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Is There Equipose Between Phenytoin and Levetiracetam for Seizure Prevention in Traumatic Brain Injury?

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Trauma specialists, emergency room physicians, neurosurgeons, psychiatrists, and neurologists frequently encounter patients with acute moderate or severe traumatic brain injury (TBI). At the time of presentation, these patients are usually placed on an antiepileptic medication (AED) for seizure prevention. The current standard—supported by the 2003 practice parameter published by the Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN)—is that these patients should be placed prophylactically on an AED for the first 7 days. If patients do not experience seizures, it is recommended that they are weaned off the AED.¹ This recommendation is based on two facts: 1) there is a significantly lower occurrence of short-term seizures in patients placed on phenytoin (PHT) versus placebo, and 2) whether these patients are weaned off AED or remain on it, their long-term seizure outcome is unchanged. In general, the Brain Trauma Foundation (<http://tbguidelines.org/gliHome.aspx>; accessed 1/13/15) agrees with the recommendation from QSS of the AAN by stating, based on the review of the 1996–2006 literature, that the use of AED is indicated to decrease the incidence of early post-traumatic seizures within 7 days of injury but not for prevention of long-term seizures and post-traumatic epilepsy. These recommendations are based on studies published more than 10 years ago and may not reflect current practices and the availability of newer treatments, such as levetiracetam (LEV).

Observational and prospective studies conducted in the last 10 years in the critical care setting provide evidence for a trend in seizure prevention after TBI—a gradual but steady shift away from PHT to LEV with some suggesting that it may be time to replace PHT with LEV in the critical care setting.² However, is this shift justified by the currently available data? Sometimes, where clear scientific evidence is lacking, expert consensus needs to be used to guide therapy choices. This commentary will focus only on the use of prophylactic AEDs in

the setting of acute TBI and the issue of presence (or absence) of equipose between PHT and LEV.

In 1987, Benjamin Freedman provided the main and alternative definitions of equipose.³ *Equipose* is defined primarily as “a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm of the trial” with the alternative definition being the “present or imminent controversy in the clinical community over the preferred treatment” with the requirement of equipose satisfied if there is a genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment.³ So, is there equipose between these two treatments? Comparative studies of PHT and LEV in the setting of TBI provide conflicting evidence with some of them suggesting that LEV may improve long-term outcomes,^{4,5} while others suggesting lack of superiority of LEV over PHT.⁶ ***So, what is the physician to do in this setting?***

To answer this question, we enlisted the help from the “Quantitative Practical Use-Driven Learning Survey in Epilepsy” (Q-PULSE) panel established in 2012 by the American Epilepsy Society.⁷ The panel consisted of epilepsy specialists selected from epilepsy centers belonging to the National Association of Epilepsy Centers (NAEC) representing a broad cross-section of centers across the United States. The aim of the Q-PULSE is to capture expert opinion where quality (Class I) scientific data are not readily available by having the panel members complete an online survey.

For this survey, the questions were created by the author with the help and comments from the Q-PULSE Steering Committee. The committee approved the final version of the survey. The questions revolved around the choice of the AED for seizure prevention in the setting of acute moderate or severe TBI. Out of 146 members of the Q-PULSE panel, 91 (62%) responded. The survey opened on November 16, 2014 and closed on December 5, 2014.

Survey Results

The panel was asked to answer 5 questions. The questions and a summary of responses are provided below.

Question 1. Do you feel there is therapeutic equipoise between phenytoin and levetiracetam used for seizure prevention in patients with moderate or severe traumatic brain injury within the first seven days after injury?

Question 2. Assuming there are no medical contra-indications at the time it is initiated, which anti-epileptic drug do you use at your center as a first choice for seizure prevention (i.e. the patient has not had a seizure) in moderate to severe traumatic brain injury within the first 1-7 days?

Discussion

The results of this Q-PULSE survey provide expert opinion regarding the use of AEDs in the setting of seizure prevention after TBI. Since the initial publication of the AAN guideline, several changes have occurred in how we practice medicine. Of importance for the setting of seizure prevention in patients

with moderate or severe TBI is the fact that new AEDs became available and are now in widespread use. Unfortunately, the use of these medications in this setting is not supported by Class I evidence. Thus, in place of such evidence, expert opinion is needed and frequently used.

