Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus

Michael S. Saporito,[1] Donna Henry,[1] Melissa L. Barker-Haliski,[2] Cameron S. Metcalf,[3] Julia Tsai,[1] Albena Patroneva,[1] and Steve White.[2]

[1]Marinus Pharmaceuticals, Radnor, PA [2]University of Utah, Salt Lake City, UT [3]Neuroadjuvants, Inc. Salt Lake City, UT.

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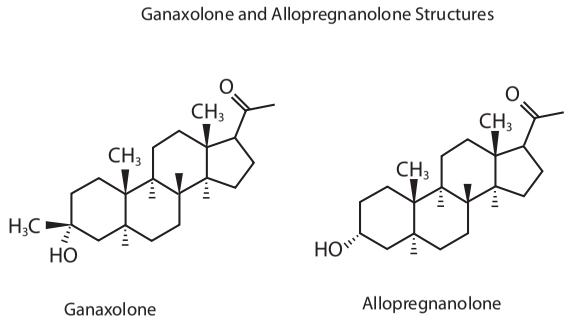
OVERVIEW

- Convulsive status epilepticus (CSE) can be modeled in experimental animals by administration of lithium and pilocarpine. Rats subjected to experimental CSE are refractory to benzodiazepine if treatment is initiated ≥ 15 min after seizure onset; thus modeling a treatment resistant form of CSE. This treatment resistant form of the disease is considered to be a clinically translatable model of the disease.
- Ganaxolone (GNX) is a CNS-selective modulator of gamma-aminobutyric acid A ($GABA_A$). It acts as a positive allosteric modulator of the $GABA_A$ receptor with anticonvulsant and anxiolytic effects **(Figure 1).**
- The current studies were conducted to evaluate the dose- and time-dependent therapeutic potential of intravenously, (IV) administered GNX for the treatment of CSE in this clinically translatable rodent model. Moreover, these studies measured behavioral seizures and survival, and complement studies that measured seizures by EEG activity.

METHODS

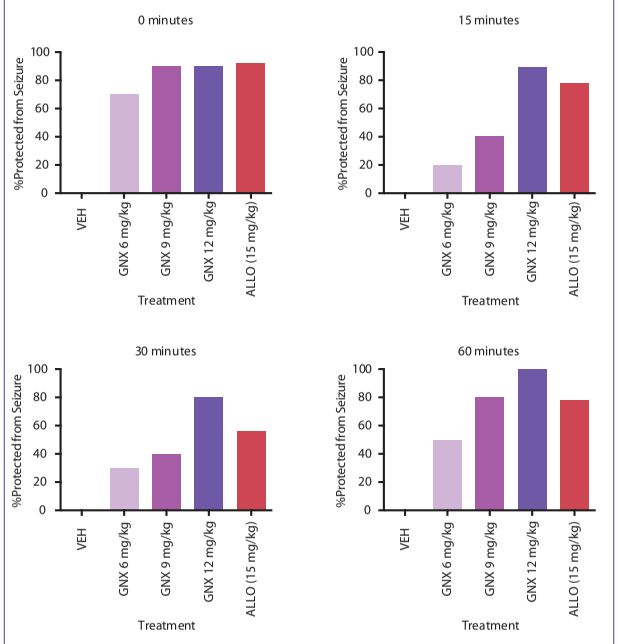
- Juvenile male Sprague-Dawley rats 5 weeks of age and weighing between 100 and 125 grams were used for these studies.
- CSE was induced by the administration of lithium chloride (127 mg/kg, intraperitoneal (i.p.), 24 hours prior to the study day) and pilocarpine (50 mg/kg, i.p.).
- Animals were monitored for seizure activity according to the Racine scale (Racine 1972). Any rat not showing convulsive seizure activity (stage 3 or greater) within 45 minutes of pilocarpine administration was excluded from the study prior to any administration of investigational compound or vehicle (VEH).
- GNX and ALLO were formulated to a concentration of 2.5 mg/mL in 30% Captisol. Dose volumes were adjusted so that animals received GNX dose-levels of 6, 9, 12 mg/kg and an ALLO dose-level of 15 mg/kg.

