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

Ekaterina Gibiansky, PhD1, Leonid Gibiansky, PhD2
1Guilford Pharmaceuticals, Baltimore MD, USA; 2Metrum Research Group, Avon CT, USA

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 (≤2 h) 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 GPI 15715 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 (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 215 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 (≤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 37-180 kg), BMI, Lab values: ceramidine clearance, albumin, ALP, ALT, AST, bilirubin, Fentanyl: 0.5-3.5 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 215 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.

Results:
- Propofol Cmax (4-5 minutes post-dose) ~1/LBW0.45.
- At fentanyl doses used in the study, fentanyl effect on MOAA/S score below 5 by the time of AQUAVAN dosing sedation was very small. Only 7 (5%) patients had fentanyl effect on sedation. Fentanyl did not affect PK or PD.
- Gender and body weight (WT) were strongly correlated. 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.
- 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.
- Age did not affect PK, but increased the PD effect. A
- 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 Cmax (end of the injection) ~1/LBW.
  - Propofol Cmax (~4.5 minutes post-dose) ~1/LBW.
  - There was no fentanyl effect on GPI 15715 or propofol PK.
  - Gender and body weight (WT) were strongly correlated.
  - 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.

Continuous Population Model for MOAA/S score
Expected score (ESC) = a Hill function of propofol effect-site concentration.