Questions 3 and 4. Would you change your choice of preventative medication (again, assuming the patient has not had any seizures) after the first seven (7) days? If yes, to which AED would you change?

Question 5. Please rank from 1-5 (1=not a consideration, 5=very important consideration) the impact of these factors on your decision on which anti-epileptic drug to use for first-line prevention in moderate or severe traumatic brain injury.

A clear example of an equipoise between the two treatments is the study in which prospective data were collected from two institutions—University of Southern California (USC) and University of Maryland (UM)—the institutional preference at USC is to use LEV in this setting while at UM the preference is to use PHT.⁶ In accordance with the institutional protocols, the majority of the 406 LEV-treated TBI patients enrolled in

the study came from USC (81%), while 97% of the 407 patients treated with PHT came from UM. Thus, based on the enrollment pattern in this study, the equipoise between PHT and LEV appears to be self-evident—patterns of AED use between two major trauma centers are disparate despite expertise available at both—and the Q-PULSE experts have agreed with the notion of equipoise with 73% of them responding with

an affirmative “YES” answer to the first question. The Q-PULSE experts felt, based on the currently available data, that LEV can be used in place of PHT and vice versa. Of importance is that 86% of the responders felt that scientific data played substantial consideration in their decision (Question 5).

Despite the implied equipoise from the current survey between the AEDs, 74% of the respondents indicated their first choice would be LEV, 10% indicated PHT, and 11% had no preference. Is this personal preference/experience, hospital protocol, AED price, or some other factor talking? Irrespective of the reason for this, the finding is clearly in line with the observed evolution in the treatment of patients with TBI with a gradual switch from PHT to LEV for seizure prophylaxis that is not sufficiently supported by Class I data. This observed change in practice pattern is likely related to multiple factors of which the clinicians are aware; that is, negative effects of PHT on post-injury recovery and long-term cognitive performance, high potential for pharmacokinetic interactions of PHT and concomitant medications, better cognitive outcomes of LEV in the setting of intracranial hemorrhage and long-term efficacy perceived to be similar between these AEDs.^{4–6, 8, 9} However, only certain parameters of practice patterns change, which is reflected in the responses to the next questions (Questions 3 and 4)—the majority of the experts agrees that the AED should be discontinued after 7 days.

So, based on this Q-PULSE, one can draw two conclusions: 1) there appears to be, perceived by the majority, equipoise between PHT and LEV for seizure prophylaxis, and 2) the experts follow the published guideline while incorporating new developments into their treatment approaches. Another

conclusion is also self-evident: more data are needed to guide the choices of physicians treating patients with moderate or severe TBI in the acute setting.

References

1. Chang B, Lowenstein D. Practice parameter: Antiepileptic drug prophylaxis in severe traumatic brain injury. *Neurology* 2003;60:10–16.
2. Fountain N. Should levetiracetam replace phenytoin for seizure prophylaxis after neurosurgery? *Epilepsy Curr* 2009;9:71–72.
3. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141–145.
4. Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care* 2010;12:165–172.
5. Taylor S, Heinrichs RJ, Janzen JM, Ehtisham A. Levetiracetam is associated with improved cognitive outcome for patients with intracranial hemorrhage. *Neurocrit Care* 2011;15:80–84.
6. Inaba K, Menaker J, Branco BC, Gooch J, Okoye OT, Herrold J, Scalea TM, Dubose J, Demetriades D. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. *J Trauma Acute Care Surg* 2013;74:766–773.
7. French JA. Taking the “pulse” of our society with Q-PULSE. *Epilepsy Curr* 2013;13:304.
8. Jones KE, Puccio AM, Harshman KJ, Falcione B, Benedict N, Jankowitz BT, Stippler M, Fischer M, Sauber-Schatz EK, Fabio A, Darby JM, Okonkwo DO. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus* 2008;25:E3.
9. Szaflarski JP, Nazzari Y, Dreier LE. Post-traumatic epilepsy: Current and emerging treatment options. *Neuropsychiatr Dis Treat* 2014;10:1469–1477.