Figure 1. Ganaxolone is a synthetic analog of the endogenous neurosteroid GABA modulator allopregnanolone



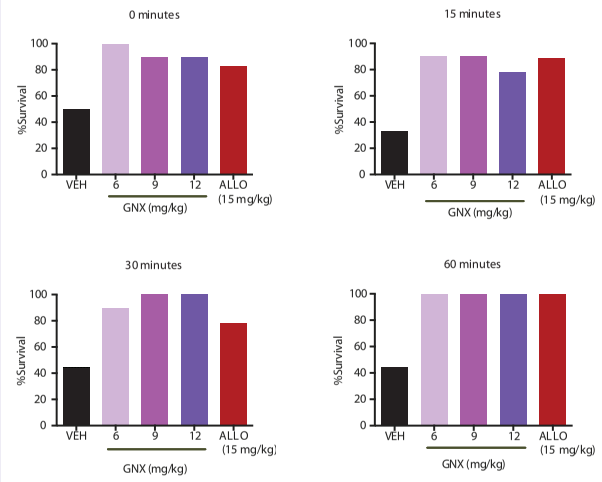
- Compounds were administered via IV administration at time of CSE onset (time 0) and 15, 30, and 60 minutes after onset.
- After compound administration, animals were observed for the presence or absence of convulsive seizures (stage 3 or greater) for an additional 2 hours. Animals that did not exhibit a convulsive seizure during that time period were considered protected **(Figure 2)**.
- All animals were retained for 24 hours following onset of CSE for assessment of weight change and survival. The number of rats that survived the treatment paradigm in each group was also recorded and compared between study groups and time points. All surviving rats were euthanized 24 hours after CSE onset **(Figure 3).**

Figure 2. Ganaxolone blocks Convulsive Status Epilepticus (CSE)



Convulsive Status Epilepticus was induced by administration of lithium followed by pilocarpine. Vehicle, ganaxolone or allopregnanolone were adminstered by IV bolus injection at time of CSE (time 0) and 15, 30 or 60 minutes after CSE.

Figure 3. Ganaxolone increases survival in rats subjected to Convulsive Status Epilepticus (CSE)



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CONCLUSIONS

- Lithium-pilocarpine administration produced a convulsive status epilepticus.
- This CSE is reported to be resistant to diazepam administration when initiated after 15 minutes and thus represents a treatment resistant form of CSE and is considered a clinically translatable model of the affliction.
- GNX IV halted CSE and produced a dose-dependent reduction in seizures associated with CSE when administered at 3 different doses over four separate time points after the first observed convulsive seizure.
- Significant activity of GNX was observed at a dose of 6 mg/kg and maximal protection at dose levels between 9 and 12 mg/kg.
- GNX IV promoted survival at rates similar to those observed with administration of allopregnanolone as measured at 24 hours after CSE onset in CSE induced rats.

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Ganaxolone Administered Intravenously P
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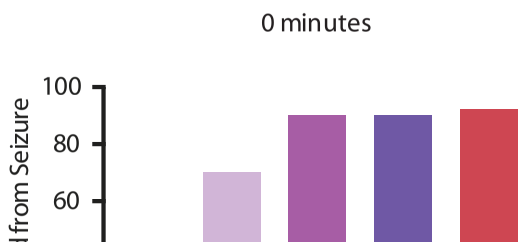

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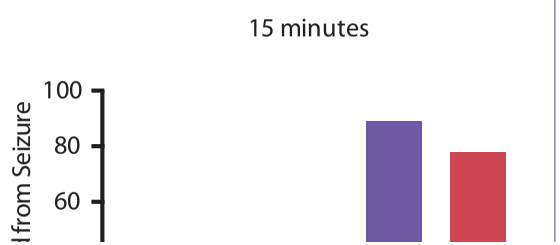

