Advances in Epilepsy in 2013 for the Neurohospitalist

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Introduction

After consulting on patients with cerebrovascular disease, addressing the problem of seizures and status epilepticus is one of the most important roles of the neurohospitalist.^{1,2} Status epilepticus refractory to benzodiazepines and second-line drugs such as levetiracetam, phenytoin, and valproate is usually treated with intravenous (IV) anesthetic drugs such as midazolam, pentobarbital, and propofol. Despite such treatment, refractory status epilepticus often results in high mortality. A recent retrospective observational cohort study of 111 patients with refractory status epilepticus revealed a mortality of 38%.³ Important articles published in 2013 suggest that ketamine and immunotherapy may improve outcomes in selected patients with status epilepticus.

Ketamine

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has been proposed as an alternative therapeutic agent for the treatment of refractory status epilepticus. A multicenter retrospective review suggested that ketamine offered “possible” or “likely” responses in 32% of episodes.⁴ The mortality rate was lower when status epilepticus resolved within 24 hours of ketamine administration. In a prior pilot study, IV ketamine was associated with resolution of refractory status epilepticus in 6 (67%) of 9 children who had failed at least 1 conventional anesthetic such as midazolam, propofol, or thiopental.⁵ There were no significant adverse reactions. As an NMDA antagonist, ketamine may have the additional benefit of protecting against glutamate-induced neurotoxicity.

Autoimmune Encephalitis

It has recently been recognized that seizures may develop in patients due to antibodies against cell surface antigens and synaptic proteins.⁶ Target antigens include the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA,

γ -aminobutyric acid-B, and glycine receptors. Other auto-antigens include the leucine-rich glioma-inactivate 1 and contactin-associated protein-like 2. Pandit et al. report 15 patients with antibody-proven autoimmune encephalitis and seizures, 4 of whom presented with status epilepticus.⁷ In all, 10 (67%) patients became seizure free and 94% had significant improvement in their neurological status after treatment with steroids, IV immunoglobulin (IVIG), or other immunotherapy. Although rare, this diagnosis should be considered in patients who present with seizures and status epilepticus who fail to respond to conventional therapy.

Two US Food and Drug Administration Approvals

Neurohospitalists should be aware that the US Food and Drug Administration (FDA) approved eslicarbazepine acetate (Aptiom) as an oral adjunctive treatment for partial seizures in adults in November, 2013.⁸ Its primary mechanism of action is on voltage-gated sodium channels, similar to carbamazepine and oxcarbazepine. In 3 phase III studies, the median relative reduction in seizure frequency was 35% (800 mg/d) and 39% (1200 mg/d) versus placebo (15%).⁸ As a once-a-day drug, it may become a popular outpatient choice. Its most common adverse events are dizziness, somnolence, and headache.

A brain implant, the NeuroPace RNS System, which detects seizures and aborts them with an electric shock, also received FDA approval in November, 2013.⁹ The device is indicated in patients with intractable partial epilepsy who have no more than 2 epileptic foci and average at least 3 seizures a

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month. In a multicenter, randomized, double blind trial, the treatment group ($N = 97$) had a seizure reduction of 37.9% compared to the sham treatment group ($N = 94$) of 17.3% ($P = .012$). Overall quality of life improved ($P < .02$) without deterioration of mood or neuropsychological function.⁹ Neurohospitalists may be asked to see these patients for uncontrolled seizures or status epilepticus and should be aware of this new device. According to the manual, patients cannot have magnetic resonance imaging, diathermy, electroconvulsive therapy, or transcranial magnetic stimulation. Due to strict surgical and expertise criteria, the NeuroPace RNS System is only available in selected epilepsy centers around the nation at the moment.

Conclusions

Neurohospitalists frequently care for patients with status epilepticus, which may lead to significant morbidity and mortality. Further research will determine whether ketamine proves a valuable treatment for refractory status epilepticus in adults and/or children. In the meantime, because of the poor outcomes associated with this condition, ketamine should be considered in difficult cases. Neurohospitalists treating refractory status epilepticus should also bear in mind the unlikely possibility of autoimmune encephalitis, which may respond to a trial of steroids, IVIG, or other immunotherapy. Two FDA approvals this year, eslicarbazepine acetate and the NeuroPace RNS System, represent important new options for the treatment of epilepsy. Neurohospitalists may benefit from all of these advances in their care of people with seizures and status epilepticus.

Declaration of Conflicting Interests

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