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Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus (P4.212)

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Abstract

Objective: These studies were designed to evaluate the potential of ganaxolone (GNX) for the treatment of status epilepticus (SE). Further studies were conducted to clarify the activities of GNX on the human progesterone (PGR) receptor. **Background:** Ganaxolone is an analog of the neurosteroid GABA modulator allopregnanolone (ALLO) and is in development for treatment of epilepsy. **Methods:** SE was induced by lithium chloride and pilocarpine administration to Sprague-Dawley rats. Seizure response was measured by electroencephalographic recordings through cortical electrodes. Compounds were administered via IV injections 15 or 60 minutes after SE onset. Seizure response was measured for 5 hrs. GNX and ALLO activities on PGR function were evaluated in HEK-293 cells containing the human PGR receptor. **Results:** Lithium-pilocarpine induced seizures were sustained for 6 hrs. This seizure activity was resistant to diazepam (10 mg/kg), but GNX (12 or 15 mg/kg; bolus IV) elicited a complete block of SE when administered 15 or 60 min after SE onset. The GNX antiepileptic activity was durable, with activity observed for at least 5 hrs. ALLO (15 mg/kg; IV) also blocked SE when administered 15 minutes after SE onset. However, the duration of antiepileptic activity was brief (<1 hr). Further, when administered 60 min after SE onset, ALLO only produced a minimal block of the seizure. GNX was devoid of any PGR activity, whereas ALLO (EC₅₀=270 nM) elicited a partial agonist response. **Conclusion:** GNX produced an anti-epileptic response in a diazepam resistant model of SE with IV injection. The GNX response was more durable and effective than ALLO. GNX is also available as an oral formulation allowing the possibility that GNX can be administered orally after SE to prevent subsequent seizure activity. Finally, data is presented showing that GNX is devoid of PGR activities, indicating that the risk of progesterone-mediated side-effects are minimal.

Disclosure: Dr. Saporito has nothing to disclose. Dr. Tsai has nothing to disclose. Dr. Patroneva has received personal compensation for activities with Marinus Pharmaceuticals, Inc.

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