Study supports alternative anti-seizure medication following acute brain injury

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A study by researchers at the University of Cincinnati Neuroscience Institute (UCNI) at University Hospital supports the use of an alternative medication to prevent seizures in patients who have suffered a life-threatening traumatic brain injury or bleeding stroke.

This randomized study supports earlier indications that the anti-seizure medication levetiracetam, marketed as Keppra, was as effective at preventing seizures as the traditional medication, phenytoin, marketed as Dilantin, while producing fewer negative side effects. Patients treated with Keppra also had improved long-term outcomes, the researchers found.

The study will be published in the April 2010 issue of the journal, *Neurocritical Care*; it appeared online on Nov. 7, 2009.

The study of anti-seizure medications in the neuroscience intensive care unit (NSICU) at UC Health University Hospital is part of a focused, ongoing effort to harness scientific evidence to improve treatments and outcomes for patients. Seizures are common following severe brain injury, and minimizing or eliminating them is a primary objective of neurocritical care.

The study was led by Lori Shutter, MD, associate professor of neurosurgery and neurology and director of neurocritical care at UCNI. The published article was written by co-investigator Jerzy Szaflarski, MD, PhD, associate professor of neurology.

"We continue to make incremental, meaningful strides in the care of patients who are hospitalized in the NSICU following subarachnoid hemorrhage or traumatic brain injury," Shutter says. (A subarachnoid hemorrhage, a type of bleeding stroke, occurs when blood seeps into the subarachnoid space between the brain and the skull.)

Dilantin has traditionally been the standard of care in preventing seizures, which afflict 25 to 30 percent of patients who have suffered a traumatic brain injury or subarachnoid hemorrhage. Keppra is an established anti-seizure medication given to people with epilepsy (defined as having more than one seizure), but its effectiveness for preventing seizures in patients after a brain injury had not been proven. The study sought to establish the drug's safety and effectiveness in this group of patients.

Although the number of patients in the study was small (52), the results appear to be an indicator that Keppra might be an appropriate alternative to Dilantin for preventing seizures and improving outcomes of patients who have suffered a traumatic brain injury or subarachnoid hemorrhage.

"Preventing seizures is a critical part of protecting a patient's brain from further injury following trauma or stroke," Szaflarski says. Seizures in the neurocritical care setting can result in aneurysm rupture, increased pressure on the brain, oxygen deprivation, physical injury and death. Seizures can be visible (overt), or undetectable to the human eye (covert).

Despite being the standard of care in the neurocritical care setting, Dilantin is linked to many serious and harmful side effects, including medication interactions, rash, fever, low blood pressure, heart arrhythmias, toxicity and organ abnormalities. Previously, the UCNI team, led by Szaflarski, had reported that patients in the NSICU who were treated with Keppra or whose medication was switched to Keppra

had fewer complications and shorter hospital stays than those who continued treatment with Dilantin.

This experience led to the newly published study, which compared the safety of Keppra to that of Dilantin and compared the drugs' effect on seizure activity and long-term outcomes. Patients enrolled in the study underwent continuous EEG monitoring for up to 72 hours. EEG, which stands for electroencephalogram, produces a recording of electrical activity in the brain. Two-thirds of the patients were randomly assigned to receive Keppra, while one-third were randomly assigned to receive Dilantin. The physicians were blinded to which medication the patient received.

The results showed that while patients experienced the same outcomes relating to seizure activity and survival, those treated with Keppra suffered fewer side effects and had better long-term outcomes when examined at three- and six-month intervals following their hospital discharge.

Shutter notes that the study results had an immediate impact on research protocols for other studies in the NSICU that were not allowing use of Keppra. After this study, the protocols were modified to allow Keppra's use.

Michael Privitera, MD, professor of neurology and director of the UC Epilepsy Center, points to the Keppra study as an example of UCNI's expansion of clinical and research projects associated with the continuous monitoring for seizures in the NSICU. In 2009 more than 200 critically ill patients were monitored in an effort to quantify overt and covert seizures, including life-threatening status epilepticus, a state of continuous brain seizure activity.

"Rapid and accurate detection of seizure activity leads to treatment that

can protect nerve cells from damage, especially in cases of subarachnoid hemorrhage or traumatic brain injury," Privitera says. "All of the neurologists and neurointensivists have been trained to perform the initial interpretations of EEG tracings, and our epilepsy staff can verify and read the EEG remotely. University Hospital is the only hospital in the Tristate area with this capability."

The importance of the Keppra study's publication was acknowledged this month, when the article was selected for inclusion in London-based Faculty of 1000 Medicine (www.f1000medicine.com), a literature-awareness service whose mission is to identify and evaluate "the most important articles published in Medicine." Recommendations come from a faculty of more than 2,000 researchers and clinicians.

Jane Hunter, managing director of Faculty of 1000, stated that the article's identification and inclusion provides recognition "of its scientific merit and the positive contribution it makes to the medical literature."

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