Neurology Asia 2006; 11 : 19 – 23

Risk of seizure recurrence after antiepileptic drug withdrawal, an Indian study

Archana VERMA *DM (Neurology) MD*, Surendra MISRA *DM (Neurology) FRCP (Edin)*

Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Abstract

Objective: 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. *Methods:* This is a prospective study of 136 patients with epilepsy. The patients were randomized into 2 groups: Group A (56 patients) was treated with AEDs for 2 years and Group B (80 patients) were treated for 4 years. The patients were evaluated periodically during and at least 18 months after the tapering of drugs. *Results:* Seizure recurred in 30 patients (31%) during the follow up period of 18 months. The length of time the patients were free of seizure before drug withdrawal began (2 years versus 4 years) did not significantly influence the risk of recurrence. Longer duration of active epilepsy (relative risk 2.86, 95% CI 2.35-3.48) and higher number of seizures prior to the seizure control (relative risk 1.50, 95% CI 1.30-1.73) increased the risk of recurrence. *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.

INTRODUCTION

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. [1-3]

To date, there are few studies on the risk of seizure recurrence after AED withdrawal in Asia. In this study, we compared seizure recurrence during and after withdrawal of AED in a group of epilepsy patients with seizure free for either 2 or 4 years. The risk factors for seizure recurrence was also determined.

METHODS

One hundred and thirty six patients with epilepsy in Neurology Clinic of Sir Sunder Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, were prospectively studied. The study was carried out from March 1997 to September 2004. The epilepsy diagnosis was established by obtaining detailed history and descriptions from an eyewitnesses. All patients had Electroencephalography (EEG) and CT brain scan.

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.

Address for correspondence: Dr. Archana Verma, New L- 23 Hyderabad colony, Banaras Hindu University, Varanasi 221 005 INDIA. Phone: 0542-2366769. Email: archanashiva@sify. Com.

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

Out of 136 patients who were initially considered for the study, 97 patients completed the study. The details are as shown in Table 1. Among the 97 patients, 62 were males and 35 were females with mean age of 20.3 ± 7.2 years. The demographic and clinical characteristics of the patients are shown in Table 2. There was no statistically significant difference between the groups regarding the demographic and clinical characteristics. As for the AEDs taken, they were: phenytoin (300 to 400 mg/day), 38 patients; valproic acid (600-1200 mg/day), 24 patients; carbamazepine (600 to 1000 mg/day), 24 patients; phenobarbital (60-150 mg/day), 16 patients; other drugs, 9 patients.

Table 3 shows the seizure recurrence rate and the various factors. As shown, 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.

Table 1: Study completion status

	Group A	Group B
Number of patients initially randomized	56	80
Had seizure recurrence before start of drug withdrawal	5	12
Poor compliance	3	6
Lost to follow up	6	7
Completed study	42	55

Group A: 2 years seizure free before AED withdrawal
Group B: 4 years seizure free before AED withdrawal

The seizure recurrence rate was 31% during 18 months follow up period, 38% in the 2 years seizure free group and 26% in 4 years seizure free group. Figure 1 shows the proportion of the patients remaining seizures free after commencing drug tapering in the two groups. The percentage of seizure recurrence rate in the two years seizure free group was more than the four years seizure free group, but the difference was not statistically significant ($z = 1.34$, $p = 0.16$). Out of 30 patients with seizure recurrence, 12 patients had seizure recurrence during drug tapering and 18 after drug tapering in a follow up period of 18 months. The response to resumption of AED after seizure recurrence was good in all cases.

DISCUSSION

In the present study overall risk of seizure recurrence was 31% during 18 months follow up period. Based on a meta-analysis of literature the risk after the drug withdrawal was 25% at one year and 29% at two years.[6] Almost half of the recurrence occurs within 6 months of medication withdrawal and 60% to 80% within one year.[6-8]

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.[9-11] 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.[9,11] 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. 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.[12] A longer seizure free period before drug tapering would introduce bias in that more patients entering the study would be truly in remission. This is supported in this study, where there were more patients in the 4 years seizure free group (Group B, 12/80 patients, 15%) who had seizure recurrence before start of drug withdrawal, as compared to the 2 years seizure free group (Group A, 5/56 patients, 9%)and this observation was also noted by Berg *et al*.[13] Nevertheless, there are several advantages to a shorter duration of

