

Pediatric super-refractory status epilepticus treated with allopregnanolone

Eileen Broomall MD¹, JoAnne E. Natale MD², Michele Grimason APN¹, Joshua Goldstein MD¹,
Craig M. Smith MD¹, Celia Chang MD³, Stephen Kaness MD PhD⁴, Michael A. Rogawski MD
PhD³, and Mark S. Wainwright MD PhD¹

¹Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Ann & Robert H. Lurie
Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago
IL, Departments of ²Pediatrics and ³Neurology, University of California, Davis School of
Medicine, Sacramento, CA, ⁴Sage Therapeutics, Cambridge MA

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Corresponding author:

Mark S. Wainwright MD PhD
Division of Neurology no. 51
Ann & Robert H. Lurie Children's Hospital of Chicago
225 E. Chicago Avenue, Chicago, IL 60611
Email: m-wainwright@northwestern.edu

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ABSTRACT

Super-refractory status epilepticus is a life-threatening condition. Resistance to benzodiazepine and barbiturate treatment for this disorder is thought to be due to internalization of synaptic GABA_A receptors, and withdrawal of benzodiazepines and barbiturates during treatment often triggers seizure recurrence. The neurosteroid allopregnanolone acts as a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors. Here we describe the use of allopregnanolone in two pediatric patients with super-refractory status epilepticus. This treatment allowed the general anesthetic infusions to be weaned with resolution of status epilepticus. This is the first report of allopregnanolone use to treat status epilepticus in children.

Introduction

Super-refractory status epilepticus (SRSE), or seizures continuing for longer than 24 hours despite general anesthesia, is a neurologic emergency with high morbidity and mortality.¹ SRSE is often managed with benzodiazepines and barbiturates or general anesthesia, but treatment is limited by side effects and pharmacoresistance.²

Resistance to benzodiazepines is thought to be due to internalization of synaptic, but not extrasynaptic, GABA_A receptors.³ The neurosteroid allopregnanolone is a metabolite of progesterone, and has been proposed as a novel treatment for SE.^{4,5} Allopregnanolone acts as a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors, and terminates benzodiazepine-refractory SE in animal models.⁶ The potentiating effect of allopregnanolone on extrasynaptic GABA_A receptors enhances tonic inhibition.⁷

We previously reported the treatment of new onset SRSE with allopregnanolone in a 23-year-old man.⁸ Here we describe the first use of allopregnanolone to treat SRSE in two children.

Patients and Methods

Case 1 is a healthy 11 year-old girl who presented to another hospital (day zero in Fig. 1A) in SE. She was positive for anti-thyroglobulin, anti-Gad-65 and anti-microsomal antibodies. She was treated with 6 days of intravenous (IV) methylprednisolone, plasmapheresis (5 exchanges over 5 days), IVIG (2 g/kg), and rituximab (375 mg/m²). Convulsive and non-convulsive seizures were treated with multiple IV antiseizure agents, including continuous infusions of pentobarbital and propofol. She received maintenance doses of phenytoin, levetiracetam and phenobarbital. Two attempts to reduce burst suppression resulted in breakthrough seizures. On hospital day (HD) 16 she was transferred to our hospital. At the time

of transfer she was being treated with four antiseizure agents and in pentobarbital-induced burst suppression.

Treatment for SRSE was continued with a combination of the ketogenic diet, additional IV methylprednisolone and continued pentobarbital (day 16, Fig. 1A). Subsequent other therapies included magnesium infusion, mild hypothermia, ketamine and repeated immunotherapy with IVIG, steroids, cyclophosphamide and rituximab (Fig. 1A). Continuous EEG (cEEG) monitoring was used to confirm the presence of burst suppression, and to monitor the response to reduction in the rate of pentobarbital infusion. On HDs 19, 21, 37, and 45 (Fig. 1A) the pentobarbital rate was slowly reduced in the presence of midazolam and other agents including the ketogenic diet, and felbamate. A felbamate level on HD 41 was 19.0 µg/ml (normal range 30-50). β-OH-butyrate levels on HD 27 and 69 were 1.49 and 3.17 mmol/L (range 0.04 – 0.18).

