Population Pharmacokinetic Model of Sedative Doses of GPI 15715 and Propofol Liberated from GPI 15715

Ekaterina Gibiansky, PhD[1], Leonid Gibiansky, PhD[2], Javier Enriquez[1]

[1]Guilford Pharmaceuticals, Inc., Baltimore, MD, [2]Metrum Research Group LLC, Avon, CT

ABSTRACT

BACKGROUND: AQUAVAN® Injection (GPI 15715, AQUAVAN) is a water soluble prodrug of propofol. The pharmacokinetics of propofol derived from AQUAVAN differ from those of propofol lipid emulsions. We developed a population pharmacokinetic (PK) model of GPI 15715 and propofol from AQUAVAN and identified covariates that influenced their PK. **METHODS:** In a Phase II colonoscopy sedation study, 5 minutes after intravenous fentanyl citrate dose (11–201 µg) patients received an AQUAVAN bolus and up to 4 supplemental intravenous doses (total dose 495–1675 mg). A total of 597 GPI 15715 and 599 propofol concentrations from 69 males and 89 females were analyzed using NONMEM. Covariates included age (20–85 y, 18 patients ≥65 y), weight (WT 45–140 kg), lean body weight (LBW 37–81 kg), body mass index (BMI), gender, fentanyl citrate exposure, albumin, creatinine clearance, and laboratory values. **RESULTS:** Linear 2-compartment models for GPI 15715 and propofol with a delay compartment between them described the data. CL^{GPI}, V_c^{GPI} and V_c^{PR} increased proportionally with LBW. Model parameters (%SE) under assumption of 100% metabolism of AQUAVAN to propofol were: CL^{GPI}=0.30 L/min (8%), V_c^{GPI}=6.1 L (5%), K_{12}^{GPI}=0.020 min^{-1} (24%), K_{21}^{GPI}=0.0062 min^{-1} (21%), K^{GPI-PR}=0.98 min^{-1} (14%), V_c^{PR}=6.9 L (fixed), K_{10}^{PR} =0.66 min^{-1} (8%), K_{12}^{PR}=0.73 min^{-1} (11%), K_{21}^{PR}=0.038 min^{-1} (20%), CL^{GPI}_{LBW}=2.5%/kg (11%), $V_{c\ LBW}^{GPI}$=1.8%/kg (19%), $V_{c\ LBW}^{PR}$=1.4%/kg (20%). **CONCLUSIONS:** A linear population PK model adequately described the data. LBW was a better predictor of propofol concentrations than WT. Fentanyl citrate did not affect PK values. No clinically significant influence of age was detected.

INTRODUCTION

AQUAVAN® Injection (AQUAVAN, GPI 15715) is a water-soluble prodrug of the sedative-hypnotic drug propofol. It is metabolized to propofol via hydroxylation by alkaline phosphatases. Clinical studies showed that the PK and pharmacodynamic properties of propofol differ considerably between AQUAVAN and the current lipid emulsion formulation, and suggested that AQUAVAN may have utility in sedation for short (<2h) diagnostic and therapeutic procedures. Simulations based on the developed PK/PD model suggested that a bolus AQUAVAN dose of approximately 10 to 12.5 mg/kg followed by an additional small dose 3 to 5 minutes later may provide sedation for a short procedure (15–20 min) to 90% of patients. A Phase II study was performed to assess AQUAVAN for sedation during colonoscopy procedure. A population PK model of AQUAVAN and propofol was developed to identify covariates that influenced their PK properties.

STUDY DESIGN

Controlled-Effect Trial:

Randomized, open-label, Phase-II, dose-ranging, adaptive-dose trial investigating several dose levels of AQUAVAN to produce a desired level of sedation during elective colonoscopy. Patients were administered a bolus dose of AQUAVAN 5 minutes following pre-medication with fentanyl citrate. If the required level of sedation was not attained by 5 minutes, a supplemental dose of AQUAVAN was administered. Supplemental doses could be repeated (up to 4 times, with intervals ≥3 min) for inducing and maintaining sedation during colonoscopy procedure. Four venous blood samples were drawn for determination of GPI 15715 and propofol in plasma.

Dosing:

- **AQUAVAN:** Initial bolus of 7.5 to 12.5 mg/kg with supplemental doses (when given) of approximately 25% of the initial dose (several patients got 50%). The total administered dose ranged from 495 to 1680 mg.
- **Fentanyl citrate:** 0.5 to 1.5 µg/kg. The maximum administered dose was 200 µg.

Pharmacokinetic Data:

- 158 patients: 69 males, 89 females; age 20 to 85 years, weight 45 to140 kg, LBW 37 to 81 kg.
- 282 AQUAVAN doses administered.
- 597 GPI 15715 and 599 propofol plasma concentrations determined.

Objectives of the PK Analysis:

- To develop a PK model of GPI 15715 and propofol derived from AQUAVAN.
- To identify covariates of propofol exposure.

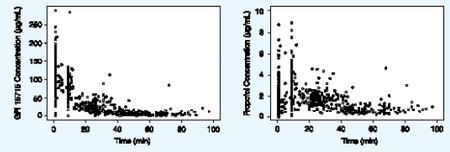

Figure 1. GPI 15715 (left) and propofol (right) plasma concentrations vs. time post initial AQUAVAN dose.

METHODS

Population PK Modeling:

- Concentrations of GPI 15715 and propofol were modeled simultaneously using nonlinear mixed-effects modeling software NONMEM (Version V, GloboMax LLC, Hanover, MD). The first-order conditional estimation method with η–ε interaction (FOCEI) was used.

Modeling Steps:

1. Base model for GPI 15715: structural (number and structure of compartments, linear/nonlinear) and error models (inter-individual variance-covariance matrix and residual) optimized.
2. Covariate model for GPI 15715: covariates accepted at pre-screen (NONMEM run with 1 covariate at a time) are included in the full model after colinearity evaluation. Then, model reduction was conducted using a stepwise backward elimination.
3. Base model for propofol with fixed population estimates for GPI 15715.
4. Covariate model for propofol with fixed population estimates for GPI 15715 (same procedure as for GPI 15715).
5. Refining combined model: refitting with simultaneous estimation of all parameters, choosing among highly correlated covariates (WT, LBW, BMI).
6. Predictive check: 500 trials were simulated using the final model. Statistics of interest were computed for each subject in each trial and for observed data. Statistics of interest were GPI 15715 and propofol concentrations at 9 minutes (it approximates maximum plasma concentrations [C_{max}] for propofol), and mean concentration (approximates area under the curve [AUC]). Percentiles (25%, 50%, 75% and 95%) of the statistics of interest were computed for the observed data and for each of the simulated studies. Then, simulated distributions of each percentile were compared with the observed values.

Error Models:

- Exponential inter-subject variability in parameters (e.g., clearance [CL]): $CL = \theta \cdot e^{\eta}$, where θ is the typical value, and η is a random variable. Correlation between the inter-subject variances was explored.
- Combined (additive and proportional) residual variability implemented as $Ln(Y) = Ln(F)+W\varepsilon$, where Y is the observed plasma concentration, F is the predicted value, ε is the residual variability and $W=[\theta_1/F^2+\theta_2]^{1/2}$.

Covariates Explored:

- **Demographics:** gender, WT, age, race, body surface, LBW, BMI.
- **Laboratory values:** albumin, alanine transaminase, aspartate transaminase, total bilirubin, estimated creatinine clearance, alkaline phosphatase.
- **Fentanyl exposure:** initial and total doses and weight-normalized doses of fentanyl, fentanyl plasma concentrations at 1 minute and 9 minutes.
- **AQUAVAN dose:** total and weight-normalized dose.

RESULTS

PK Model:

A linear 5-compartment model that includes 2 compartments for GPI 15715, 2 compartments for propofol, and an intermediate (delay) compartment between GPI 15715 and propofol (Figure 2) described the data. The model assumed complete metabolism of GPI 15715 to propofol. The model parameters are summarized in Tables 1 and 2.

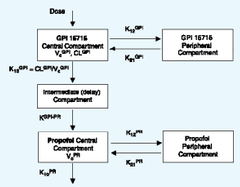

Figure 2. Compartmental model of GPI 15715 and propofol. V_c^{GPI}, V_c^{PR}=volumes of central compartments for GPI 15715 and propofol, respectively; CL^{GPI}=clearance of GPI 15715 (metabolism to propofol); K values indicate respective rate constants.

Covariate Effects:

Lean body weight: GPI 15715 volume (V_c^{GPI}) and clearance (CL^{GPI}), and propofol volume (V_c^{PR}) increased with increasing LBW, by 1.8%, 2.5%, and 1.4%, respectively, for each kilogram of LBW (from 55 kg). Following administration of the same dose (in mg), the predicted propofol maximum concentration (C_{max}^{PR}) was 20% higher in patients with LBW of 35 kg and 20% lower in patients with LBW of 85 kg compared to those with a LBW of 55 kg (Figure 3).

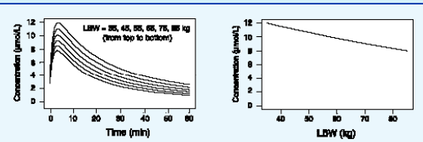

Figure 3. Dependence of propofol concentration over time (left) and propofol C_{max} on lean body weight (right) following bolus AQUAVAN dose of 800 mg.

Gender: gender was strongly correlated with WT and LBW. After accounting for LBW, no additional dependencies on gender were evident.

Fentanyl: no influence of fentanyl dose or exposure on GPI 15715 and propofol pharmacokinetics was detected.

Age: about 10% of patients (18 of 158) were older than 65 years. Older age (>65 y) was not associated with changes in the PK of either GPI 15715 or propofol.

Other covariates: no dependencies were detected.

Model Evaluation

- No bias in the model predictions was evident (Figure 4).
- No pattern in distribution of weighted residuals over time was noted (Figure 5).

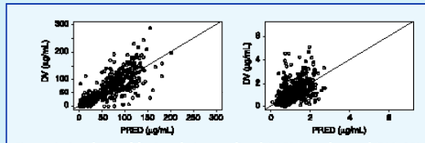

Figure 4. Goodness-of-fit: Population predicted (PRED) vs. observed (DV) GPI 15715 (left) and propofol (right) plasma concentrations.

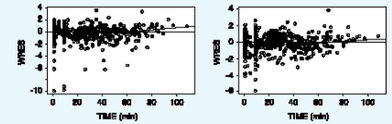

Figure 5. Goodness-of-fit: GPI 15715 (left) and propofol (right) weighted residuals (WRES) vs. time post initial AQUAVAN dose.

Simulations

- There was an excellent agreement between distributions of observed and simulated propofol concentrations at 9 minutes (Figure 6).
- There was less than a 10% difference between propofol concentrations at 25th, 50th, 75th and 95th percentiles of observed values and centers of simulated distributions (Figure 7).

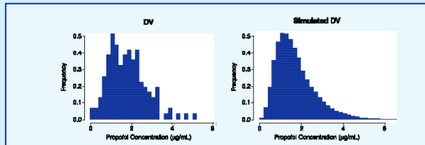

Figure 6. Distribution of propofol concentrations at 9 minutes post initial AQUAVAN dose: observed (left) and simulated concentrations from the model in 500 trials (right).

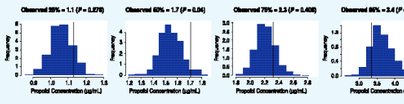

Figure 7. Percentiles of propofol concentrations at 9 minutes: observed (vertical line) and distribution in 500 simulated trials (histogram).

Table 1. Fixed-Effect Parameters of the Final PK Model

	Parameter	Estimate	%RSE*
GPI 15715	V_c^{GPI} (L)	6.08	4.6%
	K_{12}^{GPI} (min^{-1})	0.0198	24%
	K_{21}^{GPI} (min^{-1})	0.00617	21%
	CL^{GPI} (L/min)	0.298	8.0%
Propofol	K^{GPI-PR} (min^{-1})	0.982	14%
	V_c^{PR} (L)	6.91 Fixed†	
	K_{10}^{PR} (min^{-1})	0.655	8.0%
	K_{12}^{PR} (min^{-1})	0.732	11%
	K_{21}^{PR} (min^{-1})	0.0383	20%
Covariate effects	$V_{c\ LBW}^{GPI}$	0.194	19%
(no units)	CL^{GPI}_{LBW}	0.270	11%
	$V_{c\ LBW}^{PR}$	0.155	20%

* %RSE=percent relative standard error.
† Volume of the propofol central compartment V_c^{PR} was fixed as data were insufficient for its estimation. Population and individual predictions of propofol concentrations were nearly independent of V_c^{PR} in a wide range of the parameter values. With V_c^{PR} changing, parameters of the model changed accordingly to maintain the same predictions and the same propofol clearance, CL^{PR} ($CL^{PR}=K_{10}^{PR} * V_c^{PR}$=4.53 L/min). V_c^{GPI}, V_c^{PR}=volumes of central compartments for GPI 15715 and propofol, respectively. CL^{GPI}_{LBW}=clearance of GPI 15715 (metabolism to propofol). $V_c^{GPI}{}_{LBW}$, CL^{GPI}_{LBW}, Vc^{PR}_{LBW}=effect of lean body weight on V_c^{GPI}, CL^{GPI} and V_c^{PR}, respectively. K values indicate respective rate constants.

Table 2. Random-Effect Parameters of the Final PK Model

Variability	Parameter	Estimate	%RSE *	
Inter-individual	$\omega^2_{V_c^{GPI}}$	0.0727	29%	CV=27.5%
	$\omega_{K^{GPI-PR}\omega_{Vc}{}^{GPI}}$	-0.239	15%	R= -0.886
	$\omega^2_{K^{GPI-PR}}$	1	23%	CV=131%
	$\omega_{K12^{GPI}\omega_{K^{GPI-PR}}}$	0.271	46%	R=0.266
	$\omega^2_{K12^{GPI}}$	1.04	49%	CV=135%
	$\omega_{Vc^{PR}\omega_{K12^{GPI}}}$	-0.136	48%	R= -0.504
	$\omega^2_{Vc^{PR}}$	0.0699	29%	CV=26.9%
Residual (intra-individual)	$\sigma^2_{GPI^{ADD}}$	7.52	44%	SD=2.74 (µg/mL)
	$\sigma^2_{GPI^{PROP}}$	0.16	20%	CV=40.0%
	$\sigma^2_{PR^{ADD}}$	0.0109	33%	SD=0.104 (µg/mL)
	$\sigma^2_{PR^{PROP}}$	0.143	12%	CV=37.8%

* %RSE = percent relative standard error; ω^2 = variances of the respective inter-individual random effects; σ^2 = variances of the respective intra-individual random effects; ^{ADD} and ^{PROP} indicate additive and proportional residual errors, respectively; CV=coefficient of variation; R=correlation coefficient; SD=standard deviation. CV=coefficient of variation; R=correlation coefficient; SD=standard deviation.

CONCLUSIONS

- A linear 5-compartment model describes the pharmacokinetics of propofol following administration of sedative doses of AQUAVAN.
- Lean body weight was the best predictor of propofol concentrations, with C_{max} increased by 20% when LBW decreased from 55 to 35 kg, and decreased by 20% when LBW increased from 55 to 85 kg.
- Neither fentanyl dose nor fentanyl exposure influenced the pharmacokinetics of propofol following AQUAVAN administration.
- Age did not influence pharmacokinetics of propofol (based on 18 patients older than 65).

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