Table 2: Demographic and clinical characteristics of patients undergoing AED withdrawal

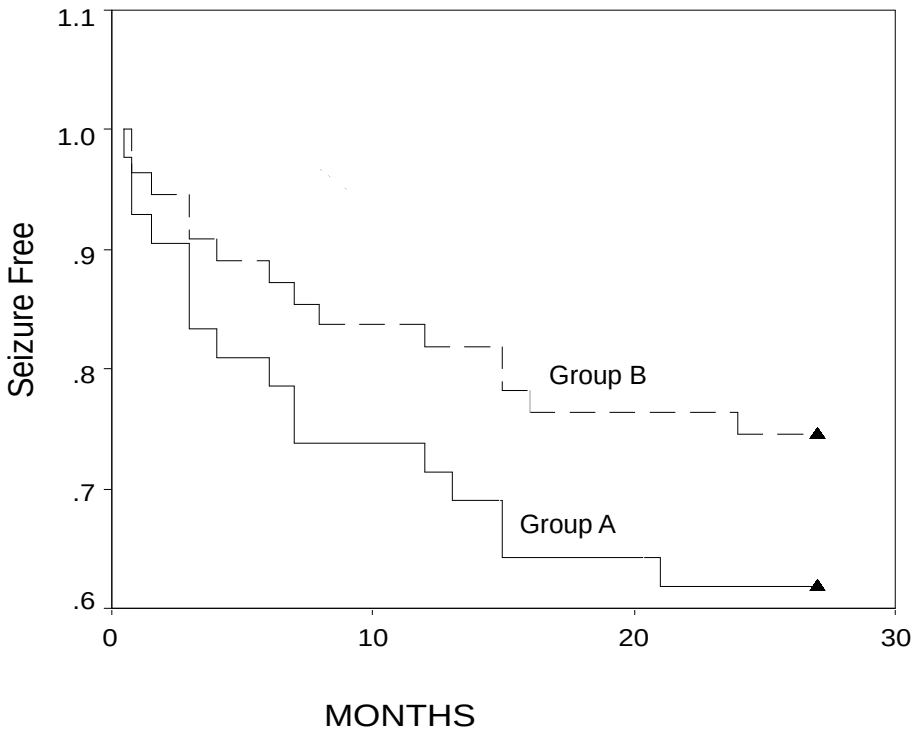
	2 yr seizure free group (n=42)		4 yr seizure free group (n=55)		P value
Age in years	No.	%	No.	%	
12-20	26	62	35	64	NS
> 20	16	38	20	36	
Age of first seizure					
12-20	32	76	40	73	NS
>20	10	24	15	27	
Sex					
Male	26	62	36	65	NS
Female	16	38	19	35	
Education					
Illiterate	3	7	7	13	NS
Can read and write but no schooling	6	14	9	16	
Primary	6	14	22	40	
High school	20	48	12	22	
College	7	17	5	9	
Type of seizure					
Partial	7	17	15	27	NS
Generalized	35	83	40	73	
No. of AEDs					
1	38	90	49	89	NS
>1	4	10	6	11	
AEDs withdrawn					
Phenytoin	18	38	20	32	NS
Valproic acid	10	21	14	22	
Carbamazepine	10	21	14	22	
Phenobarbital	6	12	10	16	
Others	4	8	5	8	
Family history of epilepsy					
Yes	6	15	10	18	NS
No	36	85	45	82	
Duration of active epilepsy					
3 years	26	62	31	56	NS
>3 years	16	38	24	44	
Total No. of seizure					
3	18	43	20	36	NS
>3	24	57	35	64	

Table 3: Risk factors for seizure recurrence during and after tapering of AED

Factors	Relative Risks	95% CI
No. of drugs	1.74	0.79-3.81
Time period	1.49	1.22-1.82
Family history of epilepsy	0.57	0.26-1.27
Duration of active epilepsy*	2.86	2.35-3.48
Total no. of seizures*	1.50	1.30-1.73

CI: Confidence interval
*P<0.05
No. of drugs: The number of AED prior to AED withdrawal, monotherapy versus polytherapy .
Time period: The duration patient were seizure free before AED withdrawal, 2 years versus 4 years.

