Effectiveness of the First Antiepileptic Drug in the Treatment of Epilepsy in Children

Sangeeta Basu[1*], C D Aundhakar[2], Jitendra Kumar[3], Amit Galgali[4], Rakesh Patil[5], Sharanabasav Kirdi[6]

[1, 3,4,5,6]Resident, [2]Professor, Department of Pediatrics, Krishna Institute of Medical Sciences Deemed University, Karad, Maharashtra, INDIA.

[*]Corresponding Address:

sangb69@hotmail.com

Research Article

Abstract: Seizures are the most common pediatric neurologic disorder, with 4% to 10 % of children suffering at least one seizure in the first 16 years of life. [3] If the response of the first antiepileptic drug trial is a powerful marker of outcome, then the early identification of patients who are at risk to fail the initial antiepileptic drug trial should be a priority. The AED chosen for the initial therapy should be one that is for the highly effective for the particular seizure type or syndrome and that is safe and well tolerated. We conclude that presence of history of seizures in family members and the presence of microcephaly can have a significant role to play in the outcome of the trial with the first AED. Good seizure control can be achieved by using mono therapy with the standard first line AED drugs in moderate doses.

Keywords: First Antiepileptic Drug, Epilepsy.

Introduction

Seizures are the most common pediatric neurologic disorder, with 4% to 10 % of children suffering at least one seizure in the first 16 years of life. The incidence is highest in children younger than 3 years of age, with a decreasing frequency in older children. Epidemiologic studies reveal that approximately 150,000 children will sustain a first-time, unprovoked seizure each year, and of those, 30,000 will develop epilepsy.[1] Epilepsy is disorder of the brain that is characterized by an enduring predisposition to generate seizure. WHO estimates that eight people per 1000 worldwide have this disease.[2] the majority of children and adults with epilepsy are effectively treated with antiepileptic drugs but approximately 30-40% patients have persistent seizures despite antiepileptic drugs. Both population-based and hospital –based studies have found that the response to the initial antiepileptic drug trial carries significant implications for long term prognosis.[3] If the response of the first antiepileptic drug trial is a powerful marker of outcome, then the early identification of patients who are at risk to fail the initial antiepileptic drug trial should be a priority. The AED chosen for the initial therapy should be one that is for the highly effective for the particular seizure type or syndrome and that is safe and well tolerated. For patients with epilepsy, effective seizure control is the most important determinant of good quality of life. To achieve this, AED dosages should be individualized to maximize therapeutic benefit and to avoid most, if not all, adverse effects. In view of these facts we decided to study the effectiveness of the first AED in control of epilepsy with relation to variables like age, sex, family history, clinical presentation, EEG and imaging and to study the mean dose for first line AEDs (Carbamazepine, valproate, Phenytoin) in relation to type of seizure and seizure control.

Materials and Methods

This was a hospital based retrospective and prospective study. In our study all children between the ages of 1 month to 14 years that have been evaluated and treated in the department of pediatrics, Krishna institute of medical sciences from September 2011 to December 2013 and followed up for a minimum of 1 year were included. All newly diagnosed cases of epilepsy and those who presented with untreated epilepsy were included in the study. According to our study all children who presented with epilepsy and those who were evaluated and treated, those who had adequately documented history of one or more clinically definite, spontaneous, unprovoked a febrile epileptic seizures, those who had come for a minimum follow up of 1 year. And a minimum of 3 follow–ups during the first year (to ensure compliance) were all included in our study. Based on our exclusion criteria, children already treated with antiepileptic drugs (other than short-acting drugs to treat status epilepticus), children requiring more than one AED at initiation of treatment (during the first admission or the first OPD visit), children having acute symptomatic seizures (metabolic disorders, poisons, CNS infections, head injury or neurodegenerative disorder), children who had their onset of seizure in the neonatal period. And those with cerebral palsy were all excluded from our study. The choice of AED and the discretion of the treating physician and the response to the treatment were studied. Each patients response to the first antiepileptic drug was classified as: 1.Seizure freedom 2.persistent seizures despite optimal dosage. 3. Withdrawal of the drug due to adverse effects. The outcome variables studied were:

