

Assessing Recurrence Rate in Patients with Epilepsy During and After Discontinuation of Antiepileptic Drug (AED) Treatment: An Observational Study

Satya Prakash Singh¹, Asha Kumari², Kanchan Kumari³

¹Tutor, Department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

²Assistant Professor and HOD, Department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

³Tutor, Department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

Received: 15-06-2023 / Revised: 10-07-2023 / Accepted: 09-08-2023

Corresponding author: Dr. Satya Prakash Singh

Conflict of interest: Nil

Abstract:

Aim: The aim of the present study was to assess the recurrence rate in patients with epilepsy during and after discontinuation of antiepileptic drug (AED) treatment who had been seizure free for either 2 or 4 years and to identify the risk factors for recurrence of seizures.

Methods: The present study was conducted at Department of Pharmacology and One hundred patients with epilepsy were prospectively studied for the period of 1 year. The epilepsy diagnosis was established by obtaining detailed history and descriptions from an eyewitness. All patients had Electroencephalography (EEG) and CT brain scan.

Results: There was no statistically significant difference between the groups regarding the demographic and clinical characteristics. There was significant correlation between the risk of seizure recurrence, duration of active seizure and number of seizures prior to seizure control. No significant correlation was found with the number of AEDs, the duration of seizure free period before drug withdrawal and family history of epilepsy.

Conclusion: The risk of recurrence during drug tapering after discontinuation of AEDs was related to the duration of active disease and number of seizures prior to control.

Keywords: Antiepileptic Drug, Epilepsy, Withdrawal.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Drug therapy is still the main treatment of epilepsy at present. [1] With antiepileptic drugs (AEDs), about 70% of patients with newly diagnosed epilepsy become seizure-free. [2] For patients who attain long term remission under AED treatment, the most important concern is “when is it suitable to discontinue AEDs and does it relapse after withdrawal?” This issue remains difficult for clinicians, especially for adult neurologists, because the recurrence of seizures in adult patients with epilepsy causes more serious social consequences, such as unemployment, losing driver's license, injury, and even death. Although discontinuing AEDs increases the risk of recurrence, it may improve behavior and cognitive function [3-5] and also reduces the financial burden of the cost of medication. Therefore, it is essential for clinicians to assess the relapse risk and predictive factors for seizure relapse after

withdrawal. In the past decades, numerous studies on AED withdrawal have estimated the relapse risk. The relapse risk after withdrawal in patients who were seizure-free for at least 2 years fluctuated from 12% to 67%. [6-8] In addition, many factors have been implicated in previous studies to affect the rate of seizure recurrence. However, the risk factors associated with a seizure relapse are yet to be fully identified and still remain controversial.

However, patients have a high risk of seizure recurrence after drug withdrawal. In a small prospective study of adult patients, relapse occurred in 57% of the group (42.8% did not relapse) during a 4-year discontinuation program. [9] Several factors are thought to influence seizure recurrence after drug withdrawal: age at seizure onset, duration of active disease, number of years of seizure remission, a history of treatment with multiple AEDs [10], hippocampal atrophy [11],

partial onset seizures, the presence of multiple types of seizures, focal epileptiform abnormalities on (electroencephalography) EEG readings, and increased EEG abnormalities during or after AED discontinuation. [12] In 2015, Lamberink et al [13] conducted a meta-analysis of 61 studies published between 1981 and November 2014 on the withdrawal of seizure-free patients from AEDs after medical or surgical treatment. The results showed significant variability in the risk of recurrent seizures in patients who were seizure-free for at least 2 years after treatment.

The aim of the present study was to assess the recurrence rate in patients with epilepsy during and after discontinuation of antiepileptic drug (AED) treatment who had been seizures free for either 2 or 4 years and to identify the risk factors for recurrence of seizures.

Materials and Methods

The present study was conducted at Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India and One hundred patients with epilepsy were prospectively studied for the period of 1 year. The epilepsy diagnosis was established by obtaining detailed history and descriptions from an eye witnesses. All patients had Electroencephalography (EEG) and CT brain scan.

Group A: 2 years seizure free before AED withdrawal (N=50)

Group B: 4 years seizure free before AED withdrawal (N=50)

The definition of epilepsy was 2 or more unprovoked seizures occurring at least 24 hours apart.⁴ Patients should have normal EEG at the time of tapering of drug and had no seizures for

approximately 12 months. Patients with progressive neurological disabilities, cerebral palsy, severe mental retardation, juvenile myoclonic epilepsy, acute symptomatic seizures and previous unsuccessful attempts at AED withdrawal were excluded.