Figure 1: Proportions of patients remaining seizure free after AED withdrawal according to the seizure free duration before AED tapering. Group A: seizure free 2 years before AED withdrawal, Group B: seizure free 4 years before AED withdrawal.



treatment. Medication expenses will be lower. The length of time during which a patient must be restricted to from the activities such as driving may be reduced. Likewise the outcome of the attempt to discontinue treatment may be known sooner, shortening the period of adjustment for the patient. In brief, our data indicated that a similar risk of seizure recurrence in patients who were seizure free for 2 years or 4 years, favoring the early withdrawal of AED when a decision is made to discontinue the medication.

Our study also showed that longer duration of active epilepsy and higher number of seizures prior to the control increased the risk of seizure recurrence after AED withdrawal. Both these factors are indicative of more severe disease, and are consistent with other previous studies.[14-19]

REFERENCES

1. Specchio LM,Tramacere L, Neve A La, Beghi E. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. *J Neurol Neurosurg Psychiatry* 2002 ; 72: 22-5.
2. Callaghan N,Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. *N Eng J Med* 1988; 318: 942-6.
3. Merritt HH. Medical treatment in epilepsy. *BMJ* 1958; 1: 666-9.
4. Commission on Epidemiology and prognosis of the International League against epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993; 34: 592-6.
5. Kaplan EL, Meier P. Non parametric estimation for incomplete observation. *Journal of American Statistical Association* 1958; 53: 457-81.
6. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: A meta-analysis. *Neurology* 1994; 44: 601-8.
7. Shinnar S, Berg AT, Moshe SL. What happens to the children with epilepsy who experience a seizure recurrence after withdrawal of antiepileptic drugs. *Ann Neurol* 1996; 40: 301-2.
8. Shinnar S, Berg AT, Moshe SL. Discontinuing antiepileptic drugs in children with epilepsy: A prospective study. *Ann Neurol* 1994; 35: 534-45.
9. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet* 1991; 337: 1175-80.
10. Shinnar S, Vining EPG, Mellits ED, *et al*. Discontinuing antiepileptic medication in children with epilepsy after two years without seizures: a prospective study. *N Eng J Med* 1985; 313: 976-80.
11. Mastropaolo C, Tondi M, Carboni F, Manca S, Zoroddu F. Prognosis after therapy discontinuation in children with epilepsy. *Eur Neurol* 1992; 32: 141-5.
12. Tennison M, Greenwood R, Lewis D, Thorn M. Rate of taper of anti-epileptic drugs and the risk of seizure recurrence in children. *N Eng J Med* 1994; 330: 1407-10.
13. Berg AT, Shinnar S ,Chadwick D. Discontinuing antiepileptic drugs. In: Engel J Jr, Pedley TA, eds: Epilepsy: A comprehensive textbook. Philadelphia: Lippincott-Raven Publishers, 1997: 1275-84.
14. Specchio LM, Tramacere L, Neve LAA, Beghi E. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. *J Neurol Neurosurg Psychiatry* 2002; 72: 22-5.
15. Lamdhade SJ, Taori GM. Study of factors responsible for recurrence of seizures in controlled epileptic for more than 1 years after withdrawal of antiepileptic drugs. *Neurology India* 2002; 50: 295-300.
16. Oller Dourella L, Oller FV. Suppression of antiepileptic treatment. *Eur Neurol* 1987; 27: 106-13.
17. Matricardi M, Brinciotti M, Benedetti P. Outcome after discontinuation of antiepileptic therapy in children with epilepsy. *Epilepsia* 1989; 30: 582-9.
18. Dooley J, Gordon K, Camfield P, Camfield C, Simth E. Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: A prospective study. *Neurology* 1996; 46: 969-74.
19. Emerson R, D'Souza BJ, Vining EP, Hoden KR, Mellits ED, Freeman JF. Stopping medication in children with epilepsy: predictors of outcome. *N Eng J Med* 1981; 304: 1125-9.