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

- Prediction of large molecule pharmacokinetics (PK) in humans following subcutaneous (SC) administration in animal species is complicated by interspecies differences in anatomy and physiology
- Traditional allometry typically requires multiple animal species, which for large molecules may not be biologically relevant
- Scaling PK parameters does not provide information related to the exposure-time course following SC administration and limits First-in-Human planning
- Combining population PK (POPPK) modeling and allometric scaling factors offers an opportunity to predict the time course and interindividual variation of a SC administered drug in humans from a single, biologically relevant animal species
- 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 in non-human primates can similarly predict the time course of the same drug in a population of humans receiving escalating doses
- A secondary objective was to compare the prediction accuracy of empirically selected scaling factors with those obtained from experimental data
- As an exploratory objective, the elementary Dedrick plot was evaluated for utility in predicting the same pegylated peptide in a population of humans

Methods

The compound is a freely water soluble, linear PEG-40 conjugated peptide, with a molecular weight of approximately 44 kDa (name and pharmacologic class withheld for commercial and proprietary purposes).

Concentration data was obtained for 9 non-naïve (previous exposure to other experimental treatments) female cynomolgus monkeys (mean weight 3.4 kg), each receiving either a single 7 mg/kg intravenous dose (n=3), seven daily repeat SC 7 mg/kg doses (n=3) or a single 7 mg/kg SC dose (n=3). The SC doses were administered to the back region of the animal. Data was also provided by the Sponsor for the same peptide measured in 20 human males (weight range 60-80 kg) receiving escalating SC fixed dose between 45 mg and 720 mg, into the abdominal region.

Prior to assessing the concentration data for model fit and scaling, the raw data was plotted, followed by non-compartmental analysis (NCA) to obtain initial estimates of the relevant PK parameters. NCA and descriptive statistics were performed using Phoenix v 1.3 WinNonlin version 6.3[®] (Pharsight, a Certara Company) and Excel (Microsoft).

Population Pharmacokinetic Modeling

Prior to scaling to human exposure, concentration data obtained from primates was first fit to a compartmental PK model using population PK estimation methods. Betweensubject variability was modeled assuming a log-normally distributed model such that:

$P_{i} = TVP * exp\eta p$ Equation 1.

Where P_i represents the pharmacokinetic structural parameter in the ith individual and is equal to a typical value of the parameter (TVP, i.e. the population mean value) plus some deviation (η) from that population mean value. Each η_n was assumed to be log-normally distributed with a mean of 0 and a variance of ω^2 .

Residual error was modeled as a proportional error model for the base model taking the form of: Equation 2. $C_{observed} = C * (1 + \varepsilon)$

Where C_{observed} is the observed concentration, C is the population predicted value and ϵ is the deviation from the population predicted value and is assumed to be normally distributed with a mean of 0 and variance of σ^2 .

The final model was selected based on individual data fit from diagnostic plots as well as the Akaike information criterion. Qualitative model discrimination was performed using visual predictive checks (VPC) where the model-predicted median and 95th percentile of the simulations are overlayed with the observed data. Adequate fit is judged when the observed datapoints fall largely within the 95th percentile of the modelpredicted concentrations.

Population PK model development was performed using Phoenix NLME version 1.2 (Pharsight, a Certara company) using the First-Order Conditional Estimation with Interaction algorthimn. Concentrations below the limit of quantitation (BLQ) were set to missing in all instances.

Model-Based Scaling Following final model development, human exposure after a single, SC dose of the pegylated conjugate was simulated by incorporating allometric scaling factors directly into the model prior to simulation. Population-predicted typical values of structural parameters estimated in the primate were multiplied by weight-based ratio of human: monkey, raised to an exponent using the form in Equation 3.

Equation 3.

Prior to simulating the scaled concentrations for the human population, 1000 unique individual body weights for humans was first simulated assuming the same range of body weight as in the human observed dataset (i.e. 60-80 kg).

Four scenarios were tested. The first scenario employed a fitting process, whereby the exponent was estimated in Phoenix NLME using the naïve pooled engine for the first dosing cohort (i.e. 45 mg) and then the estimated scaling factors were used to predict the concentrations for all 5 dosing cohorts simultaneously. Additional scenarios, testing theoretical allometric scaling previously demonstrated to support allometric scaling of IV administered large molecules, were applied to CL and V parameters. Scaling of the absorption processes assumed an inverse relationship with species body weight based on previous observations in SC administered macromolecules. Model comparison evaluation of the four scenarios was based on an objective function calculated as the absolute, average % deviation of the median predicted concentration vs. median observed concentration at each nominal time point for each study cohort.

Elementary Dedrick Plots Plasma concentration and time scales following a single SC dose to both cynomologus and humans were normalized and plotted as elementary Dedrick plots using the normalization methods in Equations 4 and 5 and assuming exponent values for c and b of 1 and 0.85 for apparent extravascular volume (V/F) and clearance (CL/F), respectively.

Equation 4.

