POPULATION PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL INCORPORATING LYMPHATIC UPTAKE FOR A SUBCUTANEOUSLY ADMINISTERED PEGYLATED PEPTIDE

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Background

- Whole body physiologically-based PK (WB-PBPK) modeling with lymphatic distribution has been performed following IV administration of monoclonal antibodies
- Drug transit from the lymphatics to the venous compartments has been previously quantified as a transit time which is not anatomical or physiologic in nature
- Population PBPK algorithms have not previously reported mean and variance for lymphatic system parameters
- Using a WB-PBPK model we characterized the subcutaneous (SC) time course of a pegylated peptide conjugate in primates then scaled the mean time course in humans at three different dose levels in a First-In-Human single ascending dose study[1]
- To further investigate the contribution of local lymphatic capillary drainage from the SC space, and to explore the interindividual variability of lymphatic parameters, we expanded our previous work by developing a population (pop) WB-PBPK model

Objective

To develop a pop-WB-PBPK model to account for interindividual variability in the SC time course of a pegylated (PEG) peptide.

Methods

All observed human data was derived from a single study where a proprietary (name and target withheld for commercial proprietary purposes) freely water soluble, linear PEG-40 conjugated peptide, with a molecular weight of approximately 40 kDa was administered to 20 healthy Australian male subjects, 18-55 years of age and within a weight range of 60-80 kg. Each subject received a single, SC administered dose between 45 mg and 720 mg into the abdominal region with sequential PK sampling post-dose until approximately 1050 hours. The concentration of the injection ranged from 100 mg/mL to 150 mg/mL with multiple injections for some dose levels such that the volume in any single injection would not exceed 2 mL.

Model Structure

The PBPK model and sub-compartment structure are graphically depicted in Figures 1a and 1b and are partially based on that developed by Shah and Betts[2]. The overall structure consists of a unique compartment for each of the venous and arterial circulation, a lymph node compartment and 15 individual organs where each organ consists of a vascular and interstitial sub-compartment. The skin interstitial compartment is further sub-divided into a depot and residual space where the SC dose inputs directly into the depot. The SC depot volume was parameterized as being equivalent to the total injection volume, which varied from 0.45-4.8 mL depending on the dose level and concentration injected. An intermediate anatomical lymphatic drainage compartment (LDC) was added to account for the lymphatic capillaries surrounding the SC depot which subsequently drains into lymphatic collectors prior to reaching the larger lymphatic duct.

Virtual Population Development

A virtual population of 1000 male subjects with body size consistent with the human study was simulated by the sampling of each organ compartment mass for each individual in the virtual population. All model compartments, with the exception of skin, blood and lymph were scaled according to equation (1), where the mean mass of each organ O, denoted M_0^{mean}, is dependent on the sex- and race-dependent body height of the individual (H_{indiv}), and where H_{ref} are M_0^{ref} body height and organ mass of a reference individual[3].

$$M_0^{mean} = M_0^{ref} \times \left(\frac{H_{indiv}}{H_{ref}}\right)^{3/4} \quad (1)$$

Blood and lymph mass means were scaled based on body weight (W, equation 2) as opposed to height.

$$M_0^{mean} = M_0^{ref} \times \left(\frac{W_{indiv}}{W_{ref}}\right)^{3/4} \quad (2)$$

Skin mass was scaled based on body surface area (BSA) as per equation 3 ($a = 0.0235, b = 0.515, c = 0.422$)

$$M_{skin}^{mean} = M_{skin}^{ref} \left(\frac{BSA_{indiv}}{BSA_{ref}}\right) \quad (3)$$

$$BSA_{indiv} = a \times (W_{indiv})^b (H_{indiv})^c \quad (4)$$

The total body mass (BM) of a virtual individual was then calculated as the sum of the bloodless organ masses, lymph mass, skin mass and blood mass. Individual organ blood flows (QB) were obtained by multiplying the organ weight of the individual by the reference perfusion value.

