Optimal Design To Estimate the Time Varying Receptor Occupancy Relationship in a PET Experiment

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Stefano Zamuner, Roberto Gomeni
CPK-M&S GSK
Why Study PK/RO?

- Positron emission tomography (PET) is one of the most effective imaging in vivo techniques to estimate RO.
- The assessment of the RO-time profile is critical to predict the time course of pharmacological response.
Why Study PK/RO?

- To characterise the shape and location of the concentration-RO curve
- To explain variability in response
- To rationalise dose/dosing regimen selection
- To predict the time course of pharmacological response (therapeutic & toxic)
- To understand complex relations (tolerance, sensitisation)
Experimental design issues in a PET study

• Cost and ethical reasons limit the total number of subjects (usually $n < 20$) and the number of PET scans per individual ($\leq 3$ scans)

• Uncertainty in the structure of the mechanistic model relating RO and PK (*Equilibration delay*, *Mechanistic delay*, *Tolerance*)

• Inter- and intra-subject variability in PK and in drug-to-receptor binding resulting in an overall inflation in variability

• Need to estimate typical exposure/RO link in a target patient population (fraction of subjects achieving an ‘effective’ RO in a chronic treatment)
Time course RO – Mechanistic models

• Typically a direct link between plasma concentrations and RO is assumed

• To account for delay/hysteresis between occupancy levels and plasma concentration the following models* can be applied:

Effect Compartment Model

\[
\frac{dC_E}{dt} = k_{eo} \cdot (C_P - C_E) \quad \rightarrow \quad \%RO = 100 \frac{C_E}{EC_{50} + C_E}
\]

Receptor Association-Dissociation Model

\[
\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO
\]

Combined Biophase / Receptor Association-Dissociation Model

\[
\frac{dRO}{dt} = k_{on} \cdot C_E \cdot (R_T - RO) - k_{off} \cdot RO
\]

*Rassen et al., Anesthesiology. 2006; 104-1232-42
Optimal Population Design

\[ CP_i = f(\theta_{CP_i}, \xi_{CP_i}) + \varepsilon_{CP_i} \]  
Population PK model (fixed effect)

\[ RO_i = g(CP_i, \theta_{RO_i}, \xi_{RO_i}) + \varepsilon_{RO_i} \]  
Population PK/RO model (fixed effect)

\[ \theta_i \in N(\Phi, \Omega) \]  
Population PK/RO parameters (random effect)

\[ \Xi \]  
Population design vector of PK and RO sampling times (\( \xi \))

\[ \Psi \]  
Vector of population fixed (\( \Phi \)) and random effect (\( \Omega \)) parameters

For a given individual with design \( \xi \)

\[ M_F(\Psi, \xi) = E \left( -\frac{\partial^2 l(\Psi; y)}{\partial \Psi \partial \psi^T} \right) \]

\( l(\Psi; y) \) is the log-likelihood of vector of observation \( y \) of individual for the population parameters

**Population Fisher information matrix (PFIM):**

\[ M_F(\Psi, \Xi) = \sum_{i=1}^{N} M_F(\Psi, \xi_i) \]

Designs are optimized maximizing the determinant of the PFIM with respect to \( \Xi \) assuming known \( \Psi \)

\[ \det[M_F(\Psi, \Xi)]^{\frac{1}{\text{dim}(\Psi)}} \]
Case study: Optimal study design

• PK/PD model was defined using pre-clinical data (kon/koff) and human PK data (considered fixed)

• Optimal design was performed to allocate PET scans at the most informative time-points

• Various designs exploring the influence of optimizing the PET scan time allocation, the number of subjects to elementary design and the number of dose levels were considered

• Optimisation was performed using WinPOPT®

• Study designs: 16 subjects in total, up to 4 doses (1.5, 2.5, 4 and 6 mg), and 3 PET scans per subject

Modelling time-course RO data

- A mechanistic model was developed using pre-clinical data to estimate the RO time-course and the time-varying link between PK and RO based on $k_{on}$ and $k_{off}$ parameters.

\[
\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO
\]

- $C_P =$ predicted plasma concentrations (input function)
- $R_T =$ maximum receptor occupancy (fixed at 100%)
- RO = observed receptor occupancy time course data
- $k_{on} =$ association binding rate constant
- $k_{off} =$ dissociation binding rate constant.
Preclinical data - Results

PK/RO parameters estimates

<table>
<thead>
<tr>
<th>Receptor</th>
<th>$k_{on}$ (ml.ng$^{-1}$.h$^{-1}$)</th>
<th>$k_{off}$ (h$^{-1}$)</th>
<th>$K_d=k_{off}/k_{on}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT$_{1A}$</td>
<td>0.088</td>
<td>0.221</td>
<td>2.5</td>
</tr>
<tr>
<td>5-HT$_{1B}$</td>
<td>0.088</td>
<td>0.183</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Population PK/PD model

- Optimization was performed on the PK/PD model based on pre-clinical data (kon=0.088 and koff=0.221, variability=30%) and human PK data (first order absorption with 2 comp. model)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Fixed effects</th>
<th>Between-subject variance</th>
<th>Population distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>34.9 Fixed</td>
<td>0.112 Fixed</td>
<td>Log normal</td>
</tr>
<tr>
<td>VSS (L)</td>
<td>1200 Fixed</td>
<td>0.134 Fixed</td>
<td>Log normal</td>
</tr>
<tr>
<td>Q (L/h)</td>
<td>21.7 Fixed</td>
<td>0.179 Fixed</td>
<td>Log normal</td>
</tr>
<tr>
<td>FVC</td>
<td>0.67 Fixed</td>
<td>0 Fixed</td>
<td>Normal</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>0.605 Fixed</td>
<td>0.97 Fixed</td>
<td>Log normal</td>
</tr>
<tr>
<td>Kon (h⁻¹)</td>
<td>0.088</td>
<td>0.1</td>
<td>Log normal</td>
</tr>
<tr>
<td>Koff (h⁻¹)</td>
<td>0.221</td>
<td>0.1</td>
<td>Log normal</td>
</tr>
<tr>
<td>σ²</td>
<td>0.1</td>
<td>-</td>
<td>Proportional</td>
</tr>
</tbody>
</table>
Optimality criteria improved trial efficiency