The withdrawal of AED was proposed to all eligible patients. The risks and benefits were discussed and informed consent taken. The eligible patients were allocated into 2 groups with simple random sampling technique by using coin toss system. They were to have their AEDs withdrawn after a seizure free period of either 2 or 4 years. AEDs were withdrawn over a period of 6 weeks. An EEG was obtained just before the start of the taper period. For patients receiving more than one AEDs, the AEDs were tapered sequentially over 6 weeks. Follow up information during and after the withdrawal was obtained by telephone, clinic visits and letters. All the patients were followed up for at least 18 months after the tapering of the drugs.

Statistical Analysis

The overall probability of remaining seizure free in the 2 groups was analyzed using the Kaplan Meier survival analysis.⁵ Differences in selected attributes between study groups were assessed with Pearson's chi-square test. Additional exploratory analysis of the effect of a number of additional factors, other than the rate of tapering or the duration of therapy before drug withdrawal, on the risk of seizure recurrence was performed and the relative risks and 95% confidence interval for these selected variables was calculated after adjustment for any differences in the rate or timing of drug tapering.

Results

Table 1: Demographic and clinical characteristics of patients undergoing AED withdrawal

	2 yr seizure free group (n=50)		4 yr seizure free group (n=550)		P value
	No.	%	No.	%	
<i>Age in years</i>					0.950
12-20	30	60	32	64	
> 20	20	40	18	36	
<i>Age of first seizure</i>					0.965
12-20	39	78	36	72	
>20	11	22	14	28	
<i>Sex</i>					0.890
Male	32	64	33	66	
Female	18	36	17	34	
<i>Education</i>					1.987
Illiterate	3	6	6	12	
Can read and write but no schooling	7	14	8	16	
Primary	7	14	20	40	
High school	24	48	11	22	
College	9	18	5	10	
<i>Type of seizure</i>					1.765
Partial	7	17	15	27	
Generalized	35	83	40	73	

No. of AEDs					
1	45	90	44	88	0.876
>1	5	10	6	12	
AEDs withdrawn					
Phenytoin	19	38	16	32	0.690
Valproic acid	10	20	11	22	
Carbamazepine	10	20	11	22	
Phenobarbital	6	12	8	16	
Others	5	10	4	8	
Family history of epilepsy					
Yes	7	14	10	20	0.555
No	43	86	40	80	
Duration of active epilepsy					
3 years	31	62	28	56	1.743
>3 years	19	38	22	44	
Total No. of seizure					
3	21	42	18	36	0.764
>3	29	58	32	64	

There was no statistically significant difference between the groups regarding the demographic and clinical characteristics.

Table 2: Risk factors for seizure recurrence during and after tapering of AED

Factors	Relative Risks	95% CI
No. of drugs	1.72	0.79-3.81
Time period	1.48	1.22-1.82
Family history of epilepsy	0.55	0.26-1.27
Duration of active epilepsy	2.88	2.35-3.48
Total no. of seizures	1.50	1.30-1.73

There was significant correlation between the risk of seizure recurrence, duration of active seizure and number of seizures prior to seizure control. No significant correlation was found with the number of AEDs, the duration of seizure free period before drug withdrawal and family history of epilepsy.

Discussion

The increased awareness of the potential adverse cognitive and behavioral effect of antiepileptic drug (AED) and the social stigma implicit in their use have generated much interest in attempts to discontinue treatment in selected patients with epilepsy. The decision to discontinue AED is based on the chance of remaining seizure free after the drug withdrawal compared with continuation of treatment. The risk of seizure recurrence after withdrawal of AED has been estimated to range from 10% to 70% depending up on the method and design of the study. [14-16] Other studies have conflicting results regarding the effect on the risk of seizures recurrence and the duration of seizure free period before the drug tapering is initiated. [17-19] Many studies on discontinuation of AED have shown that the longer the period a patient is seizures free while taking the drugs the better is the patient chance of remaining seizures free once the drug has been tapered. [17,19] In this study we found a trend towards lower risk of seizure recurrence in the group that has been seizure free for 4 years before the tapering was begun.

However, the rate of recurrence in 2 years and 4 years seizure free group did not reveal any statistical significance.

