Antiepileptic Drug Withdrawal

Most seizure recurrences develop during the first 6 months after Antiepileptic Drug withdrawal.

No consistent set of predictors could be identified because a large number of variables have been identified in the literature, many studies reported contradicting results, study populations varied considerably, and the quality of the original studies was often low. Meta-analysis of individual participant data is necessary, because it allows for (1) correction for differences in follow-up duration between subjects and studies, (2) a study of interaction effects, (3) calculation of more accurate estimates valid across several populations, and (4) the assessment of each predictor's effect size ¹⁾.

Seizure-free epilepsy patients on AED monotherapy who taper their medication may improve neuropsychological performance with a relative risk of seizure relapse of 2.46, compared to those continuing therapy ²⁾.

Indications for AED withdrawal

There is no agreement on how long a patient should be seizure-free before withdrawal of anticonvulsants, nor is there agreement on the prognostic value of EEGs and on the best time period over which to withdraw AEDs.

The following is based on a study of 92 patients with idiopathic epilepsy, who had been free of seizures for two years $^{3)}$

Generalization, e.g. to posttraumatic seizures, may not be appropriate. Taper was by 1 "unit" q 2 weeks (where a unit is defined as 200mg for carbamazepine or valproic acid, or 100mg for phenytoin). Follow-up: mean = 26 mos (range: 6-62).

31 patients (34%) relapsed, with the average time to relapse being 8 mos (range: 1–36). Using actuarial methods, the risk for recurrence is 5.9%/month for 3 months, then 2.7%/month for 3 months, then 0.5%/month for 3 months. Factors found to affect the likelihood of relapse include:

1. seizure type: 37% relapse rate for generalized seizures; 16% for complex or simple partial; 54% for complex partial with secondary generalization

2. number of seizures before control attained: those with \geq 100 seizures before control had statistically significant higher relapse rate than those with < 100

3. the number of drugs that had to be tried before single drug therapy successfully controlled seizures: 29% if 1st drug worked, 40% if a change to a 2nd drug was needed, and 80% if a change to a 3rd drug was required

4. Engel Epilepsy Surgery Outcome Scale : class 4 had worst prognosis for relapse. Epileptiform discharges on EEG serves to discourage AED withdrawal ⁴⁾

In a larger randomized study ⁵⁾, the most important factors identified to predict freedom from

recurrent seizures were:

- 1. longer seizure-free period
- 2. use of only one AED (vs. multiple AEDs)
- 3. seizures other than tonic-clonic seizures.

Case series

The aim of this study was to determine the outcome of antiepileptic drug (AED) withdrawal in patients who were seizure-free for more than two years.

Methods: Patients with epilepsy who were seizure-free for at least two years and decided to stop AED therapy gradually were followed up every two months for seizure relapse. The inclusion criteria were as follows: (1) diagnosis of epilepsy, defined as the following conditions: ① at least two unprovoked (or reflex) seizures occurring >24 h apart; ② one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; ③ diagnosis of an epilepsy syndrome; (2) patients remained seizure-free for at least 24 consecutive months during AED therapy; and (3) patients expressed a desire to discontinue AED therapy gradually and agreed to return for regular follow-ups. The time to a seizure relapse and predictive factors were analyzed by survival methods, including sex; age at seizure onset; number of episodes; seizure-free period before AED withdrawal; duration of follow-up after AED withdrawal; AED tapering off period (taper period); results from brain magnetic resonance (MRI); electroencephalogram (EEG) after drug withdrawal; EEG before drug withdrawal; seizure type (classified as generalized, partial, or multiple types based on history); and the number of AEDs administered for long-term seizure control. A log-rank test was used for univariate analysis, and a Cox proportional hazard model was used for multivariate analysis.

Results: We selected 94 patients (58 men, 36 women). The relapse ratio was 29.8%. Univariate analysis and multivariate Cox regression analysis indicated that withdrawal times and multiple AEDs, as well as the seizure-free period before withdrawal and abnormal EEG after drug withdrawal were significantly correlated with seizure recurrence and were significant independent predictive factors, with a hazard ratio of 0.839 and 3.971, 0.957, and 3.684, respectively.

Significance: The relapse rate in our study was similar to commonly reported overall rates for epilepsy. Distinguishing variables, such as withdrawal times, multiple AEDs, seizure-free period before withdrawal, and abnormal EEG after drug withdrawal, need to be considered when choosing to withdraw from AEDs. Therefore, our recommendation is that after two years of seizure-free survival, patients could consider withdrawal unless they have hippocampal sclerosis (HS)⁶.

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