1.Age at onset of first epileptic seizure.2.Sex 3.Seizure type 4.Family history of seizures 5.History of febrile seizures prior to presentation 6.Clinical features 7.EEG findings. 8. AED used.9.Adverse effect 10.Mean average dose of the drugs. Epilepsy in our study was defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.[4] Efficacy of a drug was defined as a reduction in seizure frequency and /or severity directly attributable to treatment, the most important outcome being prolonged periods of remission of seizures.[4] Drug tolerability was assessed by the incidence, severity and impact of drug induced adverse effects, the most important of which is discontinuation of a drug because of intolerable or life-threatening adverse reactions.[4]Seizure control was termed when there were no auras or seizures of any type for a minimum of 1 year[5].Successful treatment was defined when only one AED was used for seizure control. [5]Treatment failure was coined when more than one AED used for seizure control.[6]

Results

According to our inclusion criteria 78 children were enrolled in our study. The mean age at onset of epilepsy in our study was 6.4 years (standard deviation 4.3 years). In the present study the age groups of 1-5 years,5-10 years and >10 years had a similar presentation. Table 1 shows the age of onset of first epileptic seizure. There were 45 (57.7 %) of males and 33 (42.3 %) of females amongst those who presented with untreated epilepsy. Our study showed a male preponderance for epilepsy.

Table 1: Age at onset of first epileptic seizure

Age group	Total no of cases	Percentage
1 month-1 year	8	10.3 %
1-5 years	26	33.3 %
5-10 ears	22	28.2%
>10 years	22	28.2 %

Table 2 shows the distribution of seizure type in children with untreated epilepsy. The most common seizure type at presentation was generalized tonic-clonic seizure (53.8%),followed by complex partial seizure (44.9%).Multiple seizure types were present in 5 children (6.4%, all being a combination of GTCS with CPS.

Table 2: Distribution of seizure type in children with untreated epilepsy

Seizure type	Total no of cases (n=78)	Percentage
GTCS	42 *	53.8 %
CPS	35 *	44.9 %
Absence Seizures	5	6.4 %
Atonic	1	1.3 %

*Multiple seizure types were present in 5 subjects (GTCS + CPS) A history of febrile seizures in the past was present in 7(9%) children. History of febrile seizures in the past had no statistically significant correlation with the presence of seizure during follow up (p=0.69) or the final treatment outcome (p=0.72).12.8% of the study population had a history of seizures in family members. Statistically significant correlation was observed between the presence of seizure in family members and the presence of seizures during follow up (p=0.04). In the study group microcephaly was present in 5 children, neurocutaneous markers in 8 children, dysmorphology in 6 children and neurodeficit in 7 children. ADHD and temper tantrums requiring interventions were seen in 3 and 6 children respectively, Speech delay was present I 4 off them. Presence of microcephaly had a significant correlation with the treatment outcome (p=0.03) Out of the 5 children who had microcephaly, only 1 attained seizure control with the first AED. In the present study, 75.6 % had EEG abnormalities and in a further 10.3 %, the EEG showed borderline abnormalities. Of the abnormal EEGs. 48.7 % were generalized and 26.9 % showed focal abnormalities. Presence of EEG changes had no significant correlation with treatment success (p=0.94) in the our study. Carbamazepine was the most common drug used (57.7 %), followed by Valproate (29.5 %) and phenytoin (9.0%).2 children who presented during infancy received phenobarbitone and 1 child received Levetiracetam. These were excluded from further analysis as the sample size was small. Table 3 shows the first AED used in children with epilepsy.

