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BRIEF COMMUNICATION

First-in-man allopregnanolone use in super-refractory status epilepticus

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Abstract

Super-refractory status epilepticus (SRSE) is associated with high morbidity and mortality. Treatment of SRSE is complicated by progressive cortical hyperexcitability believed to result in part from synaptic GABA receptor internalization and desensitization. Allopregnanolone, a neurosteroid that positively modulates synaptic and extrasynaptic $GABA_A$ receptors, has been proposed as a novel treatment. We describe the first two patients with SRSE who were each successfully treated with a 120-h continuous infusion of allopregnanolone. Both patients recovered from prolonged SRSE with good cognitive outcomes.

Introduction

Super-refractory status epilepticus occurs when therapeutic coma fails to control seizures in status epilepticus.[1,2] The efficacy of therapeutic coma has not been well established and it may be associated with increased hospitalization length, cost of care, and in some cases even mortality.[3–5] When prolonged therapeutic coma is used, tachyphylaxis to anesthetics that act via $GABA_A$ receptors, such as barbiturates and benzodiazepines, is frequently observed. Both continuous seizure activity and GABAergic drugs cause synaptic $GABA_A$ receptor internalization and desensitization leading to cortical hyperexcitability.[6–8] Extrasynaptic $GABA_A$ receptors are not internalized and could be targeted during treatment of SRSE.[9] Development of treatments for status epilepticus has largely relied on application of conventional anticonvulsant and anesthetic agents without regard to mechanistic considerations. Allopregnanolone, an endogenous metabolite of progesterone, is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors making it an attractive agent for use in the treatment of SRSE.[10] Studies in animal models support the potential of allopregnanolone in the treatment of refractory status epilepticus.[9] Here, we describe the first-in-man experience with allopregnanolone in the treatment of SRSE, providing key translational proof of principle to support its clinical development as a novel therapeutic agent. Two adult patients with SRSE in therapeutic coma who had persistent seizures with repeated attempts to wean anesthetic agents were successfully weaned when allopregnanolone was added to their treatment regimen. Dose selection was based on pharmacokinetic modeling,[11] with a target plasma allopregnanolone concentration of 150 nmol/L, the physiological maximum concentration seen in pregnant women and the maximum concentration permitted at the time by the Food and Drug Administration (FDA).

