Population Pharmacokinetic/Pharmacodynamic Modeling of the Electroencephalographic Effects of Ganaxolone in Healthy Subjects

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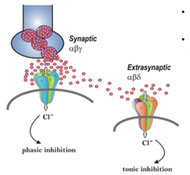
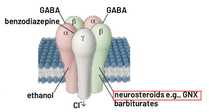
BACKGROUND

- Ganaxolone, a synthetic allopregnanolone analog, is in development for treatment of epilepsy.
- Quantitative electroencephalography (qEEG) is underexplored as a pharmacodynamic (PD) measure for CNS therapeutics.
- The objective of this study was to develop a population pharmacokinetic (PK) - PD model of ganaxolone IV administered to healthy participants.

GANAXOLONE (GNX) MECHANISM OF ACTION



- GNX is a synthetic analog of endogenous allopregnanolone and a potent positive allosteric modulator of $GABA_A$-receptors.
- GNX targets unique binding sites on $GABA_A$-receptors that are not susceptible to tolerance build up (e.g., benzodiazepines)



- GNX acts on both synaptic and extrasynaptic $GABA_A$-receptors to maximize inhibitory signaling as well as maintain activity when synaptic receptors are down-regulated

Study Design

- This was a sequential cohort evaluation of IV GNX in healthy participants. The study consists of 2 stages. The study investigated the safety, PK, and PD of IV GNX administered as an ascending bolus dose (Stage 1) and as a bolus dose followed by a continuous infusion (Stage 2).
- Neurophysiologic PD variables in this study were qualitative and quantitative EEG and BIS, particularly the timing and severity of EEG slowing in relation to the doses administered. The study also assessed the safety profile of IV GNX on electrocardiogram (ECG) parameters, vital signs, physical examination findings, and adverse events (AEs). Given the potential for sedative effects of IV GNX, an anesthesiologist was present for all dosing to maintain participant safety.
- In the 2 stages of the study, a total of up to 5 cohorts (up to 4 in Stage 1 and 1 cohort in Stage 2) were enrolled

Table 1. Stage, Cohort Design and Sample Size

Study Phase	N (Placebo Control)	Dose
Stage 1 Bolus Dose		
Cohort 1A	6	Open-label subtherapeutic anti-seizure dosing: 3 subjects received subtherapeutic dosing of 10mg IV ganaxolone over 5 minutes and 3 subjects received a higher subtherapeutic dose of 30mg
Cohort 1B	6 (2)	Therapeutic dosing- 8 subjects were randomized to receive 20mg IV ganaxolone or vehicle control (6 active : 2 control) over two minutes to achieve target concentration of 200-300ng/mL.
Cohort 1C	6 (2)	8 subjects (6 active : 2 control) were randomized to receive 30 mg IV ganaxolone or vehicle control over 1 hour
Cohort 1D	6 (2)	8 subjects (6 active : 2 control) were randomized to 10 mg IV ganaxolone over 1 hour
Stage 2 Bolus Dose + continuous infusion		
Cohort 2A	6	Open-label, 6 subjects received 6 mg over 5 minutes followed by continuous infusion of 20mg/hr over 4 hours for total dose of 86mg.

For all cohorts, safety, PK, and clinical PD parameters were measured at scheduled intervals and participants received continuous ECG, EEG, and BIS monitoring throughout the infusion. EEG and BIS monitoring continued for at least 30 minutes after the start of study drug administration or until they normalized following the infusion.

An interim PK analysis was conducted after each cohort and this PK data was used to predict the PK to inform dose and infusion rate in subsequent cohorts, as well as dosing in Stage 2.

METHODS-POPULATION PK/PD ANALYSIS

- A sequential population PK/PD model was developed to characterize the time course of qEEG alpha-power after IV administration of ganaxolone using the nonlinear mixed effects modeling software NONMEM (version 7.2).
- To develop a PK model for ganaxolone, two, three, and four-compartment structural models with linear elimination models were explored.
- Upon successful development of the PK model, the individual PK parameter estimates from the final population PK model were fixed in the PD analysis. Biophase distribution model and indirect effect models were tested in the PD analysis for alpha power.
- Age, weight, height, BMI, SCR, ALB, AST, and ALT were explored as covariaates in the PK model. Sex, race, BMI, age, ALB, and weight were explored as covariates in the PD model. A forward inclusion ($p<0.05$) and backward elimination ($p<0.01$) approach was used to evaluate covariates.
- Standard model diagnostic methods and prediction corrected visual predictive check were used for the assessment of PK/PD model performance.

RESULTS

- GNX plasma concentrations were generally proportional to the administered dose (Figure 1).
- Alpha-power analysis demonstrated clear and rapid postdose changes (Figure 2).
- Ganaxolone PK was best characterized by a 3-compartment model with first order elimination (Table 3 and Figure 3).
- Alpha-power after ganaxolone administration was best characterized by an effect compartment model (Table 4 and Figure 4, 5).
- BMI was identified as a significant covariate on CL. No covariates were identified for the PD parameters.
- The maximum increase in alpha-power from baseline in the average patient was approximately 75.3%. The ganaxolone concentration that produces 50% of the maximum effect (EC50) was 52.2 ng/mL. The Hill coefficient was estimated to be 1.28.