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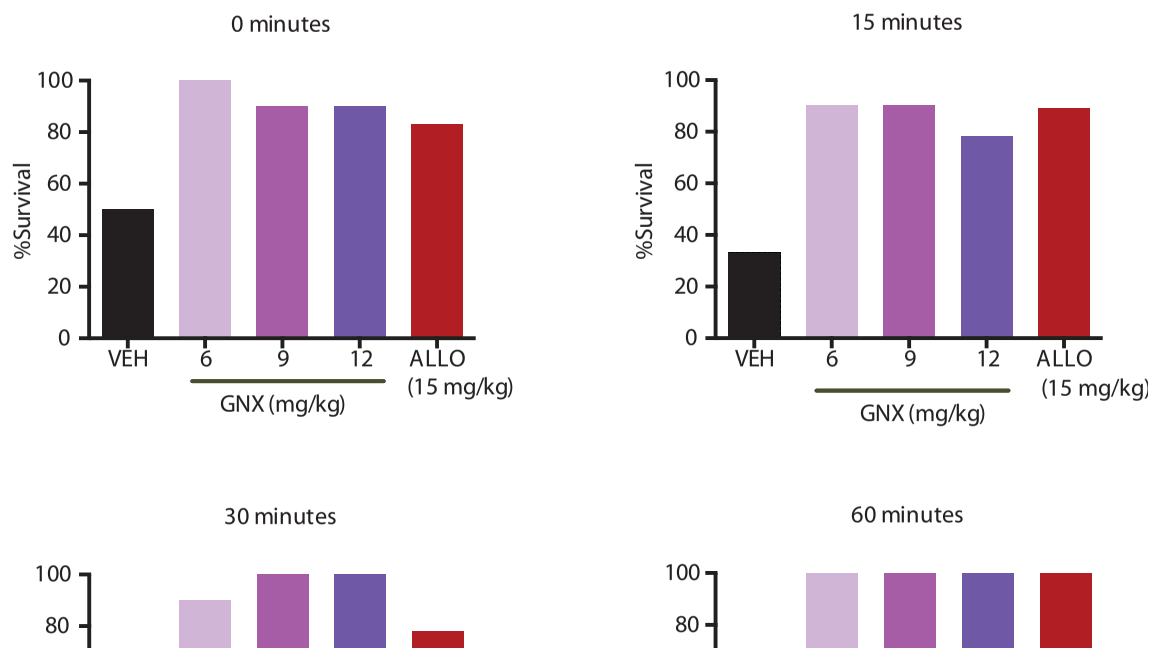

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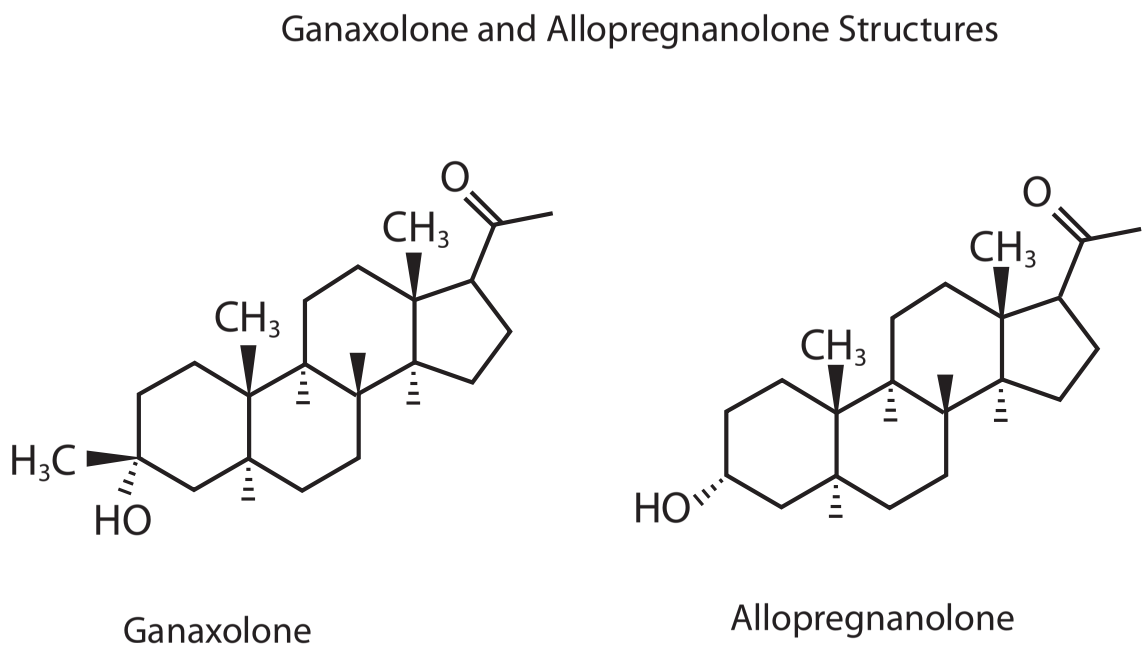

