

## SHOULD LEVETIRACETAM REPLACE PHENYTOIN FOR SEIZURE PROPHYLAXIS AFTER NEUROSURGERY?

**Efficacy and Tolerability of Levetiracetam versus Phenytoin after Supratentorial Neurosurgery.** Milligan TA, Hurwitz S, Bromfield EB. *Neurology* 2008;71(9):665–669. **BACKGROUND:** Antiepileptic drugs are routinely given after craniotomy. Though phenytoin (PHT) is still the most commonly used agent, levetiracetam (LEV) is increasingly administered for this purpose. This retrospective study compared the use of LEV and PHT as monotherapy prophylaxis following supratentorial neurosurgery. **METHODS:** Patients receiving LEV monotherapy after supratentorial craniotomy were reviewed and compared to a control group of patients receiving PHT monotherapy. **RESULTS:** One of 105 patients taking LEV and 9/210 patients taking PHT had seizures within 7 days of surgery ( $p = 0.17$ ). Adverse drug reactions requiring change in therapy during hospitalization occurred in 1/105 patients taking LEV and 38/210 patients taking PHT ( $p < 0.001$ ). Among patients followed for at least 12 months, 11/42 (26%) treated with LEV vs 42/117 (36%) treated with PHT developed epilepsy ( $p = 0.34$ ); 64% remained on LEV, while 26% remained on PHT ( $p = 0.03$ ). **CONCLUSIONS:** Both levetiracetam (LEV) and phenytoin (PHT) were associated with a low risk of early postoperative seizures and a moderate risk of later epilepsy. LEV was associated with significantly fewer early adverse reactions than PHT and with a higher retention rate in patients who were followed for at least 1 year and developed epilepsy.

### COMMENTARY

Antiepileptic drug (AED) prophylaxis to prevent seizures in a patient who has not yet had seizures but is at risk, seems like a reasonable approach; however, it is more complicated than it appears. While seizure prevention in at-risk patients seems logical at face value, this reasoning presupposes that the possibility of an adverse drug reaction from the AED is lower than the probability of harm from a seizure. Thus, in order for the approach to be valid, the population under study must: 1) be at significant risk for seizures, 2) have some expectation that the seizures might cause harm, and 3) be at low risk of an adverse drug reaction from the AED.

Neurosurgeons have considered patients to be at significant risk for seizures after supratentorial surgery (especially, following surgeries for brain tumors and traumatic brain injury), although the actual risk is highly variable and only in the range of about 3%. Additionally, even a single convulsion immediately after neurosurgery may cause harm because of the increased intracranial pressure created by strong muscular contractions. Therefore, it has been a common practice to provide phenytoin as seizure prophylaxis after neurosurgery. The main problem with this approach is that phenytoin commonly causes side effects that are annoying and, less commonly but more importantly, can cause serious reactions, including anticonvulsant hypersensitivity syndrome, serious rash, purple glove syndrome, and necrosis when extravasated. Consequently, a tug of war has persisted between proponents and adversaries of AED prophylaxis following surgery. An American Academy of Neurology practice parameter clearly suggests that AED prophylaxis is use-

ful for severe traumatic brain injury but does not recommend it for newly diagnosed brain tumors (1,2). A separate meta-analysis of the more generic case of supratentorial neurosurgery did not find AED prophylaxis to be beneficial (3). Thus, there is a need for studies that can determine the efficacy of AED prophylaxis for a variety of situations.

If an AED is to be administered, which one is the most efficacious following supratentorial neurosurgery? Increasingly, levetiracetam is replacing phenytoin for prophylaxis after neurosurgery. Levetiracetam has straightforward pharmacokinetics and few drug interactions or common side effects; it is simple to use, usually well tolerated, and available in an intravenous formulation. These properties make it well suited for use in acutely ill patients, such as in patients after craniotomy. Behavioral side effects, such as irritability, can occur but are unlikely to be manifest or an issue in acutely ill patients. The favorable characteristics of levetiracetam have led many neurosurgeons to alter their traditional practice of providing phenytoin for prophylaxis after supratentorial neurosurgery and to use levetiracetam instead. However, there is little data to support the use of levetiracetam in this manner.

In the article by Milligan et al., the investigators retrospectively reviewed their experience with 105 patients who took levetiracetam and compared it with 210 patients who used phenytoin as AED prophylaxis for seizures after supratentorial craniotomy. Not surprisingly, they found levetiracetam was better tolerated than phenytoin and seemingly equally efficacious; thus, their finding is evidence that levetiracetam may be preferable to phenytoin. However, the study suffers from the limitations of a retrospective design: the phenytoin group had higher median age, fewer primary brain tumors, and a smaller proportion with preoperative seizures, which could have skewed the results. These issues might have been addressed by a

case-control design that matched levetiracetam and phenytoin patients. It is generally believed that levetiracetam is considerably better tolerated than phenytoin in routine clinical practice, so even the small number of patients in this study allowed them to find statistical superiority of tolerability in favor of levetiracetam quite easily. However, even if one treatment were more efficacious, it probably would be superior by only a small amount. Thus, the limited number of patients in this study makes it difficult to find any expected degree of difference in efficacy between the drugs.

Despite some limitations, the study by Milligan and colleagues does report outcomes that are clinically useful and extends the general clinical observations that levetiracetam is better tolerated than phenytoin in the specific setting of AED prophylaxis after supratentorial craniotomy. A randomized, controlled trial with a placebo arm that compares phenytoin with levetiracetam would be very informative. The placebo arm would be an important aspect of the study design, since, as discussed, controversy still exists regarding across-the-board use of AED prophylaxis following supratentorial craniotomy. Such a study could allow close monitoring and adjustment of phenytoin to address its fickle nature, which might yield a smaller difference in tolerability. However, the fact that phenytoin use

requires so much care and attention is the exact reason that it is likely to lose its preeminent role in seizure prophylaxis after neurosurgery. Until a definitive study is performed, it may be reasonable to use levetiracetam instead of phenytoin for seizure prophylaxis after supratentorial craniotomy—if the practitioner chooses to use AED prophylaxis at all in this setting.

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## References

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