

Antiepileptic drugs and relapse after epilepsy surgery

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ABSTRACT – Purpose. To evaluate whether the postoperative, antiepileptic drug (AED) regimen influences seizure recurrence after anterior temporal lobectomy when considering the putative mechanism of action and possible neuroprotective effects. **Methods.** This was a retrospective study. Patients who had an anterior temporal lobectomy for refractory epilepsy, whose preoperative MRI indicated mesial temporal sclerosis, were included. Postoperative AED regimens were compared with regard to seizure-outcome, considering the putative mechanism of action (sodium channel blockers, non-sodium channel blockers, and mixed mechanisms) or possible neuroprotective effect (levetiracetam, topiramate, tiagabine and zonisamide *versus* others). Time-to-event (first seizure after surgery) analysis was used to produce a Kaplan-Meier estimate of seizure recurrence, and groups were compared using Cox proportional hazard analysis. **Results.** 226 patients (103 males and 123 females; mean age 42 ± 11 years) were studied. The rates of postoperative seizure recurrence were not significantly different between the three groups regardless of the use of AEDs with different mechanisms of action ($p = 0.23$). Fifty patients were receiving possibly neuroprotective AEDs and 176 patients were not. Rates of seizure recurrence were not significantly different between these two groups either ($p = 0.11$). The differences between one-year seizure-free rates were not significant when we compared levetiracetam *versus* phenytoin or carbamazepine. **Discussion.** There appeared to be no advantage or disadvantage to either prescribing drugs with different mechanisms of action or using drugs with possible neuroprotective effect after temporal lobectomy. Prospective studies with larger sample sizes may be of benefit to further explore this issue.

Key words: antiepileptic drugs, epilepsy surgery, mechanism of action, neuroprotection, epileptogenesis, seizure relapse

Determining the causes of seizure-relapse after epilepsy surgery is an important and unresolved issue. The underlying pathological lesion may not have been completely excised, or a

progressive epileptic process may exist (Bernasconi *et al.* 2005), so that postoperative changes in neuronal and synaptic functions might lead to development of a new epileptogenic

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zone after surgery. Another hypothesis is that surgery itself may produce an injury that ultimately leads to the development of recurrent seizures postoperatively. The delay in relapse of seizures after surgery resembles the delay seen after other brain injuries such as stroke and traumatic brain injury. These insults produce immediate brain damage, but there is usually a latent period of variable duration ranging from weeks to years between the initial brain insult and the occurrence of epilepsy (Fery 2003, Herman 2006).

The relation between the mechanism of action of antiepileptic drugs (AEDs) and their potential effects in preventing seizure recurrence after epilepsy surgery has not been tested. Likewise, the relation between the potential neuroprotective effects of AEDs and their effects in preventing seizure recurrence after epilepsy surgery has not been tested yet. However, most AEDs have been tested in animal models of focal or global ischemia and some were tested in humans for possible neuroprotective effects. The existing data are rather scanty, but some AEDs might confer a degree of neuroprotection (Stepien *et al.* 2005, Ryvlin *et al.* 2006). Levetiracetam (Wang *et al.* 2006), tiagabine (Yang *et al.* 2000), topiramate (Schubert *et al.* 2005) and zonisamide (Owen *et al.* 1997) have potential neuroprotective effects in animal studies (Stepien *et al.* 2005, Willmore *et al.* 2005, Zaremba *et al.* 2006). The neuroprotective effects of other AEDs are uncertain (Stepien *et al.* 2005) and some (e.g. phenytoin, phenobarbital, and benzodiazepines) may have detrimental effects in patients with stroke (Goldstein 2000).

The theory of neuroprotection against surgically-induced brain injury has been suggested recently (Jadhav *et al.* 2007). Brain tissue at the periphery of the operative site is at risk of injury by various means, including incisions and direct trauma, electrocautery, and retractor injury. Any form of pretreatment to limit the damage to the susceptible brain tissue during neurosurgical procedures might have a significant impact on patient recovery (Jadhav *et al.* 2007). Therefore, if the theory of surgery insult as the cause for relapse after epilepsy surgery is true, and if some AEDs have the potential to prevent epileptogenesis due to their specific mechanism of action or their potential neuroprotective effects, it is possible that administration of these AEDs could help prevent relapse after epilepsy surgery.

