Treatment of Super Refractory Status Epilepticus Using Intravenous Ganaxolone in a Patient with Lennox-Gastaut Syndrome and Angelman Syndrome

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Introduction

- Super refractory status epilepticus (SRSE) is commonly associated with severe clinical sequelae.[1]
- Prolonged seizures rapidly modify neuronal activity and synaptic function. Reduced inhibitory neurotransmission mediated by synaptic $GABA_A$ receptors is proposed to be one of the underlying mechanisms of self-sustaining status epilepticus (SE) and pharmacoresistance (e.g., to benzodiazepines).[2]
- Intravenous ganaxolone (IV GNX) is an investigational drug that acts on both synaptic and extrasynaptic $GABA_A$ receptors, and therefore may have a role in the treatment of SE (including SRSE).

Objectives

- We present a case of SRSE in a pediatric patient with *UBE3A* variant of Angelman Syndrome treated with IV GNX.

Methods (Clinical Care Course)

- A 4-year-old (27 kg) girl with a history of Lennox-Gastaut and Angelman Syndrome (*UBE3A*) presented with repetitive atonic and atypical absence seizures progressing to SE with > 100 tonic or atonic seizures per day. EEG demonstrated continuous high voltage 2-2.5 Hz spike wave activity.
- Outpatient antiseizure medications included clobazam (CBZ) and valproate (VPA). VPA level was 106 µg/mL.
- The patient was first administered rectal diazepam (1 mg/kg), followed by IV lorazepam (total 0.5 mg/kg) and loading of perampanel 32 mg and ethosuximide 40 mg/kg via gastrointestinal tube.
- EEG continued to show high-voltage, disorganized sharp and slow wave activity (Figure 1). Both drugs stopped as ineffective after two days.
- The patient was transferred to the Pediatric Intensive Care Unit and received midazolam (2 mg IV) followed by IV pentobarbital at 4.5 mg/kg/hour. Anesthetic coma with burst suppression was maintained for 4.5 days.
  - ACTH at 150 unit/m^2 which failed to allow weaning pentobarbital for burst suppression and was stopped before giving IV GNX obtained by means of an emergency IND.
  - Pentobarbital was tapered down rapidly and stopped 1.5 hours prior to IV GNX infusion (Figure 2 post pentobarbital EEG before IV GNX and ACTH trial).
- Upon SE recurrence, IV GNX was given as a bolus at 0.43 mg/kg over 5 minutes followed by a continuous infusion at 1.14 mg/kg/hour for 2 hours, 0.57 mg/kg/hour for 10 hours and 0.43 mg/kg/hour thereafter continuously, followed by a 12-hour taper on day 5.
- The patient was extubated 48 hours after starting IV GNX and transitioned to oral GNX on day 5 after IV GNX tapered off. Per protocol, total daily dose of oral GNX allowed was up to 63 mg/kg/day.
- Patient was discharged on 300mg three times a day (TID) of oral GNX solution and continued her previous ASMs (VPA and CBZ).

