Pharmacokinetics, Pharmacodynamics, and Safety Study of Intravenous Ganaxolone in Healthy Adult Volunteers

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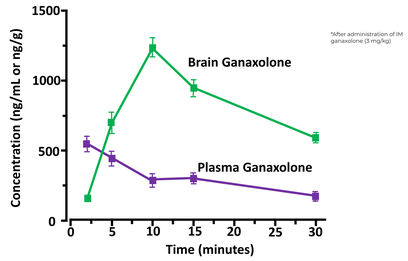
Introduction

- **Ganaxolone** (3α-hydroxy-3ß-methyl-5α-pregnan-20-one) is a **neuroactive steroid anticonvulsant** and a synthetic methyl analog of allopregnanolone[1]
- Ganaxolone acts as a **potent modulator of synaptic and extrasynaptic GABA$_A$ receptors** to potentiate dual inhibitory signaling; ie, transient (phasic) and continuous (tonic)[2-5]
  - At low concentrations, ganaxolone acts as a positive allosteric modulator by increasing the frequency and duration of channel opening
  - At high concentrations, ganaxolone acts as a direct agonist
- Ganaxolone **binds to a unique neuroactive site**, distinct from that of benzodiazepines or barbiturates, to modulate GABA$_A$ receptors[2,3]
- Ganaxolone is a lipophilic drug with **brain to plasma exposure 3:1** in pre-clinical studies (**Figure 1**)[6]

Figure 1. Brain to Plasma Levels of Ganaxolone



- A double-blind, placebo-controlled trial of IV ganaxolone in refractory status epilepticus is ongoing
- The objective of this study was to assess the pharmacokinetics (PK), pharmacodynamics (PD), and safety of IV ganaxolone in healthy volunteers

Methods

Study Design

- Phase I ascending dose trial in healthy adult volunteers (**Table 1**)

Table 1. Dose Cohort Descriptions

Stage	Type	Ganaxolone Dose	Total Dose	Controls[1]	n
1	Bolus	10 mg/5 min	10 mg	-	3
	Bolus	30 mg/5 min	30 mg	2	3
	Bolus	20 mg/2 min	20 mg	2	6
	Infusion	30 mg/h x 1 h	30 mg	2	6
	Infusion	10 mg/h x 1 h	10 mg	-	6
2	Bolus + Infusion	6 mg/5 min + 20 mg/h x 4 h	86 mg	-	6

[1]Controls received vehicle dosing similar to the respective ganaxolone group.

Pharmacokinetic Measures Assessed

- Serial plasma ganaxolone concentration sampling through 48 hours post-administration
- The PK population included subjects who received at least 1 dose and had sufficient concentration-time data
- Non-compartmental analysis in Phoenix WinNonLin (Pharsight Corporation, St. Louis, MO) was used to analyze ganaxolone PK
- PK analyses with adjusted r-square <0.8 were excluded

Pharmacodynamic Measures Assessed

- Quantitative electroencephalography (qEEG) measures
  - Relative alpha power, alpha/delta ratio, spectral edge frequency
- Bispectral index (BIS)
- Modified observers' assessment of alertness and sedation (MOAA/S)

Safety Assessments

- Subjects were monitored during and after dosing for reported adverse events, changes in vital signs, physical examination findings, ECG, and clinical laboratory tests (hem, chem, urine). Suicidality assessment (C-SSRS) was done at baseline and each subsequent visit

Results

- Thirty-six subjects were enrolled; one subject withdrew from the study during Stage 1
  - Other than sex and age (Stage 1: 80% male, mean age 33.5 years; Stage 2: 66.7% female, mean age 30.5 years), there were no notable differences in demographic variables between the two groups
- Pharmacokinetic values correlated with the dose and rate of administration (**Table 2**)
  - Ganaxolone was detected quickly in plasma with a median T_{max} of 5 minutes, when administered as a single bolus
  - C_{max} ranged from 73.8 ± 5.6 ng/mL (10 mg over 5 min) to 1240 ± 755 ng/mL (30 mg over 5 min)

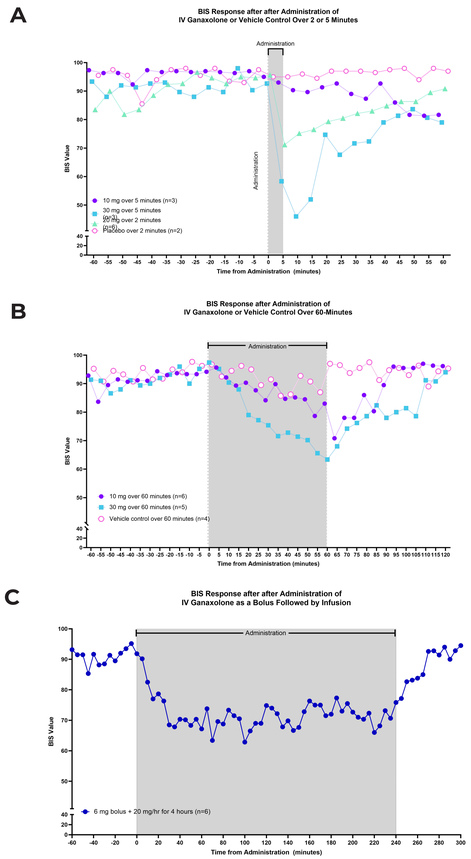
Table 2. Key Pharmacokinetic Parameters Following IV Administration of Ganaxolone