This study evaluated the relationship between the AED regimen and relapse after anterior temporal lobectomy in patients with refractory seizures due to mesial temporal sclerosis, and tried to answer whether putative mechanisms of action of AEDs play a role in the prevention of seizure recurrence after surgery. We also tried to determine if patients who, at the time of surgery and afterwards, are taking AEDs that have neuroprotective effects, are less likely to experience seizure recurrence than patients who are not taking these types of AEDs.

Patients and methods

This was a retrospective, non-randomized study. Patients having undergone standard anterior temporal lobectomy from 1994 through 2006 and with preoperative MRI positive for mesial temporal sclerosis were included (in order to have a very homogenous group of patients with similar etiology for their epilepsy and who underwent similar surgery). Patients with any additional diagnosis other than mesial temporal sclerosis (e.g. dual pathology) were excluded from the study. Only patients who were taking the same preoperative AED regimen until the first postoperative seizure or at least one year after operation were considered for the analysis; however, dose change was permitted. Since this is a retrospective review, the only possible analyses had to accommodate clinical practice. Surgical procedures did not change significantly over this period of time. Seizure outcome was monitored periodically by office visits, telephone contact, and letters. Anti-epileptic drug therapy was prescribed according to physician and patient preference, with many physicians advising maintenance of therapy for 2-5 years after surgery before considering complete drug tapering. The decision to continue taking medication for more than five years after surgery in seizure-free individuals was generally driven by patient desire, though in most cases, the number of drugs and drug doses were reduced compared to the preoperative state.

Clinical data, including age, age at surgery, gender, side of surgery, AED regimen, duration of epilepsy, history of febrile convulsion, history of secondarily generalized seizures before surgery, full scale IQ, preoperative intracranial monitoring, date of surgery, date of first recurrence, and date of last contact were collected.

In the first analysis, we categorized patients based on the putative mechanism of action of the AEDs that they were taking. Group one included patients receiving only sodium-channel blockers (phenytoin, carbamazepine, oxcarbazepine and lamotrigine); group two included patients taking AEDs with no sodium-channel blocking properties (benzodiazepines, gabapentin, levetiracetam, phenobarbital, tiagabine, and pregabalin); group three included patients receiving one or multiple drugs with different mechanisms of action, including sodium channel blocking properties (valproate, topiramate, zonisamide, or polytherapy including sodium channel blockers and non-sodium channel blockers). Variables known to be associated with favorable outcome were compared between the groups (history of febrile seizures, lack of preoperative secondarily generalized seizures, full scale IQ) (Chelune *et al.* 1998, Jeong *et al.* 2005). Other probably important variables including gender, age-at-surgery, epilepsy duration, preoperative intracranial monitoring, and side of surgery were evaluated and compared between the groups. Chi-square, Fisher exact and t-tests were used to compare the patient groups. Time-to-event (first seizure

after surgery) analysis was used to produce a Kaplan-Meier estimate of seizure recurrence. Cox proportional hazard analysis was used for statistical comparison.

In another analysis, patients were grouped based on their AED regimen considering possible neuroprotective effects. The first group included patients receiving at least one of the AEDs with possible neuroprotective effects, based on observations from the epilepsy literature and information derived predominantly from pre-clinical studies (levetiracetam, topiramate, tiagabine and zonisamide) alone or in any combination with other drugs. The second group included patients who were not taking any of these AEDs with neuroprotective effects. Chi-square and t-tests were used to compare the patient groups. Time-to-event (first seizure after surgery) analysis was used to produce a Kaplan-Meier estimate of seizure recurrence. Cox proportional hazard analysis was used for statistical comparison. This study was conducted with approval of the Thomas Jefferson University Institutional Review Board.

Results

Two hundred and twenty six patients (103 males and 123 females) were included in the analysis. The mean age of the patients was 42 ± 11 years. One hundred and forty

seven patients (65%) were on monotherapy and 79 (35%) on polytherapy. The mean number of AEDs they were taking was 1.4 ± 0.6 .

When we classified patients based on the putative mechanism of action of the AEDs which they were taking, 122 patients were taking only sodium-channel blockers, 35 patients were taking no sodium channel blocker AEDs, and 69 patients were taking one or multiple drugs with multiple mechanisms of action. *Figure 1* shows a Kaplan-Meier plot of a first seizure recurrence in these groups of patients. Cox proportional hazard analysis showed no difference between these groups ($p = 0.23$). The three groups were similar with regard to the variables known to be associated with favorable outcome (presence of early risk factors such as febrile seizures, lack of preoperative secondarily generalized seizures, full scale IQ). Distribution and characteristics of other, probably important variables including gender, age-at-surgery, epilepsy duration, side of surgery and preoperative intracranial monitoring were also similar between the groups. In addition, the three groups were similar with regard to the proportion taking AEDs at the time of relapse. Among the patients with relapse and who had been taking sodium channel blockers since surgery, four patients were not taking AEDs at the time of seizure relapse and 29 patients were taking