There was no statistically significant difference between the groups regarding the demographic and clinical characteristics. There was significant correlation between the risk of seizure recurrence, duration of active seizure and number of seizures prior to seizure control. No significant correlation was found with the number of AEDs, the duration of seizure free period before drug withdrawal and family history of epilepsy. Similarly a recent study by Tennison et al in children with epilepsy demonstrated no difference in the recurrence rate regarding the length of time the patients were free of seizures before the taper began. [20] A longer seizure free period before drug tapering would introduce bias in that more patients entering the study would be truly in remission. One study suggested that single-drug therapy decreased the chance of relapse. [21] In a recent meta-analysis, the authors found that in 8 of 23 studies, patients who received two or more types of AEDs carried a higher risk of relapse than those receiving monotherapy. [22] Seizures are generally considered to be refractory when patients receive two or more AEDs, as these patients often have limited success with drug withdrawal, although they may achieve seizure remission for a certain period of time. One study reported that the risk of relapse after a 24-month period of seizure remission was 46.7% at 3

years for drug-resistant epilepsy patients. [23] Thus, we suggest that patients be warned that receiving two or more AEDs at the point of drug withdrawal may be associated with an increased risk of relapse.

Conclusion

The risk of recurrence during drug tapering after discontinuation of AEDs was related to the duration of active disease and number of seizures prior to control.

References

1. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsy*. 1979 Dec;20(6):729-37.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine*. 2000 Feb 3;342(5):314-9.
3. Lossius MI, Hessen E, Mowinckel P, Stavem K, Erikssen J, Gulbrandsen P, Gjerstad L. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). *Epilepsia*. 2008 Mar;49(3):455-63.
4. Vining EP, Mellits ED, Dorsen MM, Cataldo MF, Quaskey SA, Spielberg SP, Freeman JM. Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. *Pediatrics*. 1987 Aug 1;80(2):165-74.
5. Gallassi R, Morreale A, Di Sarro RA, Marra M, Lugesesi E, Baruzzi A. Cognitive effects of antiepileptic drug discontinuation. *Epilepsia*. 1992 Jan 1;33: S41-4.
6. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*. 1994 Apr 1;44(4):601-.
7. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? *CNS drugs*. 2004 Apr; 18:201-12.
8. Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurologica Scandinavica*. 2005 May;111(5):291-300.
9. Aktekin B, Dogan EA, Oguz Y, Senol Y. Withdrawal of antiepileptic drugs in adult patients free of seizures for 4 years: a prospective study. *Epilepsy & Behavior*. 2006 May 1;8(3):616-9.
10. Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. *Lancet*. 1991; 337(8751): 1175-80.
11. Cardoso TA, Coan AC, Kobayashi E, Guerreiro CA, Li LM, Cendes F. Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal. *Neurology*. 2006 Jul 11;67(1):134-6.
12. Cardoso TA, Coan AC, Kobayashi E, Guerreiro CA, Li LM, Cendes F. Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal. *Neurology*. 2006 Jul 11;67(1):134-6.
13. Lamberink HJ, Otte WM, Geleijns K, Braun KP. Antiepileptic drug withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors. *Epileptic Disorders*. 2015 Sep;17(3):211-28.
14. Specchio LM, Tramacere L, La Neve A, Beghi E. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. *Journal of Neurology, Neurosurgery & Psychiatry*. 2002 Jan 1;72(1):22-5.
15. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. *New England Journal of Medicine*. 1988 Apr 14;318(15):942-6.
16. Merritt HH. Medical treatment in epilepsy. *British Medical Journal*. 1958 Mar 3;1(5072):666.
17. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet* 1991; 337: 1175-80.
18. Shinnar S, Vining EP, Mellits ED, D'souza BJ, Holden K, Baumgardner RA, Freeman JM. Discontinuing antiepileptic medication in children with epilepsy after two years without seizures: a prospective study. *New England Journal of Medicine*. 1985 Oct 17;313(16):976-80.
19. Mastropaolo C, Tondi M, Carboni F, Manca S, Zoroddu F. Prognosis after therapy discontinuation in children with epilepsy. *European neurology*. 1992 Feb 12;32(3):141-5.
20. Tennison M, Greenwood R, Lewis D, Thorn M. Rate of taper of antiepileptic drugs and the risk of seizure recurrence in children. *N Engl J Med*. 1994; 330:1407-0.
21. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. *New England Journal of Medicine*. 1988 Apr 14;318(15):942-6.
22. Beghi E, Giussani G, Grosso S, Iudice A, Neve AL, Pisani F, Specchio LM, Verrotti A, Capovilla G, Michelucci R, Zaccara G. Withdrawal of antiepileptic drugs: Guidelines of the Italian League Against Epilepsy. *Epilepsia*. 2013 Oct; 54:2-12.
23. Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, French J. Remission and relapse in a drug-resistant epilepsy population followed prospectively. *Epilepsia*. 2011 Mar;52(3):619-26.