<table>
<thead>
<tr>
<th>Number of doses (n. groups x dose)</th>
<th>Number of groups</th>
<th>Sampling times</th>
<th>Efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (2.5, 4, 6, 1.5)</td>
<td>4 (1, 1, 1, 1)</td>
<td>{6, 48}; {6, 48}; {6, 48}; {6, 48} Empirical design (1)</td>
<td>50</td>
</tr>
<tr>
<td>2 (1.5, 6)</td>
<td>8 (4, 4)</td>
<td>{5.73, 15.1}; {5.73, 15.1}; {5.73, 15.1}; {5.73, 15.1}; {10.7, 15.1}; {7.54, 11.7}; {4.74, 9.01}; {9.83, 13.9}</td>
<td>563</td>
</tr>
<tr>
<td>4 (1.5, 2.5, 4, 6)</td>
<td>8 (2, 2, 2, 2)</td>
<td>{5.73, 15.1}; {5.73, 15.1}; {4.74, 13.9}; {4.74, 13.9}; {3.90, 13.9}; {10.7, 15.1}; {8.24, 12.7}; {10.7, 15.1}</td>
<td>554</td>
</tr>
<tr>
<td>3 (2.5, 4, 6)</td>
<td>8 (3, 2, 3)</td>
<td>{4.74, 13.9}; {4.74, 13.9}; {4.74, 13.9}; {3.9, 13.9}; {3.9, 13.9}; {9.83, 13.9}; {9.83, 13.9}; {9.83, 13.9}</td>
<td>549</td>
</tr>
</tbody>
</table>

- number of groups and number of doses appear not to be relevant
- sampling time has been identified as the key driver to optimize the design
Simulation approach to assess the design performance

• Simulate RO time course with optimal and empirical time-points (~ Cmax and trough levels)

• Study design: 4 doses (1.5, 2.5, 4 and 6 mg); 4 subjects per dose (16 subjects in total)

• RO were sampled at two time-points
  – Empirical design: {6, 48} {6, 24} {3, 36} {6, 48}
  – Optimal design (at least 4 hours between two PET scans): {5.21 13.9} {3.9 13.9} {9.83 13.9} {5.73 15.1}

• Test the performance of the two approaches (bias, precision and accuracy)
PK and RO profile (typical dose)

- PK/PD model defined using pre-clinical data (kon=0.088 and koff=0.221, variability=30%) and human PK data (first order absorption with 2 comp. model)
- N=1600 subjects were generated from the PK/RO model
Simulation – Results

- 100 trials (with 16 subject/trial) where generated using a Monte Carlo simulation approach
- A non-linear mixed-effect methodology was used to estimate the kon and koff parameters with their inter-individual variability
- Performances were measured as bias, precision and accuracy on kon and koff estimates

<table>
<thead>
<tr>
<th>Performance Measure</th>
<th>Standard Kon</th>
<th>Standard Koff</th>
<th>Optimal Kon</th>
<th>Optimal Koff</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unscaled measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>ME</td>
<td>3.32</td>
<td>6.84</td>
<td>0.0274</td>
</tr>
<tr>
<td>Precision</td>
<td>Var</td>
<td>216</td>
<td>898</td>
<td>0.0692</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>14.7</td>
<td>30.0</td>
<td>0.263</td>
</tr>
<tr>
<td>Accuracy</td>
<td>MSE</td>
<td>227</td>
<td>944</td>
<td>0.0699</td>
</tr>
<tr>
<td><strong>Scaled measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>SME</td>
<td>37.7</td>
<td>31.0</td>
<td>0.311</td>
</tr>
<tr>
<td>Precision</td>
<td>CV</td>
<td>431</td>
<td>424</td>
<td>228</td>
</tr>
</tbody>
</table>

ME = mean error, Var = variance, SD = standard deviation, MSE = mean square error, SME = scaled mean error, CV = coefficient of variation

As expected the optimal study design approach provided more accurate and reliable model parameter estimates
Design of sequential PET experiments based on Optimality Criteria

1. Generate data (PK & RO) in an initial cohort of subjects (~4)
2. Set the initial dose & sampling scheme using pre-clinical PK/RO and early HVs PK as 'prior' information
3. Use Population Optimal design for next dose and sampling times selection
4. Use trial simulation to explore robustness of PK/RO model given the current sample size and evaluate potential benefit of alternative designs
5. Start a new cohort using the most performing design
6. Refine model & improve parameter estimates
7. Generate new data: PK & RO in the next cohort of subjects (~4)
Conclusions

• A mechanistic model has been proposed to estimate the RO time-course and the time-varying link between PK and RO

• Optimal study design approach provided more accurate and reliable model parameter estimates

• The use of sequential model design could increase the efficiency of the study for the PK/RO assessment especially when the human receptor kinetic model cannot be properly inferred from animal estimates

• Further work to develop a standardized methodology for the use of sequential optimal design approach is in progress