Treatment Parameters	10 mg GNX x 5 min		30 mg GNX x 5 min		20 mg GNX x2 min		30 mg/h GNX x 1 h		10 mg/h GNX x 1 h		6 mg GNX x 5 min + 20 mg/h x 4 h	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
C_{max} (ng/mL)	3	73.8 ± 5.60	3	1240 ± 755	6	441 ± 188	5[c]	257 ± 58.2	6	80.2 ± 21.4	6	215 ± 33.9
T_{max} (hr)	3	0.08 (0.08, 0.17)	3	0.08 (0.08, 0.08)	6	0.08 (0.08, 0.08)	5[c]	0.98 (0.98, 0.98)	6	0.98 (0.75, 4.00)	6	3.00 (0.08, 3.98)
AUC_{0-t} (h-ng/mL)	3	86.1 ± 26.1	3	547 ± 113	6	220 ± 32.8	5[c]	494 ± 117	6	192 ± 163	6	1270 ± 206
AUC_{0-inf} (h-ng/mL)	3	93.5 ± 27.0	2[b]	548 ± 140	5[b]	247 ± 26.1	4[b]	561 ± 113	6	210 ± 189	5[b]	1360 ± 241
t1/2 (h)	3	2.07 ± 0.193	2[b]	10.4 ± 0.264	5[b]	4.6 ± 0.855	4[b]	11 ± 1.56	6	2.41 ± 0.702	5[b]	18.2 ± 5.88
k_{el} (1/h)	3	0.337 ± 0.0327	2[b]	0.0666 ± 0.00169	5[b]	0.155 ± 0.0299	4[b]	0.0639 ± 0.00992	6	0.31 ± 0.0936	5[b]	0.0412 ± 0.0122
CL (L/h)	3	114 ± 36.5	2[b]	56.6 ± 14.4	5[b]	81.9 ± 8.75	4[b]	54.8 ± 9.25	6	67.5 ± 29.3	5[b]	64.9 ± 11.8
V_z (L)	3	344 ± 133	2[b]	852 ± 238	5[b]	546 ± 131	4[b]	886 ± 246	6	216 ± 79.1	5[b]	1710 ± 693

[a]T_{max} reported as median (minimum, maximum)
[b]n=1 removed from designated groups for analysis of AUC_{0-inf}, t1/2, k_{el}, CL, and V_z due to adjusted R^2 value <0.80 or %AUCextrap >20%
[c]One subject in this group withdrew consent after missing the Day 3 visit and was excluded from the pharmacokinetic and statistical analysis
%AUCextrap, percentage of extrapolated area under the concentration-time curve; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the concentration-time curve from time zero to t hours; CL, total body clearance; C_{max}, maximum plasma concentration; SD, standard deviation; GNX, ganaxolone; k_{el}, terminal elimination rate constant; t1/2, terminal elimination half-life; T_{max}, time to reach maximum concentration; V_z, volume of distribution

- **BIS reductions** were observed following ganaxolone administration (**Figure 2A, B, and C**)
  - After administration of an IV bolus over 2 or 5 minutes, or 60-minute infusion, time to maximal BIS reduction was a median (range) 8 minutes (5, 15), 15 minutes (5, 60), and 65 minutes (30, 120), respectively. With a lower 6 mg bolus followed by 20 mg/hr infusion, time to maximal BIS reduction was 148 minutes (35, 220)

Figure 2. BIS Response after administration of ganaxolone or placebo as an IV bolus over 2 or 5 minutes (A), IV infusion over 60 minutes (B), or IV bolus over 5 minutes followed by continuous infusion for 4 hours (C)



- Across all cohorts, deep sedation (defined as an MOAA/S score 0-1), was reported in a single patient 5 minutes post-administration of a 30 mg IV bolus over 5 minutes with return to baseline alertness 15 minutes post-administration
- **MOAA/S** did not appear to discriminate between ganaxolone doses and administration paradigms
- Rapid changes in **qEEG parameters** were more pronounced after administration of an IV bolus over 2 or 5 minutes

Safety

- Eight subjects out of 36 (22.2%) in this study reported at least one adverse event (AE), 7 out of these 8 AEs were considered treatment emergent AE (TEAE)
- TEAEs reported after receiving ganaxolone included headache (n=1), elevated lipase (n=1), and abdominal pain (n=1), whereas TEAEs reported after receiving vehicle control included constipation (n=1), nausea (n=1), decreased appetite (n=1), hypertriglyceridemia (n=1), and contact dermatitis (n=1)
  - Most were of mild severity, with a few events of moderate severity
- No deaths, severe AEs, or serious AEs (SAEs) were reported
- No cardiovascular or respiratory AEs were reported, and no clinically significant findings were reported for other laboratory values, vital signs, ECG data, physical examinations, or C-SSRS

Conclusion

- **After administration of IV ganaxolone, a dose and administration-dependent response of pharmacokinetic and pharmacodynamic effects was observed**
- **Ganaxolone was rapidly detected in plasma after administration of IV bolus**
- **More pronounced BIS and qEEG changes were observed following IV bolus administration of ganaxolone and indicated rapid brain penetration and clearance**
- **Overall, IV ganaxolone was generally well tolerated at the doses studied**
- **IV ganaxolone has favorable PK/PD properties for the potential treatment of status epilepticus**

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