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Development of a Physiologically Based Pharmacokinetic (PBPK) Model for Intra-articular Delivery

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PURPOSE

Understanding local concentrations in intra-articular tissues and fluids such as cartilage, synovial membrane, and synovial fluid are a valuable tool to predict potential pharmacodynamic effects and efficacy of injection products and describe the effect of disease states on the disposition of drug. Therefore, a PBPK model was developed that incorporates solubility, dissolution, particle size distribution, tissue or protein binding, diffusion, and uptake into systemic circulation of active pharmaceutical ingredients (APIs) in the knee joint capsule. Methotrexate (MTX) and triamcinoline acetonide (TCA) validation studies were conducted to test the new model and determine what future improvements are necessary. This first step will accelerate the development of additional elbow joint models and facilitate disease state predictions.

METHODS

Intra-articular PBPK model was implemented in GastroPlus Version 9.7®. Drug injected or dosed to the synovial fluid dissolves based on a mechanistic dissolution model or prescribed release profile. Once drug is in solution within synovial fluid, it diffuses either through the intimal and subintimal membrane into systemic circulation or into the cartilage tissue which is subdivided into 10 sublayers. The subintimal and intimal membrane of the synovium are divided into two compartments due to the relatively thin dimension in relation to the cartilage. The model diagram is displayed in Figure 1 and the physiologic input parameters are shown in Figure 2. Methotrexate (MTX) and triamcinoline acetonide (TCA) validation studies were conducted to test the new model and determine what future improvements are necessary. This first step will accelerate the development of additional elbow joint models and facilitate disease state predictions.

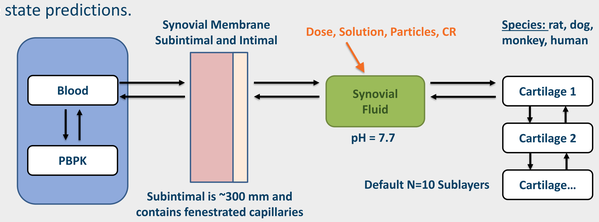

Figure 1: Intra-articular Model Schematic

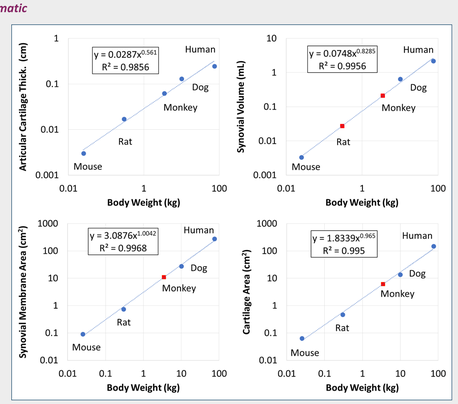

Figure 2: Measured physiologic parameters for Intra-articular mechanistic absorption model for various preclinical species and human. Red points are predicted from allometry.

RESULTS

TRIAMCINOLINE ACETONIDE (TCA) MODEL

A mechanistic absorption model was developed with compartmental PK for TCA that describes the IV and PO administration in human (Figure 3)[1,2,3]. The model was then used to predict intra-articular administration of TCA using two different methods in order to predict the PK of the 40 mg Intra-articular injection. The first method assumed the dissolution in synovial fluid was determined by the Stokes-Einstein equation and synovial fluid viscosity. The second method assumes the diffusivity of TCA in synovial fluid is equal to water with an agglomerated particle size. All other parameters were kept constant. The resulting PK predictions are shown in Figure 4.

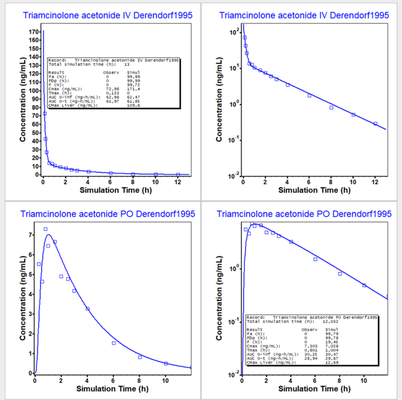

Figure 3: Baseline Model for IV and PO administration of TCA

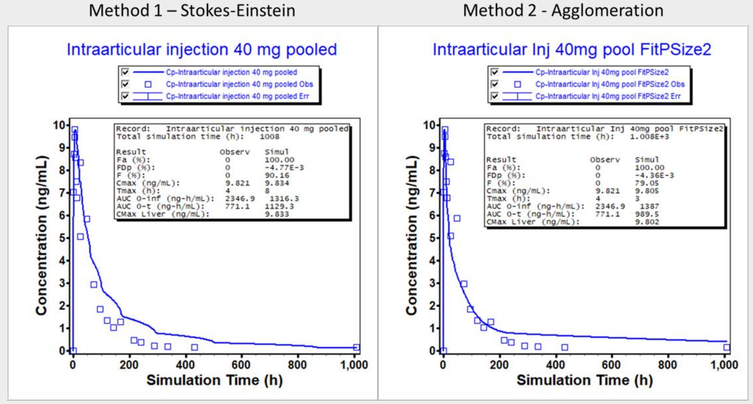

Figure 4: Prediction of dissolution/absorption of TCA from intra-articular space assuming measured particle size distribution and Stokes-Einstein diffusion coefficient (Method 1) or agglomerated particle size and diffusion coefficient in water (Method 2)

