OBJECTIVES

In this study, a physiological PK-PD model with consideration of interactions between blood pressure, pulse pressure, heart rate, and total peripheral resistance is proposed. The objective is to improve upon the previous empirical models to achieve better predictive capabilities based on actual drug mechanisms.

METHODS

The data was acquired from a previous pharmacokinetic interaction study between rosuvastatin and telmisartan using a randomized, open-label, multiple-dose, 2×2 crossover design conducted in healthy volunteers in 2012 at Severance hospital, Seoul, Korea.

In that study, rosuvastatin 20 mg and telmisartan 80 mg, each drug alone and in combination in crossover fashion, were given once daily for 6 days. Intensive blood sampling was performed on the last dosing day. Systolic and diastolic blood pressure and heart rate were measured as safety biomarkers during the study using digital blood pressure cuffs.

20 subjects who completed the monotherapy of telmisartan were used for PK/PD modeling and analysis.

1. Model Building

1.1) PK Model

Two compartment model was chosen as the basic disposition model, along which 1st order absorption model with absorption lag time best described the data. Weight has been incorporated into CI and V using the fixed allometric relationships as shown below.

No covariate was found to be statistically significant.

2) Link Model

Telmisartan exerts drug effect by binding to angiotensin II receptor type 1 (AT1). Due to the difficulty estimating rate constant of drug binding and dissociation separately, the following differential equation was used:

\[
\frac{dC_T}{dt} = k_{on}(C_T - C_s) \quad (3)
\]

where \(C_s\) and \(C_T\) represent free and receptor-bound telmisartan concentration, respectively. The rate constant \(k_{on}\) is an empirical parameter related to receptor-drug interaction.

3) PD Model

Mean arterial pressure (MAP) was chosen to be the dependent variable to be analyzed.

From physiology, assuming that mean venous pressure is negligible, the MAP can be represented as:

\[
\text{MAP} = \text{CO} \times \text{TPR} \times \text{HR} \times (1 - \text{CIRC}) \quad (7)
\]

where \(C_T = \text{CIRC} \times \text{TPR} \times \text{HR} \times \text{PP}\), and \(\text{CIRC}, \text{TPR}, \text{HR}, \text{CO}\), and \(\text{PP}\) denote stroke volume, heart rate, compliance, and pulse pressure, respectively. Eq (5) can be re-written as:

\[
\text{CIRC} = \frac{\text{MAP}}{\text{PP} \times \text{HR}} \quad (8)
\]

(1) Model of PP and HR

Simultaneous fit of PP and HR were attempted where "slow drug effect" due to volume loss and decreased CO caused by telmisartan's natriuretic effect was incorporated as an implicit inhibition function on the turnover rate of PP as follows:

\[
\frac{dPP}{dt} = k_{onPP} \times \text{PP} \times (1 - \frac{C_{tmaxPP}}{\text{IC50}_PP}) \quad (9)
\]

Assuming that phases of diurnal rhythm of PP and HR are synchronized, circadian rhythm was incorporated.

(2) Model for CTPR

Considering that vessel constriction and dilatation is governed by cytosolic calcium concentration,

\[
\frac{dC_{Ca2+}}{dt} = k_{Ca} - k_{Ca2+}C_{Ca2+} \quad (12)
\]

Since the action mechanism of angiotensin II is to increase cytosolic Ca\(^{2+}\), the binding of telmisartan to AT1 receptor will affect turnover of cytosolic Ca\(^{2+}\), resulting in vasodilation, which can be regarded as "rapid drug effect". Thus, assuming TPR is approximately directly proportional to cytosolic Ca\(^{2+}\) level and the time course of CTPR follows that of TPR with \(C\) being assumed to be constant over the observation time, CTPR can be described as:

\[
\frac{dCTPR}{dt} = k_{CTPR} \times \text{CTPR} \times (1 - \frac{C_{tmaxCTPR}}{\text{IC50}_CTPR}) \quad (13)
\]

Since it is known that TPR has a circadian rhythm in the mirror image of the other cardiovascular indices, a circadian rhythm was incorporated into CTPR as follows:

\[
\text{CTPR} = \text{CTPR}_{base} \times (1 - \text{MULT} \times \text{CIRC}) \quad (14)
\]

(3) Model for feedback

Feedback on HR was incorporated into HR as follows:

\[
\frac{d\text{HR}}{dt} = k_{HR} - k_{HR2}HR_{base} \quad (16)
\]

In the above equations, MAP is used as the driving force of negative feedback, with MAP being the baseline MAP, and \(k_i\) is the proportionality feedback constant.

2. Model Implementation

Model building procedure for MAP proceeded sequentially by first obtaining circadian, turnover rate and drug effect parameters by modeling PP and HR data together and then obtaining turnover rate, drug effect and MULT parameters for CTPR data, and finally obtaining baseline and feedback parameters by modeling PR, PP and CTPR data all together. In doing so, fixed-effect model parameters which were not estimated were fixed at their empirical Bayesian estimates obtained at the previous step, whereas random effect parameters were all estimated anew, with correlation between HR, PR, and TPR being taken into account to avoid unrealistic combination of parameters during simulation.

The VPC of the final model is shown in figure 2.

3. Analysis Software

All model parameters were estimated using NONMEM software version 7.3, with PnV version 4.2 being used for summarizing data, stepwise covariate model building, and performing VPCs. R (RStudio) and MATLAB R2013a were used for additional data exploration, manipulation, and simulation.

RESULTS

Table 1. Parameter estimates of the final PD model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTPR</td>
<td>0.050 (0.217)</td>
</tr>
<tr>
<td>HR</td>
<td>0.672 (0.248)</td>
</tr>
<tr>
<td>PP</td>
<td>0.747 (0.595)</td>
</tr>
<tr>
<td>IC50</td>
<td>1.010 (0.740)</td>
</tr>
<tr>
<td>MAP</td>
<td>3.236 (1.141)</td>
</tr>
<tr>
<td>k0</td>
<td>0.126</td>
</tr>
<tr>
<td>k0HR</td>
<td>0.893 (0.083)</td>
</tr>
<tr>
<td>k0CTPR</td>
<td>0.127 (0.060)</td>
</tr>
<tr>
<td>AMP</td>
<td>0.009 (0.011)</td>
</tr>
<tr>
<td>PHASE1</td>
<td>14.37 (7.12)</td>
</tr>
<tr>
<td>PHASE2</td>
<td>9.54 (9.08)</td>
</tr>
</tbody>
</table>

Variance Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV MAP</td>
<td>7.25 (10.88)</td>
</tr>
<tr>
<td>CV CTPR</td>
<td>15.88 (20.68)</td>
</tr>
<tr>
<td>CV PHASE1</td>
<td>6.79 (10.59)</td>
</tr>
</tbody>
</table>

Residual variability

<table>
<thead>
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<th>Parameter</th>
<th>Population estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV MAP</td>
<td>7.25 (10.88)</td>
</tr>
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<td>CV CTPR</td>
<td>15.88 (20.68)</td>
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<td>CV PHASE1</td>
<td>6.79 (10.59)</td>
</tr>
</tbody>
</table>

This work demonstrated the feasibility of using a non-invasive cardiac index (HR) in deriving a mechanistic model of telmisartan’s blood pressure lowering effect in human. The developed model can be similarly applied to antihypertensive drugs other than ARBs.

REFERENCES