Figure 1 A

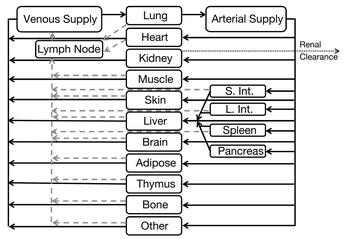


Figure 1 B

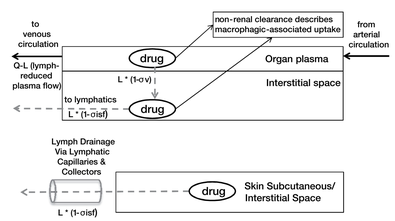


Figure 2

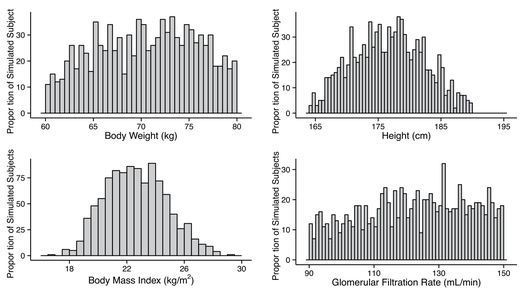


Figure 3

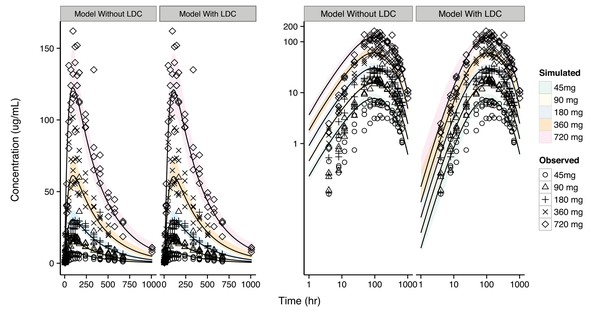
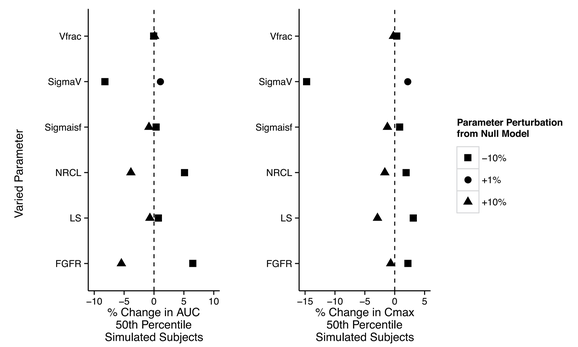
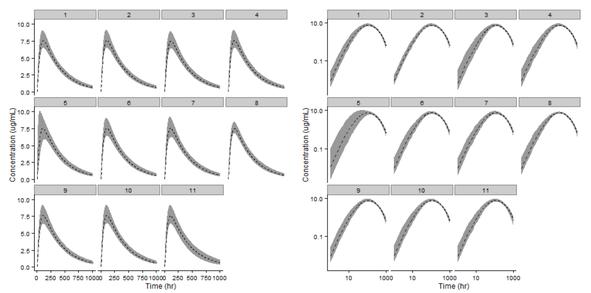


Figure 4



Vfrac=fraction of injection volume attributed to LDC; SigmaV=vascular reflection coefficient; Sigmaisf=lymphatic reflection coefficient; NRCL=non-renal clearance; LS=skin lymph flow as a fraction of blood flow; FGFR=renal clearance as a fraction of glomerular filtration rate

Figure 5



Median (dashed line) and 5th-95th percentile (shaded ribbon) following simulation of 1000 virtual individuals on linear scale (left panel) and log scale (right panel). For sub-panels 1-11 in each panel, the following unique scenarios are presented: (1) Final model (2) 0.5-fold final model CV% for Vfrac (3) 2-fold final model CV% for Vfrac (4): Addition of 10% CV% on LS (5) Addition of 50% CV% on LS (6) Addition of 10% CV% on σ_v (7) Addition of 50% CV% on σ_v (8) Removing distribution on blood mass (9) Removing distribution on lymph mass (10) Removing distribution on skin mass (11) Addition of a 20% CV% on FGFR.

Estimations

Estimation of LDC was based on the dose-normalized concentration vs. time data for all available subjects. A population estimate and interindividual coefficient of variation was estimated for LDC volume by parameterizing this parameter as a fraction of the SC depot compartment, denoted as Vfrac using, Phoenix NLME (Certara).

Model Qualification

All simulations were performed using MATLAB® (v2014b, Mathworks). Model evaluation of LDC 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.

Sensitivity Analysis

Mean parameter sensitivity was performed by perturbation of one parameter at a time (OPAT) by ±10% (except vascular reflection coefficient scaling factor, which was perturbed upwards of 1%). NCA was performed on the median simulated concentration vs. time profile to derive the $AUC_{0\text{-}inf}$ and Cmax. Distributional sensitivity was also performed by simulating 1000 individuals and either perturbing or removing a parameter distribution one at a time.

Results

- Model-simulated anthropometric characteristics (Figure 2) were consistent with a Phase I study population
- Inclusion of an LDC improved the prediction (objective function 20%) relative to the same model without LDC (objective function 100%; Figure 3)
- Interindividual variation was reasonably characterized in all phases of the concentration vs. time profile
- OPAT sensitivity (Figure 4) demonstrates that the vascular reflection coefficient and clearance parameters were most influential on the AUC
- Variability in lymph flow and LDC (Figure 5) had the greatest influence on interindividual variability of the absorption phase; peak concentration was most influenced by lymph and blood flow volume variability; and the elimination phase was most influenced by variation in the renal clearance parameter

Conclusion

- This is the first pop-WB-PBPK model in literature describing the biodistribution of macromolecules incorporating lymphatic uptake
- Population characterization allows for prediction and extrapolation of macromolecules across sub-populations (e.g. renal impairment)
- Inclusion of an anatomical space is necessary to mechanistically explain absorption by lymphatic uptake following SC administration
- Further evaluation of additional macromolecules across varying molecular classes is warranted

References

[1]Offman, E., Edginton, AN. J Pharmacokinet Pharmacodyn, 42(2):135-150.
[2]Shah D, Betts A. J Pharmacokinet Pharmacodyn, 39(1):67-86.
[3]Graf JF, Scholz BJ, Zavodszky MI. J Pharmacokinet Pharmacodyn 39(1):37-54.