METHOTREXATE (MTX) MODEL

A mechanistic absorption model was developed with compartmental PK for MTX that describes the IV and PO administration in human (Figure 5)[4]. The MTX model was built assuming a disease arthritic state with increased synovial volume and membrane area. Diffusivities were calculated using the logP SAR model then adjusted by 1000X in synovial fluid and synovium and 100X in the cartilage to best match the data. Had the diffusivity of drug in water been used, the adjustments would have been minor. Initially, fraction unbound (Fu) was assumed to be 66% based on SAR model and adjusted to 90% to fit the synovial and plasma concentrations as shown in Figure 6.

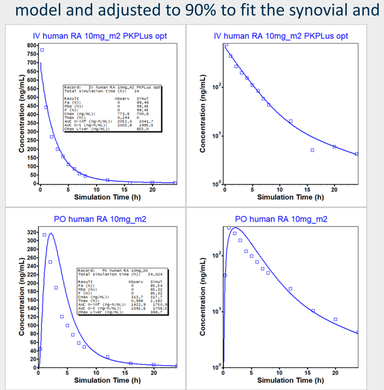

Figure 5: Baseline Model for IV and PO administration of MTX

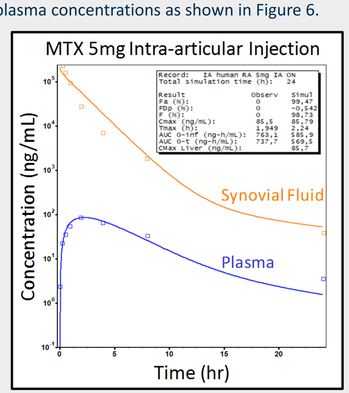

Figure 6: MTX Model Result for Intra-articular Administration

TCA AND MTX INTRA-ARTICULAR MODEL SETTINGS

The diffusion coefficients and fraction unbound in the synovial fluid, membrane, and cartilage are key aspects in the model. They can be either predicted from a simple LogP structure activity relationship (SAR), ADMET predictor (water diffusion coefficient or fraction unbound in plasma), or fit. The settings utilized in the TCA and MTX model are in Table 1 and 2.

Table 1: TCA Intra-articular Input Parameters for Fraction Unbound and Diffusivity

	Fu %	Fu Estimation Method	Diffusivity cm2/s x 10^5	Diffusion Calculation Method
Synovial Fluid	31.5	ADMET Predictor (Plasma Prediction)	$1.1x10^{-03}$ 0.62	Method 1: Stokes-Einstein Method 2: Water – AP Pred.
Intimal Membrane	13.7	Tissue Prediction from LogP	0.62	Water - AP Prediction
SubIntimal Membrane	13.7	Tissue Prediction from LogP	0.62	Water - AP Prediction
Cartilage	13.7	Tissue Prediction from LogP	0.62	Water - AP Prediction

Table 2: MTX Intra-articular Input Parameters for Fraction Unbound and Diffusivity

	Fu %	Fu Estimation Method	Diffusivity cm2/s x 10^5	Diffusion Calculation Method
Synovial Fluid	90	Fitted	1.45E-2	Fitted
Intimal Membrane	66	Tissue Prediction from LogP	1.45E-2	Fitted
SubIntimal Membrane	66	Tissue Prediction from LogP	1.45E-2	Fitted
Cartilage	66	Tissue Prediction from LogP	1.45E-3	Fitted

OBJECTIVES

- **Develop a PBPK model for intra-articular injections**
- **Calculate dissolution in synovial fluid**
- **Predict tissue concentration in cartilage, synovial membrane, and synovial fluid**
- **Test model against *in vivo* datasets**

CONCLUSIONS

The intraarticular model accounts for all relevant physiologic parameters for various preclinical species and human. It utilizes all available literature for pH, volumes, surface areas, and flows for each tissue compartment. Model validation was performed on methotrexate and triamcinoline acetonide. MTX required diffusion coefficients similar to water and a fitted Fu in synovial fluid and membrane to match the Cp-time data, while the TCA model either required the Stokes-Einstein viscosity model to predict slow diffusion or the assumption agglomeration with the diffusivity of water. Future work will aim to improve Fu and diffusivity predictions, build models for elbow joints, and provide disease state models.

REFERENCE

1. Derendorf, Hartmut, et al., Clinical Pharmacology & Therapeutics 39.3 (1986): 313-317.
2. Kraus, V. B., et al., Osteoarthritis and cartilage 26.1 (2018): 34-42.
3. Derendorf, Hartmut, et al., The Journal of Clinical Pharmacology 35.3 (1995): 302-305.
4. Wigginton, Scott M., et al., Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 23.1 (1980): 119-122.

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