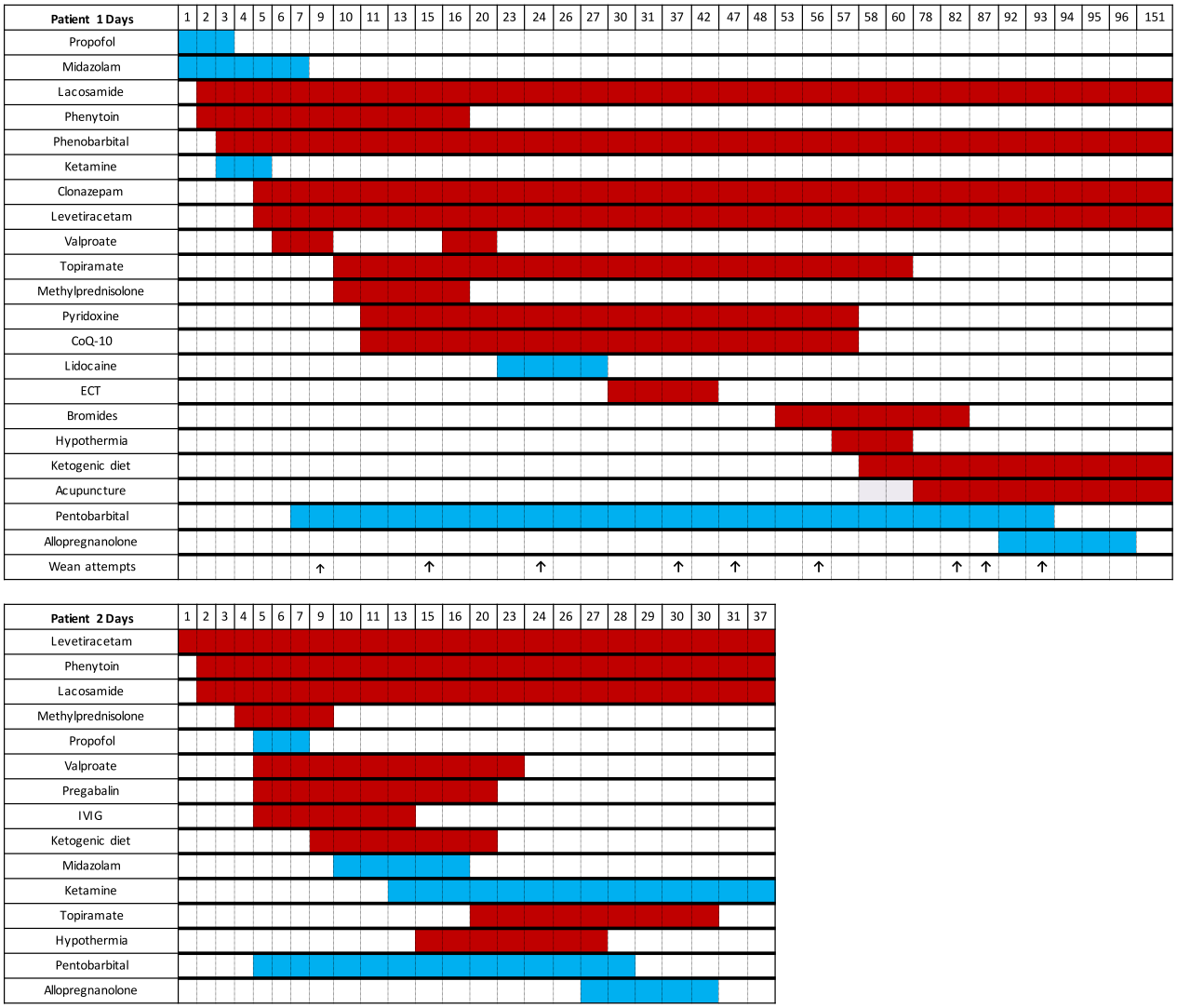

Figure 1. Graphical representation of most significant interventions during hospitalization. The color shadings correspond to the days of exposure. The blue shading represents continuous infusion and the red shading represents interval dosing. Arrows signify formal wean initiations.

Subsequent successful use of allopregnanolone in pediatric patients has been reported.[12]

Patients and Methods

Patient 1 is a 23-year-old man who presented with generalized convulsions and myoclonus, preceded by a week of malaise and headache. The seizures were medically refractory and intravenous general anesthesia was instituted. The patient underwent eight unsuccessful attempts to discontinue pentobarbital while multiple antiepileptic and immunologic interventions were administered (see Fig. 1). No clear cause for SRSE was identified. The FDA approved an emergency IND (116214) permitting allopregnanolone infusion as a bridge therapy to wean the patient off pentobarbital. Allopregnanolone (3α-hydroxy-5α-pregnan-20-one) intravenous solution, containing 6% hydroxypropyl-β-cyclodextrin (Trappsol; Cyclodextrin Technologies Development, Alachua, FL) in 0.9% sodium chloride injection, USP, was manufactured by the Good Manufacturing Products Laboratory at the University of California, Davis. The patient received 670.8 mg of allopregnanolone at 86 μg/kg/h (5.6 mg/h) by continuous infusion. During this 5-day infusion, the patient was successfully weaned from pentobarbital without recurrence of SE (Fig. 2). He remains cognitively intact and seizure free at 3-year follow up. Preliminary description of this case was reported in abstract form.[13]

Patient 2 is a 28 year-old man who was admitted for confusion. One week later, he developed SRSE of unknown