Despite appropriate drug levels and doses [felbamate (60 mg/kg/d), phenobarbital (levels 44-90 µg/mL), phenytoin (level 16.8 µg/mL), levetiracetam (dose 40 mg/kg/d), and ketogenic diet (ratio of 4.5:1)] multiple attempts to wean the pentobarbital resulted in recurrence of electrographic and clinical seizures. While weaning pentobarbital, prolonged video EEG monitoring was implemented in epochs of 12-24 hours. A mixture of primarily clinically apparent, as well as rare electrographic-only seizures were detected. These seizures were associated with a rhythmic theta-alpha focal discharge with diffuse bilateral spread. Clinical seizures consisted of a mixture of staring, eye fluttering, eye deviation, and rare focal motor convulsions. Each seizure lasted from 2 to 5 min and resolved spontaneously. Seizures increased in frequency up to 10 per hour before weaning was stopped and burst-suppression re-initiated.

On HD 52, after nearly continuous infusions of pentobarbital, midazolam and ketamine, we received FDA approval for the emergency use of allopregnanolone (3 α -hydroxy-5 α -pregnan-20-one) IV solution [0.5 mg/mL in 0.9% NaCl with 6% Captisol (Ligand Pharmaceuticals, La Jolla, CA), manufactured at the University of California, Davis]. The goal of therapy was to enable weaning from pentobarbital. Allopregnanolone was infused over 5 days (Fig. 1B), after which pentobarbital sedation was weaned and discontinued. There were no hemodynamic or metabolic derangements referable to the allopregnanolone infusion. SE did not recur after the allopregnanolone infusion, and over the remainder of the hospitalization she only had intermittent seizures 1-2 times per week that were either self-limited or responded to intranasal midazolam. She was transferred for inpatient rehabilitation, regained her ability to walk, and is now back at home, continuing to show cognitive improvement, reading, doing arithmetic and playing the piano.

Patient 2

The second patient is a 2 year-old girl with speech delay and epilepsy diagnosed 2 months earlier who presented with SE associated with a febrile illness. No infectious agents were identified. Convulsive and non-convulsive seizures were treated with increasing doses of IV levetiracetam and phenobarbital with cEEG monitoring. On HD3, high-dose midazolam and propofol infusions were added. Seizure frequency was not affected by a trial of pyridoxine followed by 5 days of IV methylprednisolone while continuing maintenance dosing of phenobarbital (10 mg/kg/day; plasma concentration 45 to >80 μ g/mL), midazolam (0.3 mg/kg/hr), and levetiracetam (105 mg/kg/day). Pentobarbital infusion produced sustained burst

suppression on HD9. Two attempts to wean midazolam during pentobarbital treatment while continuing all other medications resulted electrographic seizure recurrence. During the pentobarbital infusion, she developed hypotension requiring vasopressors, an ileus, and had persistent urinary retention.

The majority of seizures were electrographic and varied in duration from seconds to minutes. When midazolam or pentobarbital infusion rates were decreased seizures occurred up to 16 times per hour. Many arose from the right temporal region, starting in beta frequencies, evolving to slower frequencies and ending with around 3 per second sharps. None of these seizures had a clinical correlation. Other electrographic seizures started in the right frontal region with 10-12 Hz activity, followed by an increase in amplitude and decrease in frequency over the duration of the seizure which occasionally involved the entire right hemisphere. Left temporal seizures were characterized by an abrupt onset of rhythmic 2-3 Hz waveforms occurring maximally over the left mid-temporal region.

