

Abstracts

Pharmacokinetic and Pharmacodynamic (PK/PD) Relationship of Intravenous Ganaxolone in Refractory Status Epilepticus

Abstract number : 1.136

Submission category : 3. Neurophysiology / 3B. ICU EEG

Year : 2019

Submission ID : 2421131

Source : www.aesnet.org

Presentation date : 12/7/2019 6:00:00 PM

Published date : Nov 25, 2019, 12:14 PM

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Rationale: Status epilepticus (SE) is a neurologic emergency and is associated with significant medical complications including mortality. The primary treatment objective is to rapidly stop SE preferably without the use of IV anesthetics. To date, there remains a need for an IV antiseizure medication (ASM) that produces immediate and robust SE cessation, durable seizure control, and has a good safety profile. Ganaxolone (GNX) is a synthetic neurosteroid that acts as a positive allosteric modulator of GABAA receptors. Here we present PK/PD evidence of a rapid, durable, and drug exposure-dependent clinical response to IV GNX administration in patients with refractory status epilepticus

(RSE) in a Phase 2 open-label study. Methods: Two dose levels of IV GNX were assessed in subjects with RSE (defined as a failure of at least one IV AED: fosphenytoin/phenytoin, valproate, lacosamide, or levetiracetam). Cohort-A (n=5) and Cohort-B (n=5) were dosed with 500 mg/day and 714 mg/day of continuous IV GNX, respectively, for up to four days. Infusion parameters were designed to produce initial high plasma levels of GNX for several hours followed by stepped decreases of GNX dosing. Efficacy of IV GNX was evaluated as time to RSE cessation and durability of seizure suppression over 2-4 days based on continuous EEG. Results: RSE was stopped rapidly (within minutes) upon the start of IV GNX in all subjects who failed 1-4 IV ASMs (Figure 1). This response was associated with plasma GNX levels > 500 ng/mL. In Cohort-A, plasma GNX concentrations were maintained ~500 ng/mL for approximately 4 hours with good seizure suppression. Seizure relapse or abnormal EEG activity was noted at ~5-6 hours into the infusion in four out of 5 subjects which corresponded to when GNX plasma levels decreased to < 500 ng/mL. Two subjects progressed to 3rd line IV anesthetics ~48 h into the infusion. In Cohort-B, GNX plasma levels were able to be maintained ~500 ng/mL for ~8 hrs. Good seizure control was maintained in all subjects throughout the entire dosing period even when GNX plasma levels decreased < 500 ng/mL and no subjects progressed to IV anesthetics. GNX was generally well tolerated and no new safety findings emerged. Conclusions: Rapid and maintained seizure cessation is paramount in patients with RSE in order to prevent progression to 3rd line IV anesthetics which may lead to worse clinical outcomes and increased economic burden. IV GNX demonstrated immediate seizure cessation within several minutes upon drug administration as documented on EEG in all patients dosed. The durability of pharmacological response appears to correlate with GNX exposure and ability to maintain target plasma drug levels for an adequate amount of time. These data demonstrate the potential of a new RSE treatment option and support further clinical evaluation in a larger, randomized-controlled Ph3 study. Funding: This work was supported by Marinus Pharmaceuticals.

Neurophysiology

