Prediction of the effect of injection volume on the exposure to intrathecal (IT) drugs in the central nervous system (CNS)

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Objectives: To develop a physiological-based pharmacokinetic (PBPK) model to describe the injection volume effect on the CNS exposure following the IT administration in monkeys; to explore potential mechanisms of this effect by analyzing different model structures; to predict the CNS exposures for a range of volumes of injection.

Methods: Animals were dosed intrathecally with a bolus of either 0.36 mL or 1.8 mL of [64Cu]DOTA (small molecule radioactive tracer) solution. Dynamic whole-body PET scanning was performed to measure radioactivity concentration. The PBPK model has been developed based on the analysis of time-dependent radioactivity profiles in the cerebral spinal fluid (CSF), spinal cord, brain and other tissues. The model includes a number of well-stirred compartments, as shown in Fig. 1A. The inter-compartmental transfer is assumed to follow the first-order kinetics. Rates of transfer between different regions in the CSF and tissue penetration are conditional on the injection volume.

Results: Alternative model structures have been validated vs. the kinetic profiles of [64Cu]DOTA at the two volume conditions. Examples of model fits are shown in Fig. 1B. Estimation of model parameters that are conditional on the injection volume revealed that the rate constants describing transfer along the CSF and tissue penetration tend to be higher at larger volume of injection.

Conclusions: A pressure created by the larger volume of injection forces the injected solution to mix with the natural CSF more rapidly, which causes the injected substance to reach the upper CSF regions including brain faster. In the PBPK model, this effect can be accounted for through assuming the bi-directional rates of transfer along the CSF and tissue penetration to be empirical functions of the injection volume.