The Use of Quantitative EEG Spectral Analysis to Characterize IV Ganaxolone PK/PD Characteristics in Patients with Refractory Status Epilepticus

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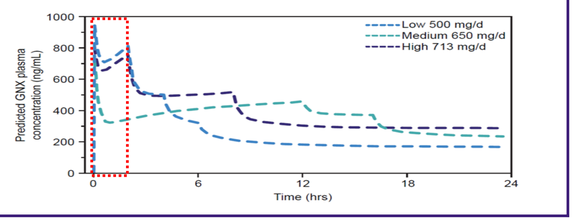
[#] At the time the study was conducted

Introduction

Ganaxolone (GNX) is a synthetic neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors and is in clinical development for the treatment of status epilepticus (SE) and rare pediatric epilepsies. GNX binds to synaptic and extrasynaptic $GABA_A$ receptors at a site distinct to enhance GABAergic inhibitory tone[1]. It has complex pharmacokinetic properties with a large volume of distribution and leads to substantial changes on EEG. In addition to evaluating the drug effects on seizures (intermittent events), the background spectral features can be useful in assessing therapeutic effects of treatment on more continuous basis.[2-4] In this study we evaluated CNS-specific pharmacokinetic and pharmacodynamic properties of intravenous GNX (IV GNX) using spectral analysis of EEG during a Phase 2 study in refractory SE (RSE) (NCT03350035). The open label phase 2 study enrolled 17 RSE patients into 3 cohorts: low, medium and high dose (Figure 1) with the goal for all cohorts to rapidly achieve high serum GNX levels.

Figure 1. Modeled Pharmacokinetic Curves for All Dose Groups



GNX: ganaxolone. The red box outlines the 2-hour epoch evaluated in this study.

Methods

- Continuous EEG data (10-20 montage) was obtained in 17 RSE patients.
  - Note: 1 patient was not included in this analysis because the IV infusion was affected by infiltration.
- EEG was conducted before, during, and after IV treatment of GNX. For this analysis, 1 hour prior to infusion and 2 hours after the infusion were analyzed (Figure 1)

Key eligibility criteria

- Diagnosed with convulsive or nonconvulsive SE.
- Failed at least one 2nd-line antiseizure medication but had not progressed to 3rd-line IV anesthetics

Dosing

- Dosing includes a bolus, 2- to 4-day maintenance infusion, and 18-hour taper (Figure 1).

EEG Analysis

- EEG preprocessing: bad channels removal + filtering [0,5-40Hz].
- The EEG was divided into 30s epochs.
- EEG spectral analysis was performed to quantify the amount of rhythmic activity of different frequencies in EEGs; delta, theta, alpha, beta and gamma.

EEG Spectral Features

- **Alpha /delta power ratio (ADPR)** and **suppression ratio (SR)** were computed from 30 min before through 2 hours after initiation of IV GNX.
- The percentage change relative to the 30min baseline period was computed for 30s epochs.

$$\text{ADPR} = \frac{\alpha/\delta - (\alpha/\delta)_{baseline}}{(\alpha/\delta)_{baseline}}\% \quad \text{and} \quad \text{SR} = \frac{SR - SR_{baseline}}{SR_{baseline}}\%$$

- The time to initial identifiable peak after the start of IV GNX and the corresponding percentage increase/decrease in ADPR and SR were assessed.

Correlation with measured serum GNX levels

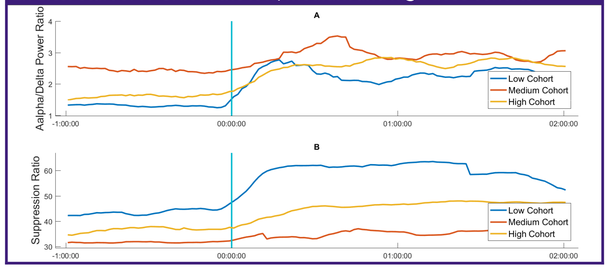
- % changes in Alpha/delta power and suppression ratio from all the subjects were correlated with serum GNX levels observed during the initial 2 hours of treatment.

Results

Alpha/delta power ratio

- A substantial increase in the alpha/delta ratio was observed immediately after the start of IV ganaxolone in 75% (12/16) patients with a median time to peak of 5 min and corresponding percentage increase of 93%, matching the observed median time to SE cessation.
- The alpha/delta ratio showed an increase in 5/5 patients of the low dose cohort, in 3/4 patients of the medium dose cohort and in 4/7 patients of the high dose cohort (Figure 2, panel A, Table 1).
- The changes in mean alpha/delta ratio normalized to baseline demonstrate changes consistent with predicted ganaxolone levels, with the medium cohort demonstrating the lowest response (Figure 3 panel A).
- A significant positive linear correlation was observed between the % change in alpha/delta ratio and the measured serum ganaxolone levels obtained within 2 hours from the initiation of the IV ganaxolone (Figure 4).

