Pharmacokinetic-Pharmacodynamic (PK-PD) Model for Tolvaptan in Patients with Hypervolemic Hyponatremia

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Objectives: To develop a PK-PD model and evaluate the impact of the V₂R antagonist tolvaptan on correcting serum [Na⁺] in patients with hypervolemic hyponatremia.

Methods: Urine and electrolyte data were obtained from 5 clinical trials (621 CHF and 39 cirrhotic patients). A PK-PD model developed in healthy subjects (ACoP6 abstract) describing dietary intake and urinary elimination of total body water (TBW) and electrolytes as well as their relative ECF:ICF distribution was modified. Initial TBW was calculated using fat free mass and hyponatremia severity. The relative ECF:ICF distribution of TBW was altered to account for ECF volume expansion. A population PK model for tolvaptan [1] was used to predict plasma tolvaptan concentrations to drive inhibition of the fractional tubular water reabsorption (FRₙ₆). For patients concurrently receiving furosemide, a population PK model [2] plus patient-specific CLcr estimates were used to predict the urinary furosemide excretion rates to drive inhibition of fractional tubular Na⁺ reabsorption (FRₙ₆Na). Monte Carlo simulation (MCS) with adaptive feedback control was performed to assess recommended tolvaptan dosing guidelines.
Results: Maximal tolvaptan-induced inhibition of FR\textsubscript{W} was lower in cirrhotic patients (5.75\%) than CHF patients (8.39\%). Cirrhotic (EC\textsubscript{50} = 222 ng/mL) and NYHA Class 3/4 CHF (EC\textsubscript{50} = 257 ng/mL) patients were also less sensitive to tolvaptan than NYHA Class 1/2 CHF patients (EC\textsubscript{50} = 108 ng/mL). Maximal furosemide-induced inhibition of FR\textsubscript{Na} was only 1.24\% suggesting diuretic resistance. MCS predicted the magnitude of the daily change in serum [Na\textsuperscript{+}] and TBW, the percentage of patients who achieve overly rapid correction or conversely required dose titration to expedite correction of serum [Na\textsuperscript{+}], and the expected duration of tolvaptan therapy.

Conclusions: A physiologically relevant PK-PD model characterizing fluid and electrolyte balance in patients with hypervolemic hyponatremia enabled assessment of the ability of tolvaptan to provide a safe and effective reduction in ECF volume and correction of serum [Na\textsuperscript{+}].

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