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Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus (I11.003)

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Abstract

OBJECTIVE: To test IV ganaxolone in a clinically translatable rodent model of status epilepticus (SE). **BACKGROUND:** Ganaxolone (GNX) is a synthetic analog of the endogenous neurosteroid GABA modulator allopregnanolone (ALLO) and is in development for treatment of epilepsy and other neuropsychiatric conditions. **DESIGN/METHODS:** Convulsive SE (CSE) was induced by the administration of lithium chloride and pilocarpine to male Sprague-Dawley rats. GNX (6, 9, 12 mg/kg) or ALLO (15 mg/kg) were administered via IV bolus injections at the time of CSE onset (time 0) or 15, 30 or 60 minutes after CSE onset, as measured by the first observed Racine Stage 3 seizure. Animals were observed for the presence of CSE (stage 3 or greater) for an additional 2 hours after compound administration. Animals that did not exhibit a convulsive seizure during that time period were considered protected. Twenty-four hours after CSE onset, surviving rats were sacrificed and blood collected for bioanalysis. **RESULTS:** Pilocarpine administration induced CSE in all animals. Vehicle administration did not affect seizure activity and notable (~50[percent]) death was observed 24 hours after CSE onset. GNX was able to halt CSE and produced a dose-dependent reduction in CSE at all time points. The ED₅₀ when administered at the onset of CSE (0 min time point) was 2.2 mg/kg, and at 60 min after CSE onset, the ED₅₀ was 6.2 mg/kg. Near complete survival was noted 24 hours after CSE onset for ALLO and all doses of GNX evaluated. **CONCLUSIONS:** IV bolus GNX produced a dose-dependent anti-convulsant effect. Administration of GNX promoted survival with activity similar to that observed with ALLO in a rat model of CSE. GNX reduced seizure activity when administration was delayed until 30 min and up to at least 60 minutes after CSE onset, a period of SE typically refractory to benzodiazepines.

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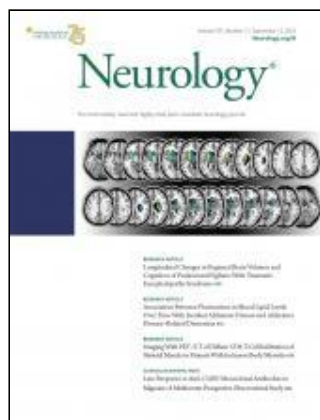
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