Table 3: First antiepileptic drug used in the children who presented with epilepsy

AED	Total no of cases	Percentage
Carbamazepine	45	57.7%
Sodium valproate	23	29.5%
Phenytoin	7	9.0%
Phenobarbitone	2	2.6%
Levetiracetam	1	1.3 %

Overall, 51 children (65.4 %) of the study group achieved seizure control with the first AED used. Treatment failed in 27 (34.6%) of them. Treatment failed due to poor control despite optimum dose in 24 (31%) of them and due to intolerable side effects in 3 of them.3 (4 %) of the children who had been on Carbamazepine had developed skin rash with oral mucosal involvement necessitating change of AED. No their adverse events were noted in the study. Better seizure control was achieved Valproate or Phenytoin in the GTCS group (86.6 %, 83.3 % respectively) Among the CPS group, Carbamazepine was effective inn seizure control for 17(65.4%) out of 26 cases (65.4%).Carbamazepine was not effective in seizure control for 7(29.6%) out of 26

cases requiring add-on drug.2 out of the 26 cases required change in medication due to adverse drug reaction. Table 4a and 4b show the response to AED in children presenting with GTCS and CPS.

Table 4a: Response to aed in children presenting with gtcs

GTCS (N=39*)				
Drug	**Seizure free n=20**	**Seizures during follow up n=18**	**Intolerable side effects n=1**	**Treatment success n=27**
Carbamazepine n=18	5 (27.8%)	12(66.7 %)	1 (5.5 %)	9 (50%)
Valproate n=15	10 (66.6 %)	5 (33.3 %)	0	13(86.6%)
Phenytoin n=16	5 (83.3 %)	1 916.7 %)	0	5 (83.3)

*3 cases excluded -2 on Phenobarbitone, 1 on Levetiracetam

Table 4 b: Response to AED in children presenting with CPS

CPS (N=30*)				
Drug	**Seizure free n=15**	**Seizures during follow up n=13**	**Intolerable side effects n=2**	**Treatment success n=19**
Carbamazepine n=26	14 (53.8 %)	10(38.5 %)	2 (7.7 %)	17 (65.4 %)
Valproate n=3	1(33.3 %)	2(66.7%)	0	2 (66.7 %)
Phenytoin n=1	0	1 (100%)	0	0

*An additional 5 subjects had both GTCS and CPS at presentation. Carbamazepine (n=45), Valproate (n=23) and Phenytoin (n=7) were the most frequently prescribed AED. The mean dose of AED at which seizure control was attained was Carbamazepine =12.9 (7.1-22) mg/kg/day, Valproate =17 (9-35) mg/kg/day and Phenytoin (4.6 -5.6) mg/kg/day. In children with newly diagnosed epilepsy monotherapy with Carbamazepine,Valproate and Phenytoin was effective in 57.8 %, 82.6% and 71.4 % respectively.

Discussion

In the present study we demonstrated the effectiveness of the first AED in control of epilepsy with relation to certain variables like age, sex, family history, clinical presentation and EEG findings. The mean age of epilepsy in our study were comparable to results found in a study by Ma.*et al*.[7] In our study all of the age groups from 1-5 yrs, 5-10 yrs and more than 10 years presented in similar portions. In most of the previous studies the most common age of onset of epilepsy was 1-5 years.[8,9.] The male ponderance in our study was supported by studies by other authors.[10.11.]Most common seizure in the study was generalized tonic-clonic followed by complex partial seizures. Similar results were found in studies by Luong mac *et al* (generalized seizures (50-69%) and partial seizures (31-50 %).[9] One major concern when dealing with children with initial Febrile seizure is the risk of subsequent epilepsy. Following a first febrile seizure,2-4 % of children will experience at least one unprovoked seizure and most of these children will subsequently develop epilepsy.[12] We did not find any such correlation in our study. Although similar to our findings Hauser *et al* had also shown a positive correlation between seizure relapse and positive family history of seizures.[13] An abnormal EEG has been a consist et predictor of recurrence, although there has not been an agreement on the nature of the predictive EEG abnormality.[13] Presence of EEG changes had no significant correlation with treatment success in the our study. The fundamental goal of AED therapy is to prevent seizures without causing side effects from the medication The AED chosen for initial therapy should be one that is highly effective for the particular seizure type or syndrome and that is safe and well tolerated. Current treatment guidelines recommend monotherapy in most cases because similar efficacy and better patient tolerability compared to polytherapy.[14] Overall, 65.4 % of the study group achieved seizure control with the first AED, which is comparable to the results from previous studies by Camfield *et al* [6] (66.2 %) and Sillanpaa *et al*. [10](64 %). Carbamazepine is one of the primary drugs for the treatment of symptomatic epilepsy with partial and generalized tonic/clonic seizures. It is the drug of first choice for all newly diagnosed partial epilepsies after the age of 2 years. One of the common side effects include the appearance of rash (Steven Johnson's and Drug Rash Eosinophilia and Systemic Symptoms-DRESS syndrome) and should be reported immediately. Similar findings were evidenced in our study as Carbamazepine was effective in controlling a significant number (65.4 %) of CPS cases. Although 2 cases required change in medicine due to the appearance of rash as a side effect. Valproate is the broad spectrum AED with efficacy for virtually all seizure types. It is proven effective both as an add-on and a single treatment for partial and generalized tonic/ clonic seizures. Phenytoin remains a first –line medication for epilepsy due to its efficacy against a range of syndromes, low cost and ease of use. [15] We achieved a good seizure control with Valproate (86.6 %) and Phenytoin (83.3 %) in the GTCS group respectively. Studies suggest that, in routine clinical practice, dosage individualization is often suboptimal.[16] this may lead to patients receiving unnecessarily large dosages. Conversely it may also lead to the patients switching to an alternative therapy without exploration of the full dosage range. Although individualization of dose is essential in epilepsy therapy,

