Current Literature

In Clinical Science

Postoperative AED Management – Not So Clear Cut

Reducing Versus Stopping Antiepileptic Medications After Temporal Lobe Surgery.

Yardi R, Irwin A, Kayyali H, Gupta A, Nair D, Gonzalez-Martinez J, Bingaman W, Najm IM, Jehi LE. *Ann Clin Transl Neurol* 2014;1:115–123.

OBJECTIVE: To study the safety of antiepileptic drug (AED) withdrawal after temporal lobe epilepsy (TLE) surgery. **METHODS:** We reviewed patients who underwent TLE surgery from 1995 to 2011, collecting data on doses, dates of AED initiation, reduction, and discontinuation. Predictors of seizure outcome were defined using Cox-proportional hazard modeling and adjusted for, while comparing longitudinal seizure-freedom in patients for whom AEDs were unchanged after resection as opposed to reduced or stopped. **RESULTS:** A total of 609 patients (86% adults) were analyzed. Follow-up ranged from 0.5 to 16.7 years. Most (64%) had hippocampal sclerosis. Overall, 229 patients had remained on their same baseline AEDs, while 380 patients stopped (127 cases) or reduced (253 cases) their AEDs. Mean timing of the earliest AED change was shorter in patients with recurrent seizures (1.04 years) compared to those seizure-free at last follow-up (1.44 years; P -value 0.03). Whether AEDs were withdrawn 12 or 24 months after surgery, there was a 10–25% higher risk of breakthrough seizures within the subsequent 2 years. However, 70% of patients with seizure recurrence after AED discontinuation re-achieved remission, as opposed to 50% of those whose seizures recurred while reducing AEDs ($P = 0.0001$). Long-term remission rates were similar in both AED discontinuation and “unchanged” groups (82% remission for AEDs withdrawn after 1 year and 90% for AEDs withdrawn after 2 years), while only 65% of patients whose recurrences started during AED reduction achieved a 2-year remission by last follow-up. **INTERPRETATION:** AED withdrawal increases the short-term risk of breakthrough seizures after TLE surgery, and may alter the long-term disease course in some patients.

Commentary

One of the dilemmas facing epileptologists and their patients following resective epilepsy surgery is how to manage the postoperative anti-epileptic drug (AED) therapy regimen over time. The timing and degree of AED changes are not uniform and, of course, needs to be individualized on a patient-by-patient basis. Should the medication be changed after 6 months, 12 months, or 24 months? Should the medication be left untouched, reduced, or should the medication be discontinued entirely? There are no straight-forward evidence based answers to these questions and, like much of the practice of epileptology, there is no one-size-fits-all. It is known that there is a significant variation in practice among epileptologists in how they approach this issue.¹ Factors influencing the decision to change AED therapy after epilepsy surgery include but are probably not limited to the following:

1. Age of the patient.
2. Degree of success of the epilepsy surgery.
3. Number of AEDs that the patient is taking.
4. Type of AEDs that the patient is taking
5. Presence or absence of adverse drug effects.
6. Pre-existing severity of the epilepsy and the patient's seizures.
7. Histopathology.
8. Postoperative EEG and imaging findings.
9. Patient comorbidities.
10. Patient preferences.

For example, pediatric epileptologists may be more aggressive in attempting to withdraw AEDs in children in comparison to adult epileptologists in an effort to maximize neurodevelopmental and educational potential. If a patient is on significant AED polytherapy at the time of operation, it may seem reasonable to at least plan and attempt to withdraw one or more AEDs slowly and sequentially over time. If a patient has evidence of a chronic adverse effect of P450 enzyme induction, such as osteoporosis, it may be wise to

slowly withdraw the offending agent.^{2,3} If a patient remains free of complex partial and secondarily generalized seizures after surgery but continues to have auras, then it may not be prudent to aggressively lower AEDs, and certainly not to attempt to withdraw medication entirely. If the patient has a history of life-threatening status epilepticus, it may also not be advisable to attempt to withdraw medical therapy completely.

The study by Yardi et al. is an attempt to answer some of the questions that challenge epileptologists in the practice of postoperative pharmacotherapy. This is a retrospective observational chart review involving 609 patients of all ages (including 85 children) who have undergone epilepsy surgery at two epilepsy surgery units in the United States (Cleveland and Kansas) between September 1995 and June 2011, 64% of whom had underlying hippocampal sclerosis. Two hundred twenty-nine (38%) patients did not undergo any change in their AED regimen, medication was reduced in 253 (42%) patients, and 127 patients (21%) had their AEDs stopped entirely. The number of AEDs at the time of surgery ranged from 1 to 5, and the number at postoperative follow-up ranged from 0 to 5 drugs. Interestingly, 123 patients were able to achieve “conversion to monotherapy” from a baseline of between 2 to 4 AEDs at the time of surgery. The mean time of initiation of drug withdrawal was 1.34 years and was sooner in children. In this study, the authors admit that it was not possible to discern in any systematic way the exact decision-making processes that underpinned AED changes in patients.

Although this article highlights some important points, it remains difficult if not impossible to be prescriptive about a uniform policy on AED management following epilepsy surgery. In general, it is my practice to attempt to achieve monotherapy with a well-tolerated non-enzyme-inducing agent following successful epilepsy surgery and to continue this agent long term. If the patient wishes to attempt a complete wean from all AEDs, then there is a discussion of the risks of late seizure relapse and implications for issues such as driving in the event of recurrence of seizures. I also discuss the “genie out the bottle” effect in patients with refractory epilepsy who have a seizure relapse in the setting of drug reduction follow-

ing a prolonged period of seizure freedom. This is where the reinstitution of the previously effective drug therapy may not regain seizure control, and is estimated to occur in about 10% of these patients.⁴ Interestingly, in the present study, seizures occurring during AED reduction appear to be more difficult to control than seizures that occur following AED discontinuation, and the authors speculated whether underlying genetic factors could be playing a role. In terms of timing, I usually begin drug reduction after about 12 months following surgery but may reduce medication sooner in the setting of significant polytherapy (three or more agents).

It is customary at this point where there is a dearth of good quality Class 1 evidence to call for a prospective randomized clinical trial of a variety of approaches to drug reduction or discontinuation following successful epilepsy surgery. However, such a trial would have many significant challenges, and I suspect that many epileptologists would not be comfortable in exposing their patients to the vagaries of randomization in this setting. We know that all our patients are different and need individualized care and follow-up along their journey, including that exciting part of their journey that follows successful and often life-changing epilepsy surgery.

by Norman Delanty, MD

References

1. Tellez-Zenteno JF, Hernandez-Ronquillo L, Moien-Afshari F. Discontinuation of antiepileptic drugs after successful epilepsy surgery: Who and when? *Epilepsy Res* 2012;102:23–33.
2. Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N, Resnick T, Benbadis SR. The consequences of refractory epilepsy and its treatment. *Epilepsy Behav* 2014;37:59–70.
3. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: Cause for concern? *Epilepsia* 2013;54:11–27.
4. Schmidt D, Baumgartner C, Löscher W. Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: A review of current clinical experience. *Epilepsia* 2004;45:179–186.