A Population Pharmacokinetic/Pharmacodynamic Approach of Drug X in Healthy Koreans

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Abstract

Objectives Drug X is a selective arginine vasopressin (AVP) V2-receptor antagonist which is used for treatment of acute and chronic hyponatremia. The aim of this study was to develop the population pharmacokinetic (PK) and pharmacodynamic (PD) model of Drug X in healthy male Koreans.

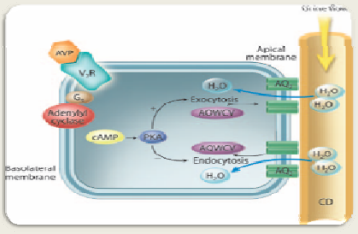
Methods A dose-block randomized, double-blinded, single-dose study was performed to evaluate pharmacokinetics and pharmacodynamics of 15, 30, and 60 mg of Drug X. Blood samples were collected up to 48 hours after drug administration. Free water clearance was estimated from 24-hour urine excretion rate (0-4, 4-8, 8-12, 12-24 hour interval), urine and plasma osmolality. Baseline for pharmacodynamic endpoints was the value of the predose sample. A non linear mixed-effect modeling approach, using NONMEM 7 (version 7.1.2) was implemented in modeling plasma Drug X concentration-time profiles and free water clearance of each timepoint.

Results A total of 473 concentrations from 36 subjects were included in population analysis. Drug X concentrations were best described by a two-compartment model with first-order absorption and elimination. The estimate of pharmacokinetic parameters and inter-individual variability (IIV, % CV) for clearance (CL) was 15.5 L/h (30.3), central volume of distribution (V2) was 49.3 L (12.9), inter-compartment clearance (Q) was 15.3 L/h (31.8), absorption rate constant (KA) was 0.27 h-1 and peripheral volume of distribution (V3) was 1360 L. Posthoc Bayesian predicted concentrations of effect compartment were used for estimate PD using sigmoid Emax model. The estimated Emax and baseline of free water clearance were 7.99 and -0.63 mL/min, respectively. The exposure associated with a 50% increase (EC50) (IIV, % CV) was 48.6 μg/L (24.5) and Hill's coefficient was 1.1.

Conclusions A PK/PD model was utilized to characterize the effect of Drug X on the free water clearance. Further studies will be needed to investigate the influence of subject's characteristics and mechanisms related to arginine vasopressin V_2 receptor.

Backgrounds

Figure 1. Vasopressin V2 receptor activation



- Decreases in blood pressure or volume can lead to profound increases in circulating levels of arginine vasopressin (AVP)[1].
- Stimulation of AVP V2-receptors increases cyclic adenosine monophosphate (cAMP) production by adenyl cyclase, which leads to synthesis and insertion of aquaporin-2 water channels in cells of the collecting tubules, allowing water reabsorption in the hypertonic medulla. [2]
- Drug X is an orally effective nonpeptide AVP V_2-receptor antagonist.
- The compound inhibits AVP-induced water reabsorption in the kidney by competitively blocking the binding of AVP to V_2-receptors.[3]

Objective

To develop the population pharmacokinetic (PK) and pharmacodynamic (PD) model of Drug X in healthy male Koreans.

Methods

Data Source

- Study design: Phase 1 Dose Escalation Study in Healthy male Koreans
- Number of subjects: 36
- Dose Groups of Drug X: 15, 30, 60 mg
- Pharmacokinetic Sampling:
- Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48 hours post-dose

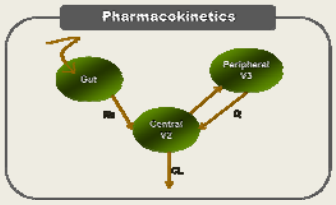
Free Water Clearance (C_{H2O})

- Pharmacodynamic parameter: Free Water Clearance [2]
- Free water clearance was estimated from 24-hour urine excretion rate (0-4, 4-8, 8-12, 12-24 hour interval), urine and plasma osmolality.
  - $C_{H2O} = V - C_{osm}$
  - V = urine excretion rate (mL/min)
  - C_{osm} = osmolar clearance or $U_{osm} \times V/P_{osm}$
  - U_{osm} = urine osmolality (mOsm/kg H_2O)
  - P_{osm} = plasma osmolality (mOsm/kg H_2O) at the end of the collection interval.
- Baseline for PD blood endpoints was the value of the pre-dose sample.