Emergency use of allopregnanolone was approved by the FDA on HD15. The goal of therapy was to enable weaning from pentobarbital and midazolam infusions, with secondary effects of discontinuing vasopressor support and to restore bowel function. Allopregnanolone was infused according to the protocol in Fig 1B, and tapered off between hours 96 and 120 as a precaution for seizure recurrence. The midazolam infusion was titrated off over the first 24 hours, followed by tapering pentobarbital from 5.0 to 0.5mg/kg/hr over 72 hours. Twice daily rufinamide dosing started at hour 48, and enteral lorazepam was started at hour 96. An electrographic seizure occurred after the allopregnanolone infusion ended, and pentobarbital was adjusted to 1 mg/kg/hr with suppression of all seizures. The patient continued on lower doses of pentobarbital (0.5-1 mg/kg/hr) for 12 additional days. As the midazolam and pentobarbital were

decreasing, the patient's blood pressure recovered, vasopressors were discontinued and the ileus resolved. The child was transferred to inpatient rehabilitation, regained milestones, and is now able to walk and speak. The etiology for her seizures remains unknown.

Allopregnanolone Dosing and Toxicity Monitoring

Both patients were treated with a continuous infusion of allopregnanolone using a similar dosing schedule combined with physiologic and laboratory monitoring (Fig. 1B). The target infusion rate of 86 $\mu\text{g}/\text{kg}/\text{hr}$ was determined by pharmacokinetic modeling to result in a steady-state level of 150 nM.⁹ Because allopregnanolone has not previously been administered to children the infusion rate was increased gradually over the first 24 h. Then, to achieve the target rapidly, a single bolus of 86 $\mu\text{g}/\text{kg}$ was administered at 24 h. In hindsight this was not needed given the peak serum level achieved (404.7 nmol) at hour 28. For patient 1 the same infusion rate was continued until hour 120, when it was discontinued. For patient 2, the infusion was tapered from hour 96-120. In both cases, the objective of treatment was to enable the withdrawal of pentobarbital and/or midazolam without the recurrence of seizures. There were no adverse drug effects detected by any of the laboratory tests used (data not shown).

In patient 1, plasma levels above the goal 150 nM were achieved after the bolus at 24 h (Fig. 2), and remained above this level for the duration of treatment. In patient 2, plasma levels were slightly below this target yet achieved the same therapeutic goal.

Discussion

Here we report the first two uses of allopregnanolone infusion in the treatment of pediatric SRSE. Treatment allowed the withdrawal of general anesthetic infusions (pentobarbital, or pentobarbital and midazolam), which had been required to prevent the

recurrence of clinical and electrographic seizures. Physiologic and laboratory monitoring showed no adverse effects of drug treatment. Withdrawal of other antiseizure agents also resulted in resolution of other complications of their use (hypotension, ileus, urinary retention). Importantly in both cases, there had been multiple unsuccessful attempts to wean barbiturates or benzodiazepines and other antiseizure drugs. Whether allopregnanolone was instrumental in achieving this response or the response was due to the cumulative effect of the preceding and concomitant treatments will require further study.

Mortality in RSE, SE resistant to two antiseizure agents, can be as high as 35%. Among survivors, there are high rates of subsequent epilepsy and severe neurologic impairment.¹

Guidelines for the treatment of RSE recommend that following appropriate treatment with benzodiazepines and antiseizure medications such as valproate, phenytoin or phenobarbital, practitioners should use continuous infusions of anticonvulsant general anesthetics such as midazolam, propofol or pentobarbital.^{10, 11} This was the approach followed in both these cases.