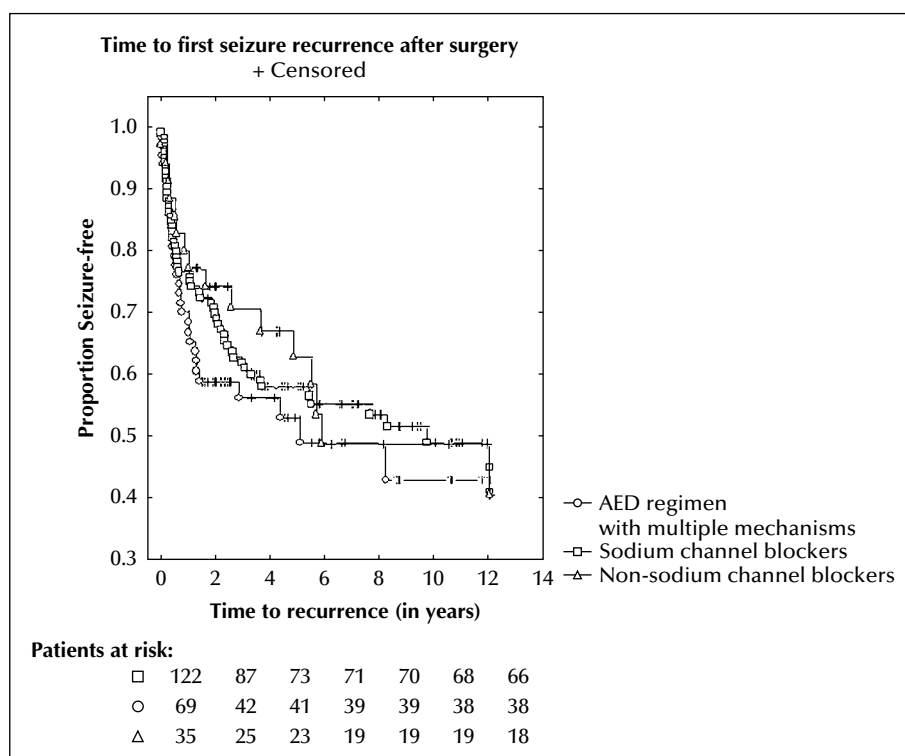


Figure 1. A Kaplan-Meier graph showing the annual rate of occurrence of a first seizure after anterior temporal lobectomy in patients taking AEDs, based on their putative mechanism of action. The number of patients taking each type of AED, at each time point, is written below the x-axis. For example, at year zero (time of surgery), 122 patients were taking sodium channel blockers, 69 were taking AEDs with mixed mechanisms (sodium channel and non-sodium channel blockers), and 35 were taking non-sodium channel blockers.

AEDs. Respectively, these figures were zero and 17 for patients taking non-sodium channel blockers, and four and 29 for patients taking AEDs with mixed mechanisms of action ($p = 0.19$). However, the mean number of AEDs taken was significantly lower in patients receiving sodium-channel blockers (sodium channel blockers: 1.09 ± 0.3 ; non-sodium channel blockers: 1.25 ± 0.5 ; AED regimen with multiple mechanisms of action: 2 ± 0.5 ; $p < 0.02$). However, Cox proportional hazard analysis showed no significant difference in seizure recurrence between patients taking monotherapy *versus* patients receiving polytherapy ($p = 0.64$). Unfortunately, there were not enough patients receiving monotherapy with any single AED to compare seizure recurrence rates between specific AEDs. In the second analysis, we dichotomized patients based on their AED regimen considering potential neuroprotective effects. The two groups (50 patients receiving possibly neuroprotective AEDs and 176 patients receiving other AEDs) were similar with regard to the variables known to be associated with favorable outcome (presence of early risk factors such as febrile seizures, lack of preoperative secondarily generalized seizures, full scale IQ). Distribution and characteristics of other, probably important variables including gender, age-at-surgery, epilepsy duration, side of surgery and preoperative intracranial monitoring were also similar between the groups. The two groups