Table 2. Demographic and Clinical Data

Variable	Median (Range) or N (%)
N	30
Age (years)	31 (23 – 50)
Total body weight (kg)	80 (50.6 – 103.6)
Height (cm)	178.2 (157 – 200)
Body mass index (kg/m2)	25.8 (19.9 – 30.7)
Serum creatinine (mg/dL)	0.9 (0.7 – 1.3)
Albumin (g/dL)	4.2 (3.8 – 4.9)
Total bilirubin (mg/dL)	0.4 (0.2 – 1.2)
Aspartate aminotransferase (IU/L)	18 (12 – 28)
Alanine aminotransferase (IU/L)	17 (8 – 36)
Female	9 (30)
Hispanic or Latino	1 (3)
Race	
White	5 (17)
Black or African American	21 (70)
Other	4 (13)

*Descriptive statistics were calculated using values at screening and one day before dosing.

Table 3. Parameter Estimates of the Final Population PK Model

Parameter	Estimate	RSE (%)	Shrinkage (%)
Structural Model			
CL (L/h)	55.8	9	
V1 (L)	48.1	16	
Q2 (L/h)	127.5	17	
V2 (L)	94.0	8	
Q3 (L/h)	35.9	15	
V3 (L)	1135	34	
BMI on CL	0.92	31	
Inter-individual Variability (%CV)			
IIV (CL)	21	30	6
IIV (V1)	77	23	2
IIV (Q2)	48	69	22
IIV (Q3)	32	53	15
Residual Variability			
Proportional error (%)	24	14	10

Table 4. Parameter Estimates of the Final population PK/PD Model for Alpha Power

Parameter	Estimate	RSE (%)	Shrinkage (%)
Structural Model			
Emax	0.753	32	
EC50 (ng/mL)	52.2	2	
E0 (%)	89.4	6	
Ke0 (1/h)	6.49	5	
Hill	1.28	34	
Inter-individual Variability (%CV)			
IIV (Emax)	71.4	65	25
IIV (E0)	11.9	90	27
IIV (HILL)	170	78	33
Residual Variability			
Proportional error (%)	29.8	9	2

Figure 1. Ganaxolone Concentration vs. Time After Dose

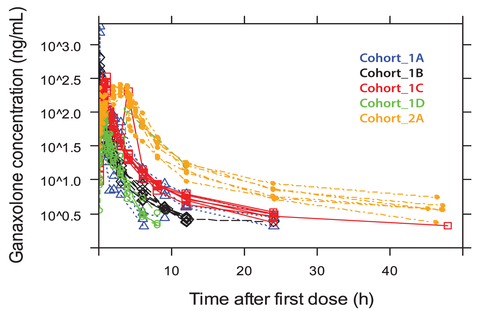
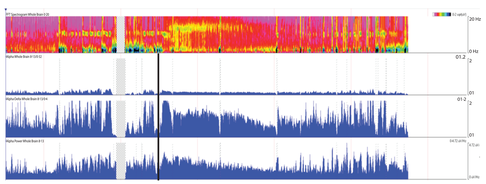
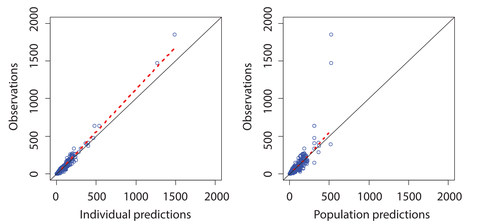


Figure 2. alpha -power changes in qEEG in a representative patient



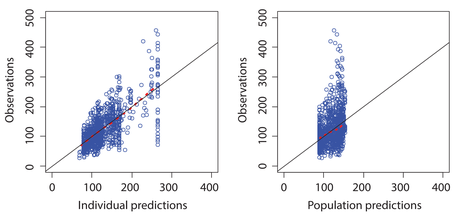
qEEG was determined using Persyst Insight II software

Figure 3. Observations vs Predictions for Ganaxolone Concentrations from the Final population PK Model



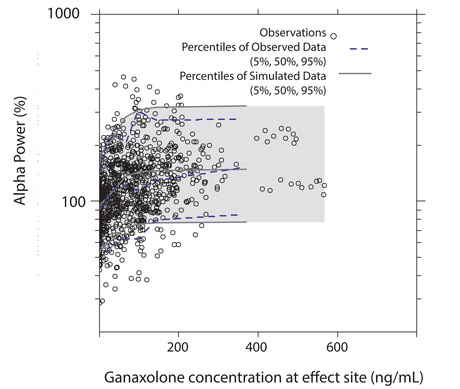
The solid black line and dashed red line represent the line of identity and LOESS smooth line, respectively.

Figure 4. Observations vs Predictions for Alpha Power from the Final population PK/PD Model



The solid black line and dashed red line represent the line of identity and LOESS smooth line, respectively.

Figure 5. Prediction Corrected Visual Predictive Check Plot for final PK/PD model



Conclusions

- Ganaxolone affected qEEG in a predictable and dose-responsive manner.
- The EC50 of ganaxolone was 52.2 ng/mL, a concentration which was achieved through IV administration.
- Future studies could determine whether reduced spike frequencies and changes in alpha-power are associated with successful seizure treatment with ganaxolone.