Before treatment with allopregnanolone we used a range of high-dose antiseizure, immune modulating, and metabolic therapies. This is consistent with common practices in the management of RSE.¹ A recent survey showed good agreement on initial treatment of SE, but patient age does appear to impact medication decisions.¹⁰ Variable combinations of general anesthetic agents, immunomodulation, epilepsy surgery, electroconvulsive therapy, hypothermia and ketogenic diet as treatment for SRSE have all been reported, and our management approach reflects the lack of data on an optimal treatment for RSE.¹¹

The dose of allopregnanolone we used was empirical and based on the maximum levels permitted by the FDA. Brain levels have been found to be comparable to plasma concentrations

(unpublished observations). If this was true for our patients, then the concentrations available at brain GABA_A receptors were likely several-fold the effective concentrations for positive modulation of these receptors.¹² The mean steady state plasma level in patient 2 (86 nm) between hours 39.5 and 95.5 of allopregnanolone infusion was lower than the goal of 150 nm. This is likely due to greater drug clearance observed at age 2 years compared to adults.¹³

There is precedent for the use of neurosteroids to treat epilepsy. Progesterone, the precursor to allopregnanolone, has shown efficacy in the treatment of catamenial epilepsy.⁴ Ganaxolone, a synthetic analog of allopregnanolone, has been studied in clinical trials for both refractory focal epilepsy and infantile spasms, with preliminary evidence of clinical benefit.^{14,15} A clinical trial of allopregnanolone is investigating its effect in traumatic brain injury.¹⁶ By acting on extrasynaptic GABA_A receptors allopregnanolone has the potential to treat RSE, where treatment resistance is believed to be due to internalization and inactivity of synaptic GABA_A receptors. Neurosteroids, including allopregnanolone, are a promising treatment for epilepsy and RSE that may overcome resistance to benzodiazepines and barbiturates. In addition, they may facilitate the withdrawal of these agents by preventing rebound seizures, a key problem in the treatment of SRSE.

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Potential Conflicts of Interest

Dr. Natale is a Co-Investigator in a Department of Defense-sponsored clinical trial of allopregnanolone in traumatic brain injury. She serves as an unpaid scientific consultant to Sage Therapeutics, and has no equity in the company. Dr. Kaner is an employee of Sage Therapeutics and has an equity holding in the company. Dr. Rogawski is the Principal Investigator in a Department of Defense-sponsored clinical trial of allopregnanolone in traumatic brain injury. He is a paid consultant to Sage Therapeutics and holds equity in the company. Dr. Wainwright serves as an unpaid scientific consultant to Sage Therapeutics, has received no payment from and has no equity in the company. The other authors have no conflicts of interest to disclose. The allopregnanolone intravenous formulation was manufactured by the University of California, Davis and was provided free of charge to the treating physicians. The material was not provided

by Sage Therapeutics and was not part of a Sage-sponsored clinical trial. Sage Therapeutics is currently developing the formulation of allopregnanolone used in this report for treatment of adults with SRSE and is the sponsor of a clinical trial of this drug in adults with SRSE. None of the authors is a patent holder for relevant inventions.

Authorship

MSW and EB conceived the project, collected data and drafted the manuscript. JAN conceived the project, collected data and revised the drafted manuscript. MG, CMS and JG revised the drafted manuscript. CC collected data and revised the drafted manuscript. SK and MAR collected and analyzed data and revised the drafted manuscript. All authors contributed to the current version of the paper including either conception, data analysis, or editing.

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Figure Legends

Figure 1. (A) Antiseizure and immunomodulatory medications used for patient 1 by day of hospitalization. Day 0 = admission date; HYP mild hypothermia; IVIG intravenous immune globulin; CPM cyclophosphamide; RTX rituximab; DEX dexamethasone; MTP methylprednisolone; FBM felbamate; CLB clobazam; LVT levetiracetam; ALLO allopregnanolone; LRZ lorazepam; PHT phenytoin; KTM ketamine; PB phenobarbital; MDZ midazolam; MG Magnesium; TPM topiramate; KGD ketogenic diet; PTB pentobarbital; LCS lacosamide; PRO propofol; PLEX plasmapheresis (B) Summary of allopregnanolone infusion protocol used for patients 1 and 2 with hemodynamic and laboratory monitoring.

