Incorporating Allometric Scaling Factors and Non-Linear Mixed-Effect Modeling to Predict Interindividual Variability in the Concentration vs. Time Course of a Pegylated Peptide following Subcutaneous Administration

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Background and Purpose

The primary objective of this work was to test the hypothesis that incorporation of allometric scaling factors into a model describing the SC time-course of a pegylated peptide would improve the prediction accuracy of the absorption phase. Between-relevant PK parameters. NCA and descriptive statistics were performed using Phoenix v 1.3.

Methods

The concentration data was measured in 20 human males (weight range 60-80 kg) receiving escalating SC fixed dose doses (n=3) or a single 7 mg/kg SC dose (n=3). The SC doses were administered to the cynomologus monkeys.

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Model-Based Scaling

Following four model development, human exposure after a single SC dose of the pegylated peptide was modeled using the population pharmacokinetic method. The concentration data is described by an ordinary differential equation (ODE) which relates the concentration of the compound at any given time to the time course of absorption and disposition processes. The concentration of the compound at any given time is described by the convolution of the input function and the impulse response function of the system.

The final model was selected based on individual data fit from diagnostic plots as well as fit to a compartmental PK model using population PK estimation methods. Between-relevant PK parameters. NCA and descriptive statistics were performed using Phoenix v 1.3.

Population Pharmacokinetic Modeling

Prior to scaling in humans, concentration data obtained from primate first pass were fit to a compartmental PK model using the population PK estimation method. The concentration data was obtained from multiple SC doses administered to cynomologus monkeys. The concentration data was then scaled to humans.

Interaction algorithm. Concentrations below the limit of quantitation (BLQ) were set to zero.

Equation 5.

\[ \text{Weight} = \text{Body Mass Index} (BMI) \times \text{Body Surface Area (BSA)} \]

Equation 6.

\[ \text{Concentration} = \frac{C_{\text{observed}}}{C_{\text{predicted}}} \]

Equation 7.

\[ \text{Residual Error} = \left| \text{Observed} - \text{Predicted} \right| \]

Equation 8.

\[ \text{Percentage Deviation} = \frac{\left| \text{Observed} - \text{Predicted} \right|}{\text{Predicted}} \times 100 \% \]

Table 2. Model-based scaling scenarios and corresponding prediction objective functions.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Parameter Exponent Source</th>
<th>Parameter Exponent Used in</th>
<th>Prediction Objective Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Fitted Exponent</td>
<td>0.87</td>
<td>3.10</td>
<td></td>
</tr>
<tr>
<td>(2) Empiric Scaling Exponent</td>
<td>CL/F, CL2/F</td>
<td>0.857</td>
<td>4.12</td>
</tr>
<tr>
<td>(3) Exponent</td>
<td>V/F, V2/F</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>(4) Empiric Scaling Exponent</td>
<td>CL/F, CL2/F</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Population PK parameter estimates obtained from administering a single intravenous intravenous single doses and SC single, and 10 day repeat doses in cynomologus monkeys.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F</td>
<td>0.87</td>
<td>0.03</td>
<td>0.81-0.94</td>
</tr>
<tr>
<td>CL2/F</td>
<td>1.28</td>
<td>0.07</td>
<td>1.15-1.43</td>
</tr>
<tr>
<td>V/F</td>
<td>1.28</td>
<td>0.07</td>
<td>1.15-1.43</td>
</tr>
</tbody>
</table>

Figure 1. Structural population pharmacokinetic model for a pegylated peptide in cynomologous monkeys.

Figure 2. Model diagnostic plots for the final population pharmacokinetic model describing a single 7 mg/kg dose administered intravenously and single and multiple 7 mg/kg doses administered subcutaneously in cynomologous monkeys.

Figure 3. 5th and 95th percentile of concentrations (solid line) and predicted pharmacokinetic parameters (dashed lines).

Figure 4. Experimentally obtained concentrations across 5 dose cohorts in humans (symbols) and 5-95th model scaled simulated concentrations (shaded region) for each corresponding dose level.

Figure 5. Elementary Dedrick Plot of experimentally obtained concentrations in humans (open circles) and cynomologus monkeys (solid lines).