identification of the optimal dose on purely clinical grounds can be difficult. We demonstrated in our study that effective seizure control can be obtained with moderate doses of AED, with the higher end of the spectrum required only in a few.

Conclusion

We conclude that presence of history of seizures in family members and the presence of microcephaly can have a significant role to play in the outcome of the trial with the first AED. Good seizure control can be achieved by using monotherapy with the standard first line AED drugs in moderate doses. Many of the common epilepsies that occur in childhood have no adult counterpart and others begin in childhood and may persist into adulthood. Thus, physicians must very often rely on their own medical judgment to select the best treatment option for an individual patient.

References

1. Friedeman, M.J and Shareiff, G.Q. Seizures in children. Pediatric Clinics of North America 2006, 53; 257-277.
2. Fact sheet: Epilepsy (internet).WHO (2012). at <http://www.who.int/mediacentre/factsheets/fs999/en/index.html
3. Kwan. P and Brodie, M.J. Early identification of refractory epilepsy. New England Journal of Medicine 2000; 342:314-319.
4. Fisher, R. S *et al.* Epileptic seizures and epilepsy: definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).Epilepsia 2005, 46; 470-472.
5. Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. Epilepsia. 1998; 39:799-803.
6. Camfield P.R, Camfield C.S, Gordon. K and Dooley.. J.M. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? Journal of Pediatrics. 1997; 131:821-824.
7. Ma, M.S *et al*. Effectiveness of the first antiepileptic drug in the treatment of pediatric epilepsy. Pediatric Neurology. 2009; 41:22-26.
8. Berg. A.T, Shinnar. S, Levy. S.R and Testa. F.M. Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia. 2005; 40:445-452.
9. Tu Luong Mac *et al*. Epidemiology, etiology and clinical management of epilepsy in Asia: a systematic review. Lancet Neurol.2007; 32:533-543.
10. Sillanappa. M, Jalava M, Kaleva o. Long term prognosis of seizures with onset in childhood. New England Journal of Medicine.1998:338; 1715-1722.
11. Canfield. P.R et *et al* .Epilepsy after a provoked seizure in childhood.Neurology.1985; 35:1657.
12. Wairuru. C.F ebrile seizures: an update. Archives of disease in childhood.2004:89:751-756.
13. Hauser. W.A, Rich S, Annegers. J.F and Anderson. Seizure recurrence after a 1st unprovoked seizure: an extended follow up. Neurology. 1990:40:1163-1170.
14. Hirtz D.*et al*. Practice parameter: treatment of the child with first unprovoked seizure; Neurology.2003; 60:166-175.
15. Glauser T *et al*. ILAE treatment guidelines; evidence based analysis of anti-epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006:47:1094-1120.
16. Perucca E, Dulac O Shorvon S. Harnessing the clinical potential of anti-epileptic drug therapy :dosage optimization.CNS drugs. 2001:15:609-621.