Figure 2. Mean Alpha delta power ratio and suppression ratio from -1h to 2h after start of IV GNX in the low, medium and high dose cohorts

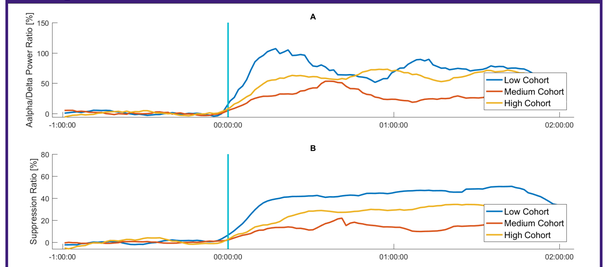


IV GNX, intravenous ganaxolone. The vertical line indicates the start of IV GNX.

Suppression ratio

- A substantial increase in the suppression ratio was observed immediately after the start of IV ganaxolone in 50% (8/16) patients with a median time to peak of 6 min and corresponding percentage increase of 53.0%, matching the observed median time to SE cessation.
- The suppression ratio showed an increase immediately after the start of IV GNX in 4/5 patient in the low dose cohort, in 3/4 in the medium dose cohort and only in 1/7 in the high dose cohort (Figure 4).
- The changes in mean suppression ratio normalized to baseline demonstrate changes consistent with predicted ganaxolone levels, with medium cohort demonstrating the lowest response (Figure 3 panel B).
- A significant positive linear correlation was found between the % change in suppression ratio and ganaxolone levels obtained within 2 hours from the initiation of the IV ganaxolone (Figure 4).

Figure 3. Mean percent changes from baseline of Alpha/Delta power and suppression ratio from -1h to 2h after start of IV GNX in the low, medium and high dose cohorts



IV GNX, intravenous ganaxolone. The vertical line indicates the start of IV GNX.

Figure 4. Correlation between EEG findings and observed plasma Ganaxolone levels

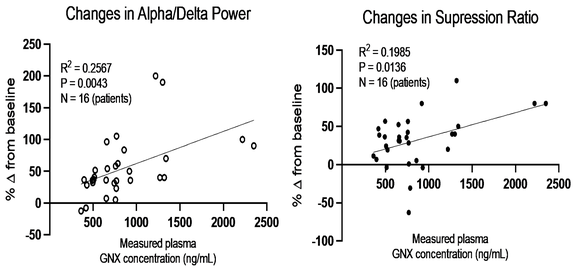


Table 1. Time to peak SR and alpha/delta ratio after IV GNX bolus

Cohort	Patient	Time to peak Alpha/delta ratio (min)	% increase Alpha/delta ratio	Time to peak SR (min)	% increase SR
Low	PAT #1	5:00	93.4	5:30	32.4
	PAT #2	2:30	75.6	3:00	110
	PAT #3	8:00	57.4	9:30	54.7
	PAT #4	4:30	261.2	7:30	74.2
	PAT #5	6:30	87.3	N/A	N/A
	MEDIAN	5:00	87.3	6:30	64.45
Medium	PAT #1	7:00	166	6:30	51.35
	PAT #2	N/A	N/A	18:00	47.53
	PAT #3	3:00	61.97	4:00	35.17
	PAT #4	6:30	140.5	N/A	N/A
	MEDIAN	6:30	140.50	6:30	47.53
High	PAT #1	N/A	N/A	N/A	N/A
	PAT #2	11:30	84.03	N/A	N/A
	PAT #3	N/A	N/A	N/A	N/A
	PAT #4	3:00	90.43	9:00	55.05
	PAT #5	N/A	N/A	N/A	N/A
	PAT #6	6:00	183	N/A	N/A
	PAT #7	2:30	102.2	N/A	N/A
	MEDIAN	3:00	102.2	9:00	55.05

GNX, ganaxolone; SR, suppression ratio; PAT, patient; N/A not applicable meaning no peak was found.

Conclusion

EEG background spectral analysis is a reasonable continuous biomarker to assess physiological activity of IV ganaxolone in humans. Relative changes in alpha/delta ratio and suppression ratio correlate with measured serum ganaxolone levels.

References

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Disclosures

Henrikas Vaitkevicius, Eva Rybak and Maciej Gasior are employees of Marinus Pharmaceuticals, Inc.
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