Pharmacokinetic-Pharmacodynamic (PK-PD) Modeling of Tolvaptan and Diuretic Use on Fluid and Electrolyte Balance in Healthy Subjects

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Objectives: To develop a PK-PD model characterizing the impact of the oral V2R antagonist tolvaptan, furosemide and hydrochlorothiazide (HCTZ) on fluid and electrolyte balance in healthy subjects.

Methods: Urine and electrolyte data were obtained from 101 subjects across 3 Phase 1 studies, including a crossover study (N=12) in which tolvaptan or furosemide/HCTZ was given alone or in combination. A series of linked indirect response models were used to describe dietary intake and urinary elimination of water and electrolytes as well as their relative ECF:ICF distribution. Synchronized cosine functions for dietary intake and renal elimination were used to characterize transient system changes in the absence of treatment. A population PK model for tolvaptan [1] was used to predict plasma tolvaptan concentrations to drive inhibition of the fractional tubular water reabsorption (FRW). Furosemide and HCTZ PK models [2,3] were employed to predict the urinary diuretic excretion rates used to drive inhibition of fractional tubular Na+ reabsorption (FRNa).

Results: Maximal tolvaptan-induced inhibition of FRW was 7.65% (vasopressin produces ~10% of water reabsorption in the collecting ducts). Tolvaptan-induced inhibition of FRW was used to stimulate relative vasopressin activity to reduce the extent of diuresis upon repeated dosing. The maximal furosemide-induced inhibition of FRNa was 18.3% (Na+-K+-Cl- transporter produces ~20% of Na+ reabsorption in the ascending limb of the loop of Henle) and for HCTZ was 2.51% (Na+-Cl- symporter produces ~3.5 to 5% of Na+ reabsorption in the proximal tubule). Diuretic-induced changes in FRNa were used to drive secondary effects such as diuresis, kaliuresis and the stimulation of relative RAAS activity causing feedback modulation.

Conclusions: A physiologically relevant PK-PD model was constructed to characterize fluid and electrolyte balance, which can be adjusted to account for pathophysiological factors explaining differences in response for fluid overload patients.

References: