Population PK/PD model of GPI 15715 and GPI 15715-derived propofol in sedation and comparison of PK/PD models for ordered categorical observations

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AQUAVAN® Injection (GPI 15715) is a novel sedative/hypnotic water-soluble propofol prodrug with PK and PD properties that significantly differ from propofol emulsion. AQUAVAN may provide mild to moderate (procedural) sedation for short (< 2h) procedures. A Phase 2 study was performed to assess AQUAVAN for sedation during colonoscopy.

Study Design: This was an effect-controlled, adaptive dose-ranging trial in 164 patients with several dose levels of AQUAVAN to produce mild to moderate sedation (Modified Observer's Assessment of Alertness/Sedation score, 2 ≤ MOAA/S ≤ 4). All patients were pre-medicated with fentanyl citrate (fentanyl).

Dosing: There were several dosing groups with different initial and supplemental AQUAVAN and fentanyl doses.

Fentanyl: 0.5 -1.5 μg/kg i.v, five minutes prior to the initial AQUAVAN dose. **AQUAVAN:** initial bolus of 7.5-12.5 mg/kg. Supplemental boluses of 1.5-5.0 mg/kg (up to 4 doses at intervals of 4-5 min, if needed for sedation). **Total AQUAVAN dose:** range 495 - 1680 mg, mean 961 mg, SD 235 mg.

Objectives: To develop a population PK model of AQUAVAN (GPI 15715) and hydrolyzed propofol in venous plasma, and PK/PD model for MOAA/S score.

Data: PK: 4 venous samples: at 1 and 9 minutes post initial AQUAVAN dose, when patient returns to MOAA/S = 5 (awake) and at discharge; **PD:** MOAA/S score recorded every minute starting at first fentanyl dose (t = -5 min) and until 2 consecutive MOAA/S scores of 5.

Covariates: Demographics: gender (43% males), weight (45-140 kg), age (20-85 years), race (121 Caucasian/18 Hispanic/ 15 Black/4 Other), body surface, lean body weight (LBW 37-81 kg), BMI; **Lab values**: creatinine clearance, albumin, ALP, ALT, AST, bilirubin; **Fentanyl**: total dose (11-200 mg), concentration at 1 and 9 minutes (0- 1660 pg/mL); **AQUAVAN total dose** (495– 1680 mg).

Database: PK:158 patients, 282 doses, 597 GPI 15715 and 599 propofol plasma concentrations. **PK/PD:** 153 patients, 275 doses and 3421 MOAA/S observations.

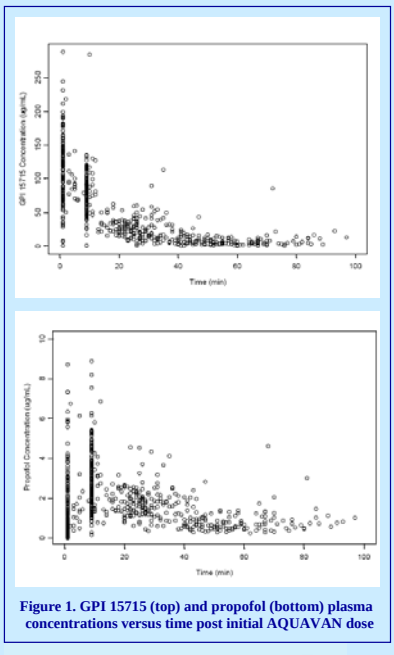

Figure 1. GPI 15715 (top) and propofol (bottom) plasma concentrations versus time post initial AQUAVAN dose

Final Population Pharmacokinetic Model

Linear 5-compartment model

Dose

GPI 15715 Central

V_1= 6.08L (28% CV), CL_{GPI}=0.298 L/min

K_{12}=0.0198 min^{-1} (135%CV)

K_{21}=0.0062 min^{-1}

GPI 15715 Peripheral

Intermediate

K_{34}=0.982 min^{-1}(131% CV)

Propofol Central

V_4=6.91L (27% CV)

K_{45}=0.732 min^{-1}

K_{54}=0.038 min^{-1}

Propofol Peripheral

K_{40}=0.655 min^{-1}

LBW dependence: V_1, V_4, and CL_{GPI} increased by 1.8%, 2.5%, and 1.4% per kg of LBW over 55 kg, respectively.

Combined Error Model:

GPI: SD = 2.74 μg/mL; CV=40%

Propofol: SD = 0.104 μg/mL; CV=40%

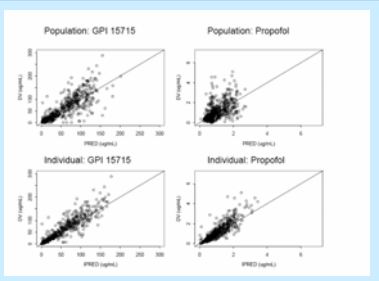

Figure 2. Predicted versus observed for PK model

Predictive check simulations: simulate 500 trials, compute propofol mean and 9-minute concentrations, find quartiles and 95th percentiles, compare observed and simulated values for these statistics **Results:** good agreement with the observed data, slight under-estimation of GPI 15715 and propofol concentrations and over-estimation of the GPI 15715 variability.

Probabilistic Population Model for MOAA/S Score

Proportional odds model: logit of probability of MOAA/S being at level i (i=0,1,..,5) is linear function of propofol concentration in the effect compartment

PK Model: Individual Estimates of Propofol Amount in Propofol Central Compartment

K_{40} K_{46}=0.001*K_{40} K_{64}=K_{E0}=2.04 min^{-1} (111% CV)

Propofol Effect Compartment

V_6= K_{46}*V_4/K_{64} C_E=A(6)/V_6

$Logit(P_i)=B_i + SLOP*C_E$

SLOP =5.83 (μg/mL)$^{-1}$ (55%CV); B_0 = -12.3 (27%CV); B_1 = 1.73; B_2 = 1.36; B_3 = 1.46; B_4 = 1.88

$SLOP_{AGE>65}$ increased 26%; K_{E0} depends on η_{K34}

Precision of parameter estimates is not known: covariance step failed; run time (days) precluded bootstrap. Expected score ESC= sum(P_i* MOAA/S_i)

Continuous Population Model for MOAA/S score

Expected score (ESC) is a Hill function of propofol effect-site concentration

PK Model: Individual Estimates of Propofol Amount in Propofol Central Compartment

K_{40} K_{46}=0.001*K_{40} K_{64}=K_{E0}=0.753 min^{-1} (112%CV)

Propofol Effect Compartment

V_6= K_{46}*V_4/K_{64} C_E=A(6)/V_6

$EFF = EFF_0+(E_{MAX}-EFF_0)*CE^{\gamma}/(CE_{50}^{\gamma}+CE^{\gamma})$

ESC = 5.5-EFF

E_{MAX} = 6 ; EFF_0 = 0.86 (43% CV); γ = 0.860

CE_{50} = 1.64 μg/mL (25% CV)

Error Model: SD= 0.86

$CE_{50\ AGE>65}$ 28% decrease; K_{E0} depends on η_{K34}

Precision of parameter estimates is not known: covariance step failed; run time (days) precluded bootstrap. Rounded expected score spans the entire MOAA/S scale.

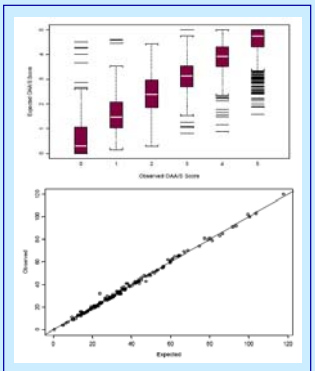

Figure 3. Expected versus observed MOAA/S score (top) and Area Under Effect (bottom, AUE=sum(5-MOAA/S))

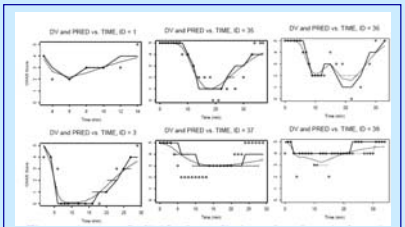

Figure 4. Individual predictions for 6 typical patients. Smooth solid: expected score, **Solid**: score with maximal probability, **Dashed**: rounded expected score, **Circles**: observed

Plots were similar for probabilistic and continuous models

Influence of Age on MOAA/S

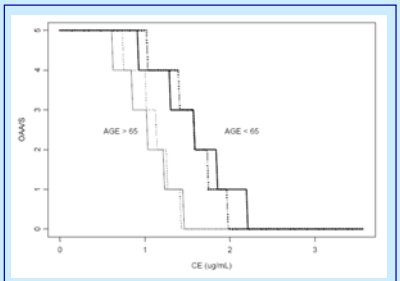

Figure 5. Expected MOAA/S score (ESC) versus effect-compartment concentration for probabilistic (solid) and continuous (dash) models.

