

CONFERENCE COVERAGE

Allopregnanolone May Treat Superrefractory Status Epilepticus Effectively*Neurology Reviews*. 2016 December;24(12):36

BALTIMORE—The investigational agent allopregnanolone may effectively treat superrefractory status epilepticus, according to research presented at the 141st Annual Meeting of the American Neurological Association. The drug appears to end seizures in patients for whom all other treatment options have failed. Unlike other current treatments, allopregnanolone does not entail risks of respiratory depression or hypotension.

“As we gain more experience with [allopregnanolone] in these superrefractory patients, I’m hoping that there’s going to be opportunities for using it in different settings in status [epilepticus],” said Michael Rogawski, MD, PhD, Professor of Neurology and Pharmacology at the University of California, Davis. The drug may be appropriate for refractory status epilepticus, for example. Dr. Rogawski and his colleagues are studying allopregnanolone in combination with diazepam and midazolam in models of status epilepticus, and results so far indicate that the medications work well in combination. “Our hope is that allopregnanolone could be used earlier on in status [epilepticus], potentially as a first-line agent, either as a replacement for benzodiazepines ... or in combination with the benzodiazepine.”

An Analog of an Anesthetic

Michael Rogawski, MD, PhD

Allopregnanolone is an analog of alphaxalone, a surgical anesthetic used commonly in the 1970s. Alphaxalone was withdrawn from the market because it was difficult and dangerous to formulate. In the mid-1980s, researchers recognized that allopregnanolone, which has a similar chemical structure to that of alphaxalone, was endogenous to the body. Allopregnanolone is a positive allosteric modulator of GABA_A receptors, and the body produces it by metabolism of progesterone.

Unlike benzodiazepines, neurosteroids such as allopregnanolone act not only on synaptic GABA_A receptors, but also on extrasynaptic GABA_A receptors, which bias neurons to be less excitable. Studies in seizure models and epilepsy models have indicated that neurosteroids are effective antiseizure agents. Dr. Rogawski and colleagues found that allopregnanolone effectively treats various models of status epilepticus.

Like other neurosteroids, allopregnanolone is highly lipophilic and easily crosses the blood–brain barrier. After intramuscular administration to mice, levels of allopregnanolone in the brain were much higher than levels in the plasma.

Results in Human Patients

After prolonged seizure activity, synaptic GABA_A receptors are internalized and become unavailable as targets for benzodiazepines. Because allopregnanolone acts on extrasynaptic GABA_A receptors, Dr. Rogawski and colleagues hypothesized that the medicine might be more effective than benzodiazepines in benzodiazepine-refractory status epilepticus. They found that when diazepam or allopregnanolone was administered to rats at 10 minutes after the onset of status epilepticus, the seizures stopped. When the drugs were administered at 40 minutes after the onset of status epilepticus, diazepam was ineffective, but allopregnanolone stopped the seizures.

To evaluate allopregnanolone in humans, Dr. Rogawski and colleagues created an IV formulation of the therapy by solubilizing it with cyclodextrins. They then gained FDA approval for clinical studies. When epilepsy centers caring for patients with superrefractory status epilepticus contacted Dr. Rogawski, they were able to obtain emergency FDA authorization to treat these patients with allopregnanolone supplied by Dr. Rogawski.

One patient was a 23-year-old man receiving barbiturate anesthesia. Every time his doctors withdrew the barbiturate anesthesia, his seizures recurred. After the patient received allopregnanolone, he was able to be weaned from the barbiturates without rebound seizure activity. The drug produced similar results in a 28-year-old man, an 11-year-old girl, and a 2-year-old girl. The investigators did not identify any treatment-related adverse events.

These patients were all critically ill, and withdrawal of life support was being considered, said Dr. Rogawski. Some did not tolerate the barbiturate anesthesia, including the 2-year-old girl, who was a patient at the UC Davis Medical Center. She developed hypotension, an ileus, and persistent urinary retention. Following allopregnanolone treatment, the dose of pentobarbital was reduced so that her blood pressure recovered and the ileus resolved. In this and the other cases, allopregnanolone seemed to be life-saving, but its efficacy will need to be validated in controlled studies, said Dr. Rogawski.

Allopregnanolone has been licensed to SAGE Therapeutics, which is studying the drug under the name SAGE-547.

—Erik Greb

Suggested Reading

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