were similar with regard to the proportion taking AEDs at the time of relapse. Among the patients taking neuroprotective AEDs, one patient was not taking AEDs at the time of seizure relapse; 22 patients were taking AED. These figures were 12 and 70 for patients taking non-neuroprotective AEDs, respectively ($p = 0.29$). However, the mean number of AEDs taken was significantly higher in patients who were receiving neuroprotective AED regimens compared with the patients taking other AEDs (1.86 ± 0.7 *versus* 1.25 ± 0.4 , respectively; $p = 0.0001$), but Cox proportional hazard analysis showed no significant difference in seizure recurrence between patients taking monotherapy *versus* patients receiving polytherapy ($p = 0.64$). Figure 2 shows a Kaplan-Meier plot of a first seizure recurrence in the two groups of patients (group 1 taking neuroprotective drugs and group 2 receiving other AEDs). Cox proportional hazard analysis showed no difference in recurrence rates between the two groups ($p = 0.11$).

In a subsidiary analysis, we compared seizure-free rates after one year for 34 patients who were receiving levetiracetam (as a potential antiepileptogenic AED [Klitgaard & Pitkanen 2003]) in mono- or polytherapy regimens *versus* 35 patients taking phenytoin in mono- or polytherapy regimens (not including levetiracetam) to evaluate whether antiepileptogenesis of AEDs play a role in the

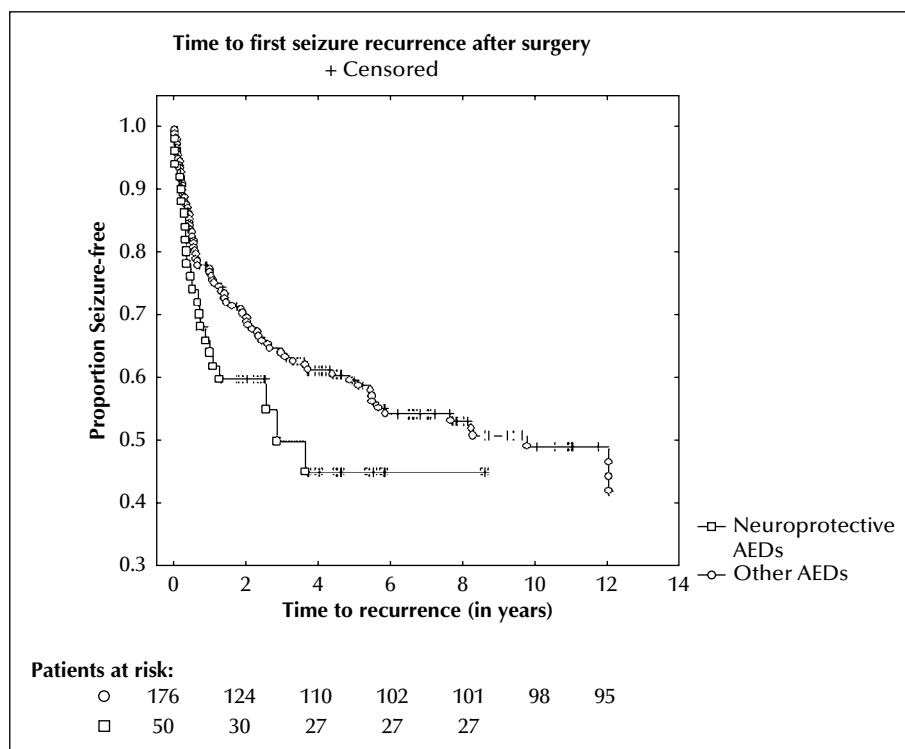


Figure 2. A Kaplan-Meier graph showing the annual rate of occurrence of a first seizure after anterior temporal lobectomy in patients taking neuroprotective AEDs or other AEDs. The number of patients taking each type of AED, at each time point, is written below the x-axis. For example, at year zero (time of surgery), 50 patients were taking neuroprotective AEDs and 176 were taking other AEDs.

prevention of seizure recurrence after surgery. There was no difference in the proportion of patients who were seizure-free one year after surgery in either group (24/34 receiving levetiracetam *versus* 27/35 seizure-free receiving phenytoin, $p = 0.76$). We also compared the first year seizure free-rates for 34 patients who were receiving levetiracetam in mono- or polytherapy regimens *versus* 106 patients receiving carbamazepine in mono- or polytherapy regimens (not including levetiracetam); again, no difference was seen ($p = 0.38$), with 77 seizure-free patients in the latter group.

