Original Research Article

Monotherapy and polytherapy in Paediatric seizures: A prospective, observational study in a tertiary care teaching hospital

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Abstract

Background: Epilepsy is a common neurological disorder in children and its treatment still remains a challenge for the physicians. Though there are a number of anti-epileptic drugs with varying mechanisms of action, their adverse effects, and drug interactions are to be analyzed before starting a therapy.
Aim: To study the pattern of prescription in the treatment of pediatric seizures.
Objectives: To observe the pharmaco-epidemiology, utilization pattern and effectiveness of monotherapy and polytherapy in the treatment of seizures in children aged above 2 years.
Materials and methods: This prospective, longitudinal study was conducted for a period of 8months in Paediatric Neurology Department of a tertiary care teaching hospital. The data collected from 41 children at the end of the study, were compiled in a specially designed data form and were analyzed.

Results: The distribution of Paediatric seizures was found to be high in male children (62%) and in the age group of 2 to 5 years (46%). GTCS (85%) was the dominant type of seizure seen in children and 83% of the children were treated with monotherapy. Polytherapy was found to be efficacious compared to monotherapy, with a good seizure control (100%: 94%), good compliance and minimal adverse effects (14.2%: 14.7%).

Conclusion: Monotherapy still remains the mainstay of treatment in pediatric seizures. Though polytherapy appears to be a better option in this study, epilepsy in children requires a long term treatment and hence adverse effects in long term and the effects of drug interactions are the main criteria to be taken care of. A study of longer duration in the treatment of pediatric seizures will provide a better knowledge in the adverse effects of polytherapy.

Key words

Anti-epileptic drugs (AEDs), Seizures, Monotherapy, Polytherapy, Paediatrics.

Introduction

Epilepsy or seizure disorder is a common neurologic disorder in the pediatric age group and occurs with a frequency of 4 -6 cases per thousand children [1]. Epilepsy, particularly childhood epilepsy, remains a challenge to treat. The management of epilepsy is primarily based on the use of anti-epileptic drugs. Surgery and diet therapy are the other modes of treating childhood seizures. The antiepileptic drugs are of two categories namely conventional drugs like sodium valproate, carbamazepine, phenobarbitone, phenytoin sodium and newer drugs like topiramate, lamotrigine, oxcarbazepine etc. Adjuvant drugs like benzodiazepines are also used in this treatment. An appropriate AED should possess the following features:

a) Achieve complete seizure control using a single drug
b) To use the most appropriate formulation to ensure that the child can take and absorb the medication.
c) Economically affordable to the patient.
d) Long term effects on growth and development of the child and short term effects on behavior, intellectual function and pattern of sleep should be taken care of.

The prescription of an AED for a newly diagnosed epileptic depends on the observed type of seizure, age, and sex of the patient and associated co-morbid conditions [2]. Most of the children (60-70%) with newly diagnosed epilepsy have seizures effectively controlled with administration of one appropriately selected AED (monotherapy) at an individualized dosage [3] and a significant proportion (30-40%) of those refractory to initial treatment may respond after switching to an alternate AED [4] or will benefit from a combination of AEDs [5] (polytherapy). No adequately controlled trial has shown the superiority of AED polytherapy compared to monotherapy in producing effective seizure control. In contrast, the efficacy of monotherapy is well established, particularly in patients with recently diagnosed seizure disorders [6].

In other global morbidities like diabetes, hypertension polytherapy is indicated as an initial mode of treatment. For example, JNC-14Guidelines for hypertension [7] advocates the combined therapy of diuretics with other hypertensives as an initial treatment immediately after the diagnosis of hypertension (strategy B). By contrast, the international and Indian Guidelines [8, 9] (ILAE and IAP -16) for treatment of epilepsy emphasizes in strict adherence to monotherapy in initial stages and reserves polytherapy for refractory cases.

In routine clinical practice, however, the benefits of monotherapy are not always adequately exploited, and sometimes treatment is considered

ineffective despite a suboptimal trial of an AED [10]. Common causes of treatment failure include the use of an insufficient dosage, inappropriate dosing schedule, and a poor patient compliance.

This study was selected to analyze the current trend of treatment in pediatric seizures in our tertiary care teaching hospital (RMMCH, Chidambaram) and to understand the advantages of monotherapy.

Materials and methods

The present study focused on the prescribing pattern of Anti-epileptic drugs (AED's) for various seizures occurring in children aged 2 to 16 years, treatment outcomes and associated adverse reactions (ADR). This study was a prospective longitudinal study [11] conducted for a period of 8 months from March to December 2016 among children attending Paediatric neurology outpatient Department of RMMCH, Chidambaram. The approval for this study was obtained from Institutional Human ethical committee. Each child had a minimum of 5 to 6 visits during the study period of 8 months. Cases of Status Epilepticus and children not willing for the study were excluded. Following data were collected and recorded in a specially designed data entry form during each visit [12].

