple studies fall within model predicted 5th and 95th percentile ranges
Clinical DDI studies design of Amlodipine (AML) with Ritonavir (RTV)

<table>
<thead>
<tr>
<th>AML</th>
<th>Glesby et al., 2005a</th>
<th>Simcyp model</th>
<th>Menon et al., 2015b</th>
<th>Simcyp model</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC ratio</td>
<td>1.89 (1.57-2.05)</td>
<td>1.97</td>
<td>2.57 (2.31-2.86)</td>
<td>2.65</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; ratio</td>
<td>1.82 (1.55-2.02)</td>
<td>1.87</td>
<td>1.26 (1.11-1.44)</td>
<td>1.68</td>
</tr>
</tbody>
</table>

a: Indinavir/Ritonavir + Amlodipine
b: Ombitasvir/Paritaprevir/Ritonavir + Amlodipine
PBPK Model Simulation of Amlodipine with Viekira Pak/Viekirax Co-administration
Ritonavir time-based changes in DDI magnitude

Ritonavir effect on amlodipine exposure decreases to 20% with respect to baseline, 5 days after stopping ritonavir.
Amlodipine steady-state PK with Ritonavir

Ritonavir effect on CYP3A4 persists for about 5 days after end of treatment
Pharmacodynamic model for blood pressure regulation
Two different PD Models were evaluated

**LINEAR MODEL**

\[ SBP = 134 + 4.85(SEX) - 1.22(C_{AVG}) \]

SBP = Systolic Blood Pressure (in mmHg)

C_{AVG} = Average plasma conc. of AML (ng/mL)

SEX = 1 for males and 0 for females

**NON-LINEAR MODEL**

\[ SBP = SBP_0 + mC \exp(-k_{eo} \cdot t) \]

SBP = Systolic Blood Pressure (in mmHg)

C = Plasma conc. of AML (ng/mL)

\( k_{eo} \) = elimination rate constant from effect compartment

*FDA Clin. Pharm. Review, Norvasc, April 2002*

*Donnelly et al., Clin. Pharm. Therap. 1993*
Amlodipine dose adjustment for 5 days post RTV stoppage

- AML 5 mg QD
- AML 2.5 mg QD + RTV 100 mg QD
- AML 2.5 mg QD
- AML 5 mg QD

2.3 mmHg
Amlodipine dose adjustment for 5 days post RTV stoppage

Switching back to the pre-ritonavir dose (5 mg) or keeping the dose at 2.5 mg for 5 days result in changes of about 3 mmHg in average systolic BP
SUMMARY

New PBPK model was developed for amlodipine oral dosage
- Incorporating CYP3A metabolism, parameters from literature
- Optimized and validated using published clinical DDI studies

Amlodipine oral dosage was simulated at steady-state along with Ritonavir co-administration
- Published RTV PBPK model was utilized, including CYP3A4 & CYP3A5 inhibition
- RTV effects on steady state amlodipine exposure was simulated

Amlodipine pharmacodynamics was modeled using previously published PK-PD relationship of AML exposure with systolic blood pressure
- Two different dose reduction schemes were analyzed for concomitant dosage of Viekira Pak and Amlodipine
- Based on the simulated effect on systolic BP, amlodipine at 50% reduced dose may be continued for 5 days after RTV is stopped, followed by a return to the full dose. Alternatively, the full dose of amlodipine may resume immediately the day after last dose of RTV