Discussion

In this study, we retrospectively reviewed the postsurgical course in 226 patients after anterior temporal lobectomy and assessed whether putative mechanisms of AED action or potential neuroprotective effects were related to seizure recurrence after surgery. The patients were well-matched with regard to different clinical variables that relate to seizure relapse after anterior temporal lobectomy (Chelune *et al.* 1998, Jeong *et al.* 2005). Only the number of AEDs which patients in each group were taking differed, but this probably did not affect the results since there is no evidence supporting the contention that the number of AEDs prevents seizure relapse. The major findings of this study are that no obvious benefit could be ascertained with regard to either of the AED characteristics. Neither putative mechanism of action nor potential neuroprotective effect appeared to protect against seizure recurrence after anterior temporal lobectomy. Lastly, levetiracetam, which may have antiepileptogenic properties, (Klitgaard and Pitkanen 2003), did not show any superiority in comparison with carbamazepine or phenytoin with regard to seizure-free rates one year after surgery in the small number of patients studied. Other studies of late seizure prevention after other types of neurosurgery have not demonstrated that epileptogenesis can be aborted (Temkin 2001). Similarly, levetiracetam did not appear to have a synergistic effect with temporal lobectomy as proposed previously (Motamedi *et al.* 2003), because it did not offer any advantage with regard to postoperative seizure-freedom compared with other AEDs.

The putative mechanism of action of the AED did not influence outcome, which was not necessarily expected. Meta-analyses have shown possible differences in efficacy among different drugs (Marson *et al.* 2002, Gamble *et al.* 2006), albeit in different populations from ours. However, there is no a priori reason to presume that one drug mechanism is inherently superior to another. The suggestion that employing agents with multiple mechanisms of action, or different drugs that work differently might be more effective is not yet supported by clinical experience or this study; rational polypharmacy may not be rational.

Neuroprotection appeared to convey no benefit to our patients. We had hoped that any surgical injury might be attenuated by pretreatment and then continued treatment with some AEDs. This lack of effect is similar to the literature experience. Why have neuroprotective drugs thus far failed to help humans? (DeGraba and Pettigrew 2000) Possible explanations include animal models not being an adequate representation of human disorders (e.g. epilepsy or stroke), complexities of translation of animal studies to human studies, potential variables such as genetic influences, variability in end-point analysis using clinical scales, and insufficient protection with regard to multiple mechanisms of neuronal injury (DeGraba and Pettigrew 2000). Alternatively, it is possible that surgery itself might occasionally cause an epileptogenic injury, or that postoperative seizures are far more likely to be related to the underlying disease state of mesial temporal sclerosis.

This study has several limitations. A prospective randomized study would have been better, and this retrospective study may have been subject to hidden biases. However, it is sometimes reasonable to examine firstly retrospectively collected data to see whether a larger randomized trial is worthwhile. Another limitation is that any drug effect might be modest, and larger numbers of patients may need to be studied to ascertain an AED effect. Also, the heterogeneity in the use of AEDs, including multiple AED combinations, and broad groupings are other major limitations of this study. It would be preferable to assess the effect of AED therapy on seizure recurrence by comparing outcomes in patients treated with monotherapy. Unfortunately, too few patients were receiving monotherapy with each AED to perform a head-to-head comparison. A multicenter study would be required to ascertain effects of individual AEDs on postoperative seizure recurrence. We could not consider the concurrent use of other non-AED drugs, which might have influenced the results because of limitations in our database. Another limitation was the impossibility of knowing about potentially subtle epileptogenic surgery complications, such as bleeding or small infarcts, which might predispose to relapse of seizures even after successful surgery. These modifying factors should be considered in any future study designed to pursue this hypothesis.

Another issue to keep in mind is that treatment with AEDs after probable epileptogenic insults is a double-edged sword (Pitkanen 2002). Administration of diazepam or phenobarbital after traumatic brain injury delays the recovery of sensorimotor performance, whereas no effect was observed after carbamazepine administration (Hernandez 1997). It has also been shown that treatment of rats with lamotrigine or carbamazepine during kindling development reduced the efficacy of these compounds in fully kindled seizures (Weiss and Post 1987, Krupp *et al.* 2000). The consequences of antiepileptogenic treatment on the later response to AEDs in animals, in which the treatment fails, present a challenge that needs to be addressed in

antiepileptogenesis studies (Pitkanen 2002). This may not be important in patients with epilepsy who are already taking AEDs, but this implies that generalization of the hypotheses tested in our study to situations other than epilepsy surgery should not be performed.

Prospective studies of these issues are worth pursuing. Additional types of experimental approaches using appropriate end points may help further evaluate these hypotheses (Faden and Stoica 2007). □

Disclosures

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