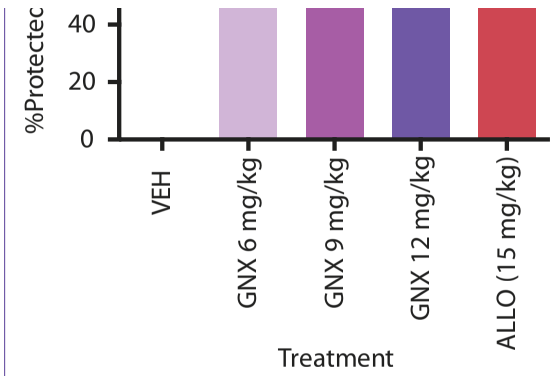

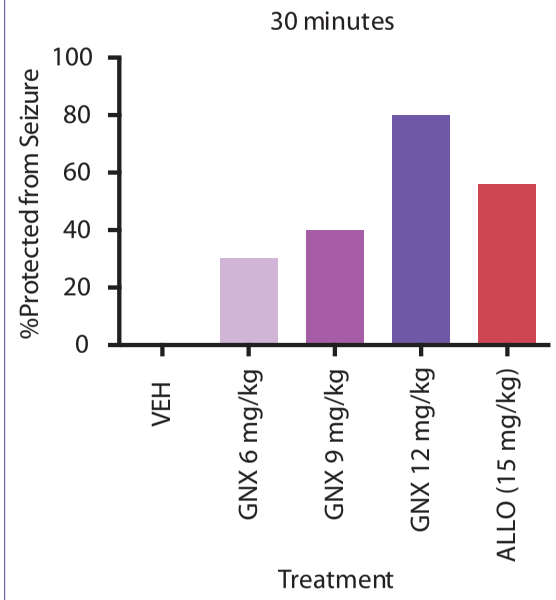

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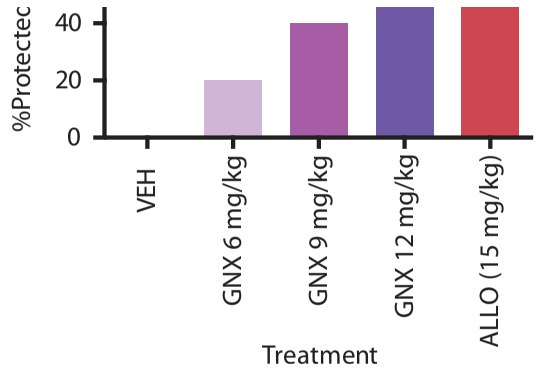

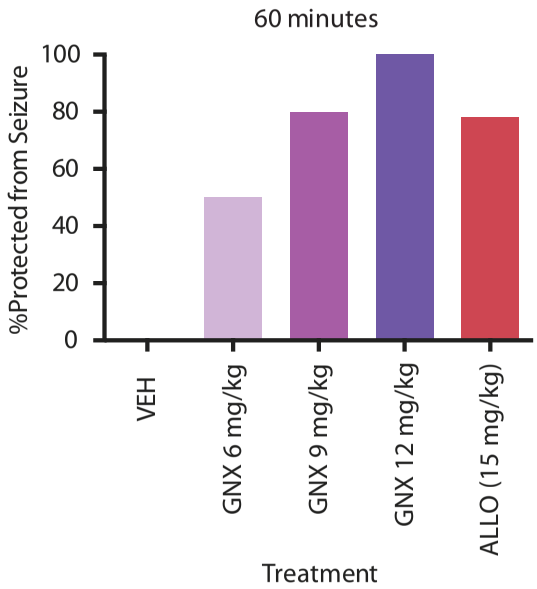

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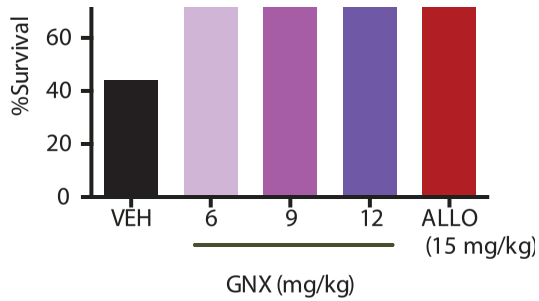

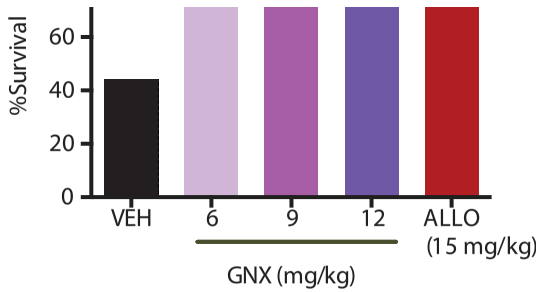

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