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

RESULTS

TRIAMCINOLONE 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). The model was then used to predict intra-articular administration of TCA using 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.

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). 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 100x in synovial fluid and synovium in the cartilage to best match the data. Had the diffusivity in drug in water been used, the adjustments would have been minor. Initially, fraction unbound (Fu) was assumed to be 66% based on SAR similarity to triamcinolone acetonide. MTX required diffusion coefficients similar to water and a fitted Fu in synovial fluid and membrane to match the C3-time data, while the TCA model either required the Stokes-Einstein viscosity model to predict slow diffusion or the assumption of 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.

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 triamcinolone acetonide. MTX required diffusion coefficients similar to water and a fitted Fu in synovial fluid and membrane to match the C3-time data, while the TCA model either required the Stokes-Einstein viscosity model to predict slow diffusion or the assumption of 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


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