Figure 2. Allopregnanolone plasma concentrations in both patients during allopregnanolone infusion.

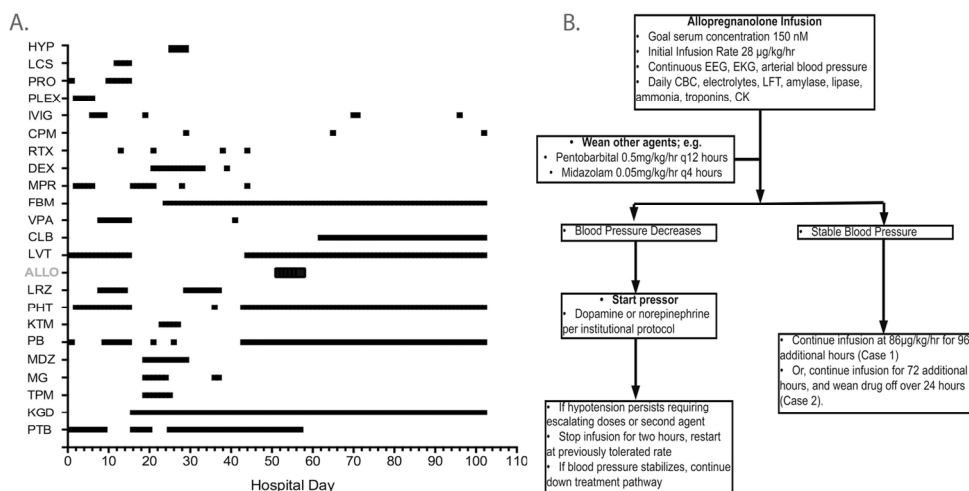


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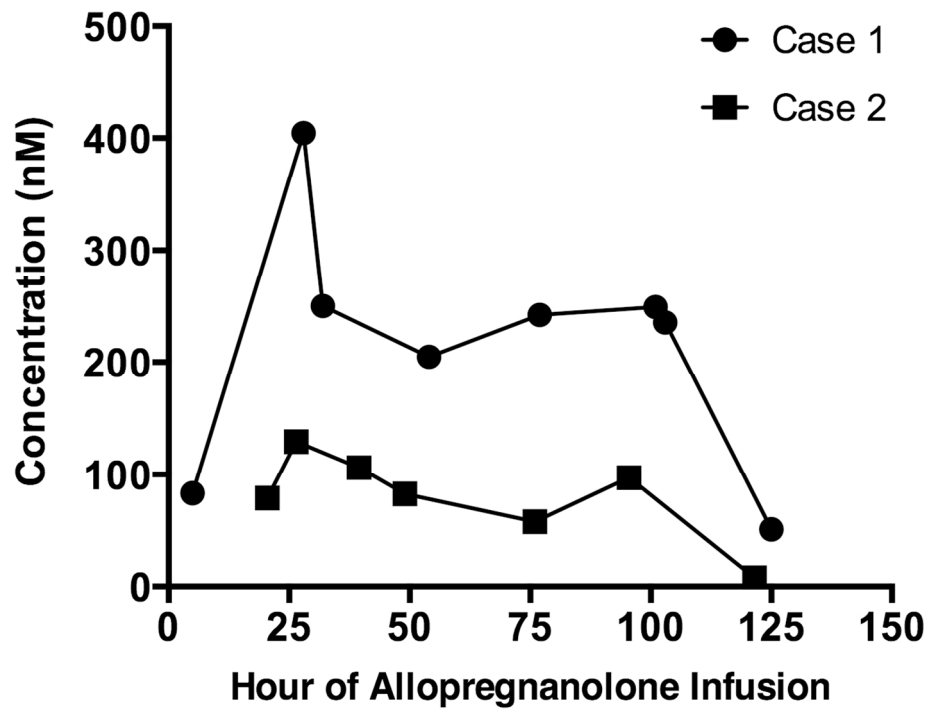


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