

A platform for mechanistic modelling of subcutaneous (SC) administration with the effect of immunogenicity within the Open Systems Pharmacology (OSP) framework

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Objectives

- Implement and interface a previously established mechanistic model framework for SC administration with the whole-body model available in PK-Sim and MoBi, then validate the model with data collected from a literature review of SC administration
- Implement and interface a previously established QSP model of immunogenicity [2,3] with the SC model and the whole-body model available in PK-Sim and MoBi

Background

Mechanistic models for SC administration in combination with physiologically-based pharmacokinetic (PBPK) modelling allow for prediction of bioavailability (F), translation from preclinical to clinical, and extrapolation to special populations. For biologics, there is potential for an immunological response, e.g., anti-drug antibodies (ADAs), which can affect the pharmacokinetics (PK), F, and efficacy of a drug. These two challenges coincide in the contexts of injectable biologics and of vaccines. Modelling both the mechanistic absorption and the body's immune response allows for a more informed prediction of the pharmacokinetics of a drug following SC administration.

Methods

The software MoBi [1] was used to implement a SC administration framework (soon to be published) within the OSP framework [1]. Data from a literature review was then used for model validation. Injection parameters and formulation properties were used with a previously established intravenous (IV) model for comparison to observed data.

For the immunogenicity model, the software MoBi [1] was again used to implement the model within the OSP framework. The implementation was then validated by comparing to the original publication's simulation results for adalimumab [2,3] (not shown).

After model validation, the immunogenicity and SC models were used to predict the immunogenic response following an injection of a hypothetical monoclonal antibody (mAb) and a hypothetical vaccine.

Results

A published PBPK model of fentanyl [4] informed systemic disposition, and the SC model predicted absorption and F after SC administration. Observed data [5] was used to validate the model predictions (Fig. 1). The predicted concentrations were within two-fold error of the observed mean data with an average fold-error of 0.7.

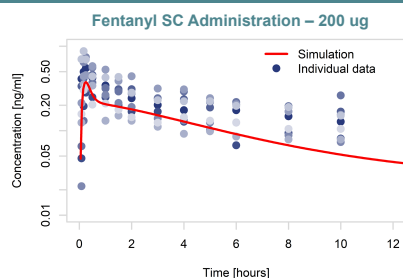


Figure 1. Observed plasma concentration-time profiles (circles) from 9 individuals [5] and the predicted plasma concentration-time profile (line) from the SC model.

With the individually validated models, a hypothetical mAb and hypothetical vaccine were simulated with varying parameters (Fig. 2). The vaccine had a stronger immune response, while the mAb was susceptible to FcRn binding. The underlying molecule properties and antigen PK affect the immunogenic response and the effect of the immune parameters (e.g. MHC binding affinity and ADA-antigen elimination) on the total ADA amounts in venous blood plasma. Additionally, the ADA amounts can affect the antigen PK.

References

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Conclusions

- An integrated model for SC administration and immunogenicity was implemented in the OSP framework. This model can, together with the whole-body PBPK model in PK-Sim [1], be used to make predictions about absorption, systemic disposition and immunogenic response after SC administration. The platform is applicable in the context of translations and biopharmaceutics for small molecules, biologics and vaccines.

Results (continued)

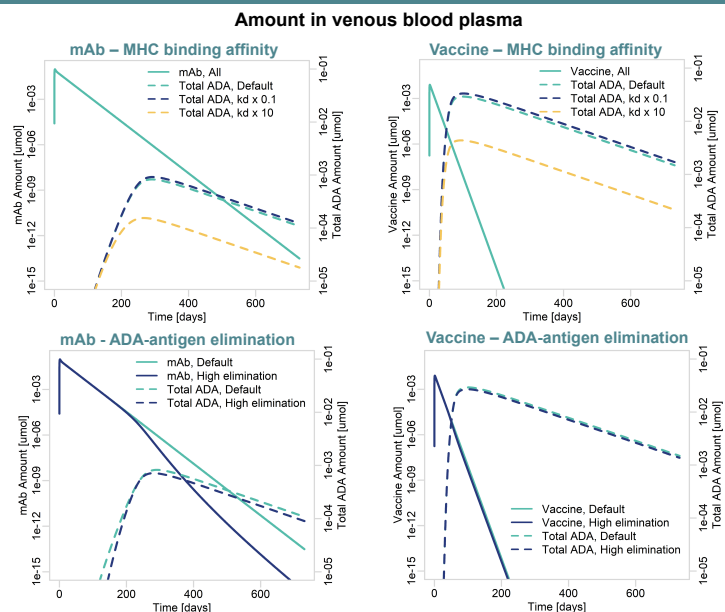


Figure 2. Simulated drug and total ADA amounts in venous blood plasma over a range of different parameters, representing hypothetical compounds

Sensitivity analysis was completed on the individual models to identify the most significant parameters with respect to the PK of the compound and the ADAs (Table 1). For the compound PK, the key SC parameters were proportion of the drug in the depot, dose volume, and extracellular fluid fraction, and the key immunogenicity parameters were F and absorption rate. This confirms the importance of mechanistic modelling of drug administration. For AUC of the ADAs, the key factors were T cell differentiation into memory T cells, T cell capacity to stimulate B cells, proliferation rate of activated T cells, and initial number of naïve T cells. For C_{max}, F, and absorption rate were additionally identified. For half-life, the key factor was the death rate of long-lived plasma cells.

Table 1. Key model parameters as identified by sensitivity analysis

Model parameter (model)	Sensitivity index (PK parameter)
Depot dispersion (SC)	0.57 (C _{max}), -1.68 (T _{max})
Dose volume (SC)	-0.45 (C _{max}), 0.61 (T _{max})
Extracellular fluid fraction (SC)	-0.33 (C _{max}), 1.22 (T _{max})
Bioavailability (imm)	1 (AUC), 1 (C _{max}), -1.69 (AUC ADA), -1.84 (C _{max} ADA)
Absorption rate (imm)	0.91 (AUC), 0.86 (C _{max}), -1.63 (AUC ADA), -1.79 (C _{max} ADA)
T cell differentiation into memory T cells (imm)	-1.97 (AUC ADA), -1.96 (C _{max} ADA)
T cell capacity to stimulate B cells (imm)	1.96 (AUC ADA), 1.9 (C _{max} ADA)
Proliferation rate of activated T cells (imm)	1.93 (AUC ADA), 2 (C _{max} ADA)
Initial number of naïve T cells (imm)	1.77 (AUC ADA), 1.67 (C _{max} ADA)
Death rate of long-lived plasma cells (imm)	0.54 (t _{1/2} ADA)

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