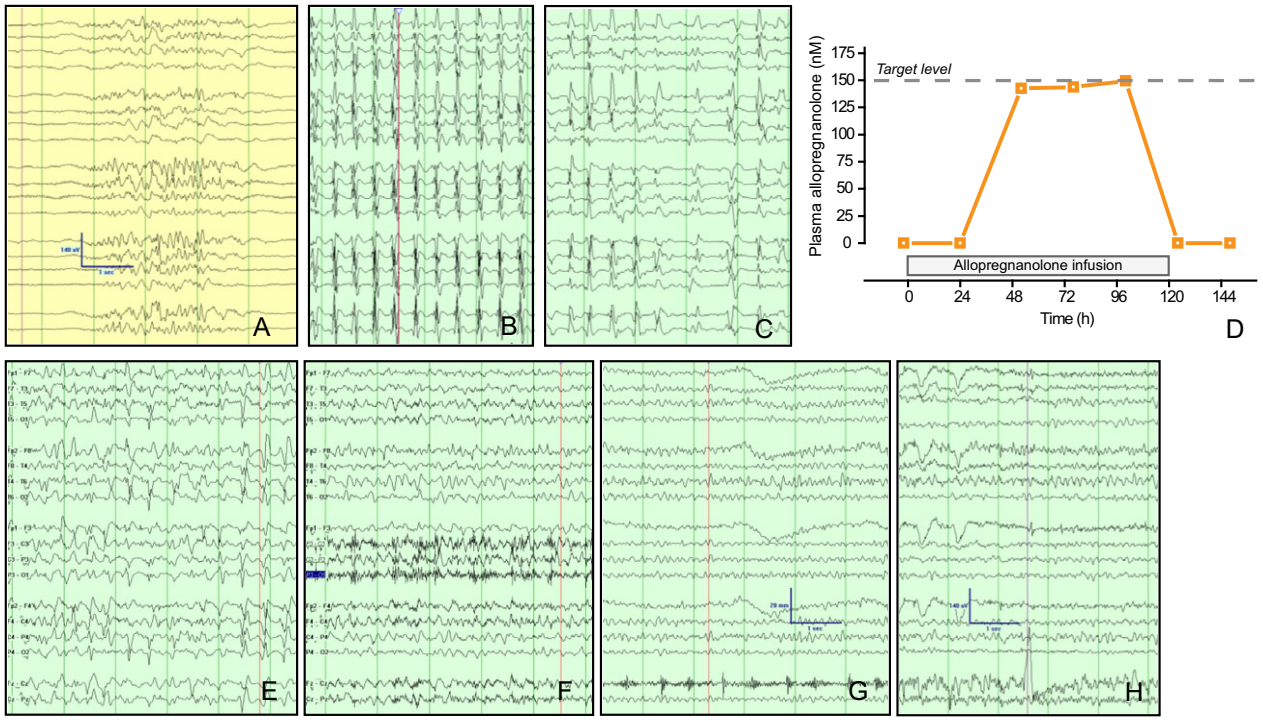

Figure 2. EEG recordings from Patient 1 illustrate cortical hyperexcitability after developing tolerance to barbiturates. Panel A, burst suppression pattern achieved with 1.5 mg/kg/h of pentobarbital. Panel B, EEG pattern 30 days later while on 1.5 mg/kg/h pentobarbital infusion. Panel C, EEG pattern 80 days later on 6 mg/kg/h of pentobarbital. Panel D, arterial plasma allopregnanolone levels. Plasma was analyzed 2 h prior to the start of the infusion and then at 24, 52, 76, 100, 124, and 148 h. Panels E-H demonstrate progressive normalization of the EEG at 12, 24, 36, and 48 h after discontinuation of pentobarbital while on allopregnanolone infusion. Scale bars, 140 μV, 1 sec.

cause. Status epilepticus recurred with each of three attempts to wean the patient from pentobarbital. An emergency IND (120079) was obtained and allopregnanolone was administered over 5 days as bridge therapy during the successful wean from pentobarbital. The formulation in this case contained sulfobutylether-β-cyclodextrin (Captisol; CyDex Pharmaceuticals, Division of Ligand Pharmaceuticals, Lenexa, KS). At 3-year follow up, the patient demonstrated good cognitive function with occasional breakthrough seizures despite five antiseizure medications.

Discussion

These cases demonstrate that allopregnanolone can be safely administered in critically ill patients with SRSE and may be an effective approach to wean patients from general anesthetics. Barbiturate-induced therapeutic coma is recognized to have high morbidity due to systemic side effects and may be associated with increased mortality.[3,14] Tolerance and physical dependence after prolonged exposure to barbiturates and benzodiazepines results in a need for increased doses of these toxic drugs and there is a high propensity for seizures recurrence.[15] Allopregnanolone has limited systemic side effects,[16] and is highly effective in terminating ongoing status epilepticus in animal models.[9,17] These cases provided critical translational evidence of the activity of allopregnanolone in patients with SRSE, that led directly to the treatment of additional patients, including two children.[12] Cumulatively, these patient experiences guided the development of the first placebo-controlled Phase III study of a novel drug for SRSE that is currently ongoing.[18,19]

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Author Contributions

HV: Conceived the project, obtained IND and IRB approvals, collected data, wrote the manuscript. WB: Conceived the project, obtained IND and IRB approvals, collected data, edited the manuscript. ESR: Conceived the project, analyzed and interpreted data, edited the manuscript. JR: Contributed to the project, sponsored the IRB approval, edited the manuscript. AH: Conceived the

project, obtained IND and IRB approvals, collected data, edited the manuscript. KR: Collected and analyzed data, edited the manuscript. MAR: Conceived the project, provided access to IND and contributed intravenous allopregnanolone solution, wrote the manuscript. AJC: Conceived, coordinated and facilitated the project, edited and revised the manuscript.

Conflicts of Interest

HV: Served as a consultant to Sage Therapeutics. WB: None. ESR: Employed by Massachusetts General Hospital, which has an Institutional Clinical Research Sponsor Agreement with Sage Therapeutics, and receives consulting fees from GLG Consulting and Guidepoint Global Consultants on the topic of status epilepticus. JR: None. AH: Serves as a consultant to UCB Pharmaceuticals, Jazz pharmaceuticals, Biogen Idec, Sage Therapeutics, Marinus Pharmaceuticals, and Turing Pharmaceuticals. Receives royalties from Demos Medical Publishing. Editor at Wolters Kluwer. KR: Was employed by Sage Therapeutics during the time the project was conceived. MAR: Previously served as a consultant to Sage Therapeutics, which has obtained a commercialization license from the Regents of the University of California and the University of California, Davis. AJC: Serves as a consultant to Sage Therapeutics.

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