Back-Stage Estimation (BSE) Method

(Kjellsson MC, Jönsson S, Karlsson MO. AAPS J. 2004; 6 (3): article 19) was applied to the probabilistic model, but showed unstable convergence. Starting from 40th iteration it was modified to allow ≤ 10% change in parameters from ith iteration to i+1th. This improved convergence. After 60 iterations no significant improvement in parameters was noticed.

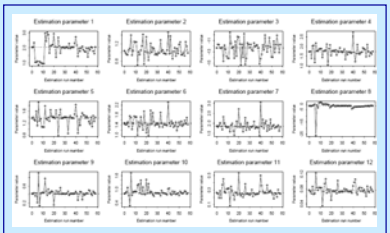

Figure 6. Iteration history of BSE estimated parameters.

Individual Predictions and Predictive Check Simulations: Sedation Levels Comparison

	Observed	Probabilistic Model: IPRED P	IPRED E	Simulation: Fixed PK P	Fixed PK E	Simulated PK P	Simulated PK E	Continuous Model: IPRED	Simulation: Fixed PK	Simulated PK
% patients with MOAA/S ≤1	56	53	42	53	50	51	48	50	50	44
% patients with MOAA/S ≤3	95	86	92	71	75	68	71	92	72	64
% patients with MOAA/S ≤4	99	97	99	83	88	81	86	99	91	86
% with MOAA/S ≤1 for >5min	35	33	29	44	41	43	40	33	40	36
% with MOAA/S ≤4 for >5min	98	96	98	79	84	76	82	97	87	83
Mean time to MOAA/S ≤ 1 (min)	7.5	6.4	6.1	4.8	4.8	4.5	4.6	6.7	5.7	5.6
Mean time to MOAA/S ≤ 4 (min)	3.0	4.3	3.8	3.8	3.6	3.8	3.5	3.7	3.1	2.9
Mean duration MOAA/S≤1 (min)	9	8	9	15	14	15	15	8	12	14
Mean duration MOAA/S≤4 (min)	20	20	23	21	22	20	22	22	23	23
% of time in MOAA/S=5	14	16	12	16	13	16	14	13	12	12
% of time in MOAA/S=2-4	62	63	72	48	55	46	54	70	61	61
% of time in MOAA/S<1	24	20	15	37	31	38	32	18	27	28

P: MOAA/S=score with maximum probability; E: MOAA/S=expected score

Summary of PK Results

- GPI 15715 and propofol central volumes, and GPI 15715 clearance increased by 1.8%, 2.5%, and 1.4% per kg of LBW, respectively.
- GPI 15715 C_{max} (end of the injection) ~1/LBW.
- Propofol C_{max} (4-5 minutes post-dose) ~1/LBW$^{0.45}$.
- There was no fentanyl effect on GPI 15715 or propofol PK.
- Gender and body weight (WT) were strongly correlated. There was no gender effect after accounting for LBW effect.
- The effect of age was not significant (10% of patients were older than 65 years of age).

Summary of PK/PD Results

- Probabilistic and continuous models adequately described the observed data with generally similar results.
- Older patients (≥ 65 years) were more sensitive to propofol. They were sedated to the same level as younger patients at approximately 33% (probabilistic model) and 25% (continuous model) lower propofol effect-site concentrations.
- At fentanyl doses used in the study, fentanyl effect on sedation was very small. Only 7 (5%) patients had MOAA/S score below 5 by the time of AQUAVAN dosing (5 min). PK/PD models were not able to distinguish fentanyl effect from the propofol effect.
- No gender effect was detected.

Conclusions:

- A linear PK model adequately described the data.
- LBW was the best predictor of propofol concentrations. Strictly weight-proportional dosing may overdose overweight individuals. Mg/kg dosing with an upper dose boundary or fixed-dose (mg) in the ranges of weights may be preferable.
- Age did not affect PK, but increased the PD effect. A reduction in dose of about 25% is indicated for patients over 65 years of age.
- Fentanyl did not affect PK or PD.
- Continuous and probabilistic PD models adequately described the data and the covariate effects.