AEDs after ICH
Preventing the prophylaxis

The chains of habit are too weak to be felt until they are too strong to be broken.
—Samuel Johnson

Has the routine use of antiepileptic drugs (AEDs) in intracerebral hemorrhage (ICH) become a habit too difficult to break? Adherents to evidence-based medicine must surely have a conniption in light of this continuing practice. The guidelines have remained clear over the years: Do not use antiseizure medications in ICH unless there has been a seizure. Yet prophylactic AED use after acute ICH remains widespread in the United States. This is brought to our attention in the current issue of Neurology®. Naidech et al.1 report on the patterns of AED use in ICH over 5 years across several academic medical centers in Chicago. Placing the study period into its historical context, it was conducted after the publication of the 2010 American Heart Association/American Stroke Association (AHA/ASA) guidelines on the management of ICH, the first to recommend against this practice.2 The authors show a widespread disregard for this expert recommendation. In fact, over the 5-year study period, the use of AEDs almost doubled, and towards the end of the study period, in 2012, 40% of all patients were given AEDs. The study was done in academic centers, commonly believed to uphold the standards of evidence-based management more strictly than others. During this study period, the use of phenytoin fell dramatically, while that of levetiracetam increased. The authors submit, as a possible explanation for the increased use of AEDs, the ease of use of levetiracetam over phenytoin, with fewer drug interactions and adverse events, despite the guideline recommendations.

However, the potential harm of preventative AED use in ICH deserves consideration. We know these medications have potential major side effects, including mood and cognitive alterations, black box warning of suicide risks, and experimental and clinical studies suggesting that some AEDs may inhibit neuroplasticity and stroke recovery.3 Some, admittedly limited, data suggest risk for adverse neurologic outcome in ICH with AED use. The best evidence probably comes from the placebo group of the Cerebral Hemorrhage and NXY-059 Trial (CHANT), a prospective trial of antioxidant neuroprotective agents in ICH.4 Those participants with ICH who received AEDs, largely phenytoin, had worse outcome. The lack of random assignment introduces the possibility of selection bias, even though the authors made statistical adjustments for baseline differences. A more recent finding from the observational Ethnic-Racial variations in Intracerebral Hemorrhage (ERICH) study did not report an adverse outcome with prophylactic use of AEDs; however, most patients were treated with levetiracetam.5

On the other hand, who are we to readily condemn the continued use of prophylactic AEDs in ICH? Not until too long ago, the AHA/ASA guidelines (1999) on the management of ICH stated that a 1 month course of prophylactic AEDs, preferably phenytoin, may be considered.6 In the 2007 guidelines, a “brief period of prophylactic antiepileptic therapy soon after ICH may reduce the risk of early seizures in patients with lobar ICH” received a Class IIb, Level of Evidence C recommendation, based on a study by Passero et al. from 2002.7,8 That observational study suggested that the early institution of AEDs prevented early seizures in patients with lobar ICH. Interestingly, most patients in this study received phenobarbital. The increased risk of epilepsy following lobart ICH is well-accepted. Cortical hemorrhage, a component of the CAVE score, along with younger age (<65 years), larger volumes (>10 mL), and early seizure (<7 days), are risk factors for later seizures.9 The overall risk of early seizures, within 7 days from ICH onset, is around 11%, and that of late seizures approximately 9%. With a high CAVE score, the risk of late seizures, and thereby epilepsy, goes up substantially, to 42%.2 Early seizures in acute ICH may worsen edema and have other adverse effects and we are all aware of the detrimental emotional impact of seizures as our patients recover.10 A more recent small study of prophylactic valproic acid, the only randomized trial of AEDs in ICH, suggested early seizure prevention (though the difference was not significant) and, interestingly, improved long-term neurologic function, but there was no difference in late seizures incidence or mortality.11

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The study by Naidech et al. leaves many questions unanswered. We know little about the duration and doses of treatment. Who are the prescribers of AEDs among the different medical services taking care of patients with ICH? Among neurologists, hospitalists, neurosurgeons, and neurointensivists, are some more likely than others to prescribe AEDs? The risk and benefit of treatment remain unknown. In the absence of good data to support a true benefit, we need to heed the current guideline recommendations. With only about one-tenth of patients with ICH developing seizures, we should avoid exposing the majority of patients to medications they will not need. How then do we break the chains of habit? It is unlikely that we will have a randomized placebo-controlled trial anytime soon to answer this question. Raising awareness of this subject, as done in the current issue of Neurology, is an important step, along with continuing reinforcing education. And always looming on the horizon is the threat of increasing oversight by accrediting and certifying agencies in regulating this practice.

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REFERENCES