Pharmacokinetic/Pharmacodynamic (PK/PD) Model for Tolvaptan in Healthy Subjects

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Abstract

Background: Direct effects, indirect effects, and competition antagonism models were evaluated to describe plasma tolvaptan concentration-effect on urine flow rate (UFR), with consideration of water intake (WIR) and concurrent diuretic use.

Methods: Serial blood and urine samples were collected in Phase 1 (60, 120, 180 mg). Serial blood samples were collected to determine tolvaptan and vasopressin concentrations in plasma. Urine output and water intake were recorded for 2 days prior to and for up to 3 days after the last dose of tolvaptan. Urine samples were collected every hour and were frozen at −70°C until analysis. Previous models were used for tolvaptan and the non-constant baseline UFR.

Results: A direct effect model, with UFR as a linear function of WIR (intercept = 265.9 mL/hr, slope = 1.52 mL/hr per 37.6 cm3), was selected for the urine output model. The final tolvaptan concentration (slope = 0.941 mL/hr per ng/mL) best described the data. The competitive antagonism model was selected for the concurrent diuretic use variable, with water intake as the independent variable (slope = −0.327 mL/hr per 100 mL). The model was generally unbiased (median PE = 1.27%).

Conclusions: Utilization of this model allows for estimation of the net urine output due to tolvaptan. Further use of this model will be feasible since serial AVP samples were not collected in the Phase 2 and 3 clinical trials in CHF and HYP patients.

Table 1: Parameter Estimates for the Competitive Antagonism Model

Parameter | Final Estimate (%SEM)
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E0 | 7.6 (6.8)
Emax | 112 (40.3)
κkin | 16.9 (27.1)
IIV of κkin (%CV) | 68.5 (81.4)
IIV of Emax (SD) | 3.4 (7.2)
IIV of κ0 (%CV) | 9.5 (6.2)
IIV of κ0 (%CV) | 87.3 (35.5)

Figure 5: Observed and Predicted UFR from the Linear Direct Effect Model within 30 min after first dose for a subject given placebo.

Figure 6: Goodness of fit plots for the Linear Direct Effect Model.

CONCLUSIONS

The linear direct effect model with baseline UFR modeled as a function of both water intake and concurrent diuretic use, provided the best fit to the observed urine data from healthy subjects and was selected for further evaluation in clinical trials in CHF and HYP patients.