Modeling

- Modeling was performed using NONMEM 7 (version 7.1.2).
- A two-compartmental model with first-order absorption and first-order elimination from the central compartment was used to fitting plasma concentrations of Drug X.

Figure 2 Schematic of the pharmacokinetic model



Models building

$$P_i = P_{pop} \times e^{\eta i}$$

- P_{pop} represents the typical parameter value in the population
- η_i is the random variable assumed to be normally distributed with a zero mean variance ω

Pharmacokinetic-Pharmacodynamic Analysis

$$\text{Free water clearance} = \text{Baseline} + \frac{E_{max} \times C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}}$$

- Bayesian estimates of the pharmacokinetic parameters for each individual were used to generate the effect site concentration.
- The effect compartment was linked to the central compartment via a standard effect model

Analysis of model

- Comparing of objective functions differences in the full and reduced model's objective function using chi-square with the number of parameters in the reduced model as the degree of freedom.

Results

- A total of 473 concentrations from 36 subjects were included in population analysis.
- Drug X concentrations were best described by a two-compartment model with first-order absorption and elimination.
- Post-hoc Bayesian predicted concentrations of effect compartment were used for estimate PD using sigmoid E_{max} model.

Pharmacokinetic, Pharmacodynamic Parameter Estimates

Table 1. Pharmacokinetic and Pharmacodynamic Parameter Estimates

		Mean (SEM)	Variability (%)
Pharmacokinetic Parameters	Clearance/F (L/hr)	15.5 (4.74)	30.3
	Vc (L)	49.3 (6.37)	12.9
	Vp (L)	1360 (88.0)	
	KA (hr^{-1})	0.27 (0.0155)	
	Q (L/hr)	15.2 (4.86)	31.8
Pharmacodynamic Parameters	E_{max} (U)	7.99 (0.772)	
	EC_{50} (ug/L)	48.6 (11.9)	24.5
	Baseline (U)	-0.632 (0.0577)	
	Shape factor	1.09 (0.127)	
	K_{e0} (hr^{-1})	0.85(0.305)	53.4

Vc: central volume of distribution, Vp: peripheral volume of distribution
Q: intercompartmental clearance

Figure 3. Diagnostic plots of the final PK model

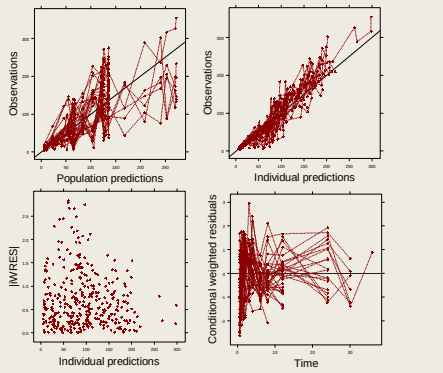


Figure 4. Representative Visual Predictive Check (VPC) of Final Pharmacokinetic Model

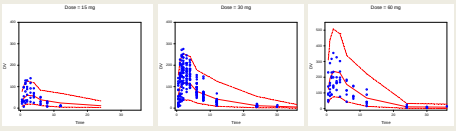


Figure 5. Diagnostic plots of the final PD model

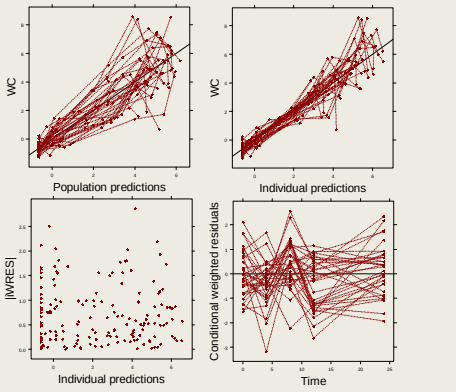
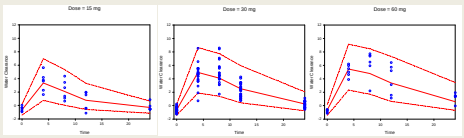


Figure 6. Representative Visual Predictive Check (VPC) of Final Pharmacodynamic Model



Conclusion

- A pharmacokinetic/pharmacodynamic model was utilized to characterize the effect of Drug X on the free water clearance.
- Further studies will be needed to investigate the influence of subject's characteristics and mechanisms related to arginine vasopressin V_2 receptor.

Acknowledgement

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- The authors don't have any conflict of interest.

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