During the study period, the following data were collected from 41 children diagnosed with seizures and on treatment with at least with one AED:

- Gender and age distribution of pediatric seizures.
- Utilization pattern of AEDs as mono and polytherapy.
- Type of epilepsy, the AEDs used in their treatment and their pattern of use in different types of epilepsy.
- Utilization pattern of individual AEDs in mono and polytherapy.
- Adverse reactions of the prescribed AEDs during the study period assessed as per Naranjo ADR probability scale [13].
- The effectiveness of a therapy assessed in terms of efficacy, compliance, and tolerability. Efficacy of an AED is assessed by seizure free interval observed during the study period while details regarding compliance are obtained by an interview with the child's attendant during each visit. Tolerability of AEDs was obtained from the previous criteria (No.5).

Results

Out of 41 children, 27 were male (65.85%) and 14 were female (34.14%). Maximum children were between the age group of 2–5 years (46.34%), as per **Table - 1** and four female children were in the age group of 11 to 16 years. As per **Table - 2**, 34 children (82.92%) were treated with AEDs as monotherapy and 6 children (14.63%) received two drug therapy, while one child (2.43%) had three drug therapy. **Table – 3** showed GTCS was the commonly observed type (85%) of pediatric seizures. Among these 35 children with GTCS, treatment was given as monotherapy in 28 children (80%) and polytherapy in 7 children(20%).The other types of seizures were treated with monotherapy only. **Table – 4** showed Sodium valproate was associated with adverse reactions in 5 children (14.70%). One adverse reaction was observed in a case treated with two drug therapy (phenobarbitone/phenytoin sodium) (14.28%). Change of AED was required in two children treated with sodium valproate. **Table – 5** showed efficacy of monotherapy (94.11%) was comparatively less than Polytherapy. Compliance was good in both forms. The percentage of tolerability or adverse reactions noted during this study (14%) was also equal.

Discussion

The age of the child affected with seizures plays an important role in prescribing an appropriate AED. For example, Sodium valproate is not prescribed in adolescent or girls in child bearing

age due to its teratogenicity [14]. In our study, only one out of 4 female children in the 10-16 age group were on treatment with sodium valproate. Generalised tonic–clonic seizures were the commonest form of seizures observed in children between 2-16 years in our study (85%). A majority of previous studies like Shaireen Usman, et al. (2013) [15] and Jincy George, et al. (2016) [16] has shown the dominance of this seizure type in children. Other types of generalized seizures like myoclonic and absence seizures was observed in 4 children (10%) and partial seizures in two children (5%). Monotherapy was the only form of treatment in these 6 children, while both mono and polytherapy was prescribed in the remaining 35 children diagnosed with GTCS type of seizures. Management of newly diagnosed epilepsy should follow the following IAP Expert Committee guidelines [9]:

a) Long term AED should be started only after second seizure [17]. AED is based on the predominant seizure type or syndrome type with possible adverse effects taken into account [17, 18].
b) Any one of the major first line anticonvulsants (phenobarbitone, phenytoin sodium, valproate, and carbamazepine) can be used first. Carbamazepine and valproate appear to be better tolerated than phenobarbitone and phenytoin sodium.
c) All drugs are started at lower doses and increased gradually up to a maximum dose till seizure control is achieved or side effects appear.
d) If no control is achieved with maximum doses of the first drug, then a second first line AED is initiated and the first drug tapered [18]. When switching AEDs, selecting an agent with a different mechanism of action may increase the likelihood of a successful treatment response. If partial control is achieved [17], then a second AED should be added. Since 35% of patients with epilepsy will not respond to monotherapy, most refractory cases become candidates for polytherapy [18, 19].

Table – 1: Gender and age distribution of Epileptic children.

Age group in years	Male children n (%)	Female children n (%)	All children n (%)
2-5	13(31.70%)	6(14.63%)	19(46.34%)
6-10	10(24.39%)	4(9.75%)	14(34.14%)
11-16	4(9.75%)	4(9.75%)	8(19.51%)

Table – 2: Utilization pattern of AEDs as Monotherapy and Polytherapy.

Drug Therapy	No. of Patients	Percentage
Monotherapy	34(41)	83%
Two drug therapy	06(41)	15%
Three drug therapy	01(41)	2%

In our study, all the above guidelines were appropriately followed. Sodium Valproate was the commonly prescribed first line AED in idiopathic generalized epilepsy (82%).It was used as a single drug in 70% of children and in combination with other AEDs in the remaining children. Various clinical trials [3, 4] have proved that initial monotherapy with Sodium valproate in newly diagnosed epilepsy achieves freedom from seizures for at least 1-year in 74% of GTCS and 62% of the partial type of seizures. In the present study, 34 children (82%) had good control of seizures during the study period with a single AED treatment while 7 children (18%) were found refractory to monotherapy. 5% of children on monotherapy required an increase of dosage of same AED for complete seizure control while 18% of children with uncontrolled

seizures with an initial AED was added a second AED like carbamazepine (5%), Phenytoin sodium (5%) and a newer AED Topiramate