References

1. Shorvon S, Ferlisi M. 2012 *Brain*
2. Joshi S, Kapur J. 2012 *Jasper's Basic Mechanisms of the Epilepsies*

Figure 1. EEG before Pentobarbital Coma Baseline Awake

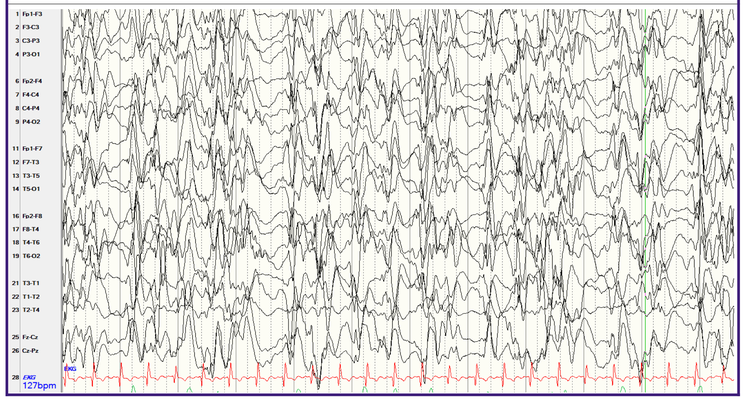


Figure 2. EEG after 5th day of ACTH and Pentobarbital 4mg/kg/hr pre-Ganaxolone

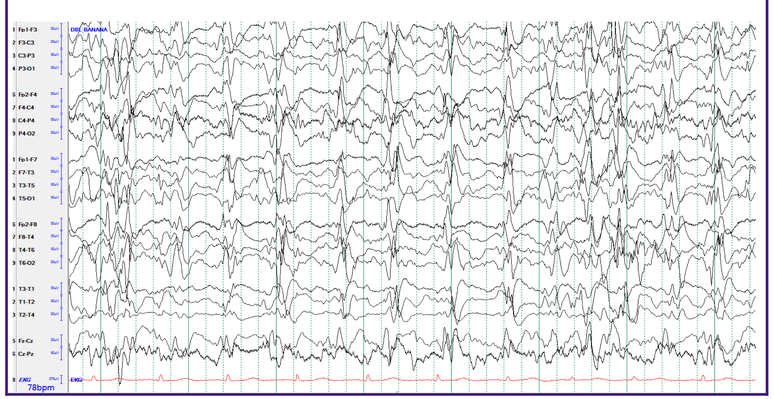


Figure 3. Asleep EEG 4 hours after Ganaxolone infusion

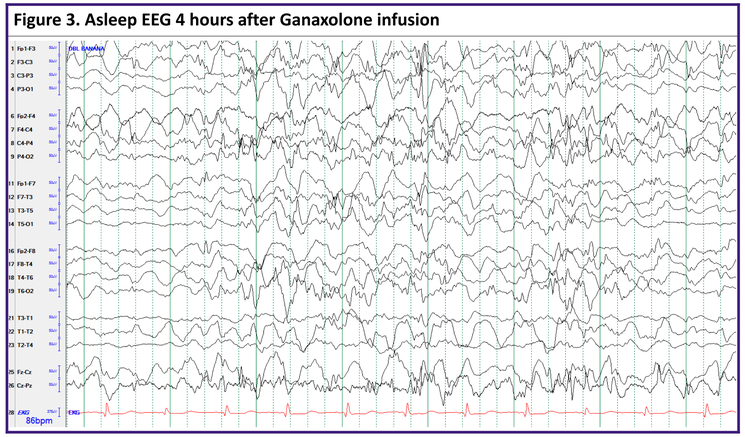
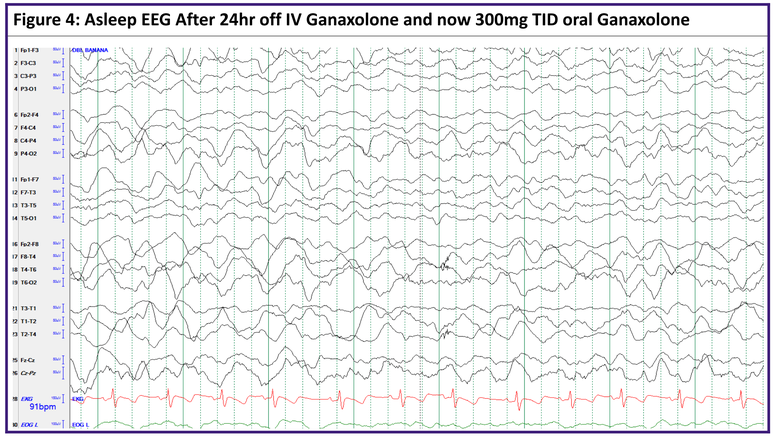


Figure 4: Asleep EEG After 24hr off IV Ganaxolone and now 300mg TID oral Ganaxolone



Results

- Rapid EEG improvements were observed to begin 10 minutes of IV GNX infusion and were seen after 4 hours (Figure 3). The EEG remained improved with no SE recurrence over the 5-day IV GNX infusion. The IV GNX taper and transition to oral GNX was successful in preventing relapse of SE and the patient was discharged 4 days later (Figure 4). At the 4-week, post-discharge clinic visit, the patient was reported to have had no clinical seizures and has returned to her prior functional baseline. EEG stability remains now 6 months post-treatment initiation on oral ganaxolone, and previous ASMs (VPA and CBZ).

Conclusions

- **Administration of IV GNX was effective in treating SRSE in this 4-year-old patient with Angelman Syndrome, perhaps especially with more refractive *UBE3A* variant.**
- **Patient successfully converted to oral GNX highlighting the potential to further evaluate the effects of IV to oral GNX transition for the treatment of SE.**
- **Additional study of IV GNX in SRSE is warranted.**