Equation

Results

Population Model Results

- specification

Aa1 and Aa2 represent the mass of drug delivered to the SC tissue for absorption via the two independent absorption processes; Ka1, Ka2 are the first-order absorption rate constants; tlag represents the lag time associated with the first absorption compartment; F1 and 1-F1 represent the fraction of the absorbed dose associated with the respective absorption compartments; V, CL, V2, CL2 are the volume and clearance associated with the central and distributional compartments.

Cl_{human} = Cl_{monkey}*(Weight_{human}/Weight_{monkey})^{0.85}

Time_{normalized} = Time_{observed}/Weight_{species} ^{c-b}

Concentration_{normalized} =Concentration_{observed}/Dose/Weight_{species}

A 2-compartment model with dual, parallel first-order absorption processes and a single linear clearance process was determined to best describe the PK after SC administration in primates (Figure 1)

PK parameters were estimated with good precision (Table 1). Population-predicted concentrations vs. observed concentration and conditional weighted residuals vs. predicted concentrations (Figure 2) suggest reasonable model prediction and

VPC (Figure 3) demonstrated that the model reproducibly predicts the observed data, regardless of route of administration (IV vs. SC) or regimen (single vs. repeat dose)

Figure 1. Structural population pharmacokinetic model for a pegylated peptide conjugate described as a 2-compartment model with parallel first-order absorption processes and linear elimination.



Table 1. Population PK parameter estimates obtained from administering 7 mg/kg intravenous single doses and SC single, and 7-day repeat doses in cynomologus monkeys.

Parameter	Estimate	Units	CV%	
V	0.11		8.77	
CI	0.00059	L/hr	7.84	
V2	0.043	L	25.85	
CI2	0.00092	L/hr	46.70	
Ka1	0.035	L/hr	17.00	
F1	0.87	L/hr	3.10	
Ka2	0.23		26.31	
Lag-Time	6.34	hr	8.08	
Residual Error	15	%	7.10	

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 to cynomologus monkeys.



Top panel: Observed vs. population predicted concentrations (closed circles) and the dashed line is the line of identity. Bottom panel: Conditional weighted residuals vs. predicted concentrations (closed circles) with loess fit (solid line).

Figure 3. 5th, 50th and 95th percentile of simulated concentrations (solid lines) vs. observed concentrations (solid circles) in cynomologus monkeys following a single intravenous dose (top panel), seven daily repeated subcutaneous doses (middle panel) and a single subcutaneous dose (bottom panel).



Model-Based Scaling

- Graphical depiction of the four scenarios is presented in Figure 4, while prediction accuracy measured by the objective function is presented in Table 2
- Scenario 3 best described the absorption, peak and elimination phase Estimation of the scaling factor exponents in the first dosing cohort (Scenario 1) resulted in a reasonable prediction of the absorption phase across all 5 dosing cohorts with the exception of the initial 10-20 hr post-dose
- Assuming a positive exponent of 1 on the absorption rate constant resulted in poor prediction accuracy of the absorption phase

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.



Time (hr)

Scenario 1: Scaling factors fit on lowest dose cohort (45 mg) and fitted exponents applied to simulations for all subsequent dosing cohorts; Scenario 2: exponent of 1 on V/F & V2/F; 0.85 on CL/F and CL2/F; -0.4 on Ka1 and Ka2; Scenario 3: exponent of 1 on V/F, V2, CL/F and CL2/F; -0.4 on Ka1 and Ka2; Scenario 4: assumes an exponent of 1 on all model parameters. Top panels display linear scale and bottom scale log-log scale.

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

Scenario	Exponent Source	Parameter	Exponent Used in Simulation
(1)	Fitted Scaling Exponent Fit from 1 st Human Dose	CL/F, CL2/F	1.42
	Cohort	V/F, V2/F	1.28
		Ka1, Ka2	-0.49
(2)	Empiric Scaling Exponent	CL/F, CL2/F	0.85
		V/F, V2/F	1
		Ka1, Ka2	-0.4
(3)	Empiric Scaling Exponent	CL/F, CL2/F	1
		V/F, V2/F	1
		Ka1, Ka2	-0.4
(4)	Empiric Scaling Exponent	CL/F, CL2/F	1
		V/F, V2/F	1
		Ka1, Ka2	1







Dedrick Plots

Elementary Dedrick plots predicted the peak and elimination phase (Figure 5) however poorly predicted the absorption phase

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



Conclusions

- Estimating the time course of an SC administered macromolecule can improve study design through optimization of the sampling time points needed to best characterize the PK of a newly developed drug
- POPPK modeling of PK data obtained following IV and SC administration in primates can provide a reasonable prediction of the time course of a pegylated macromolecule after SC administration with some overprediction in the earliest portions of the profile
- Empirically, an inverse relationship appears to exist between primates and humans in first-order absorption rate. However, further work across a wide range of molecular size and class is required to more precisely estimate this relationship
- Elementary Dedrick plots, which do not account for interspecies size relationships in absorption processes, do not allow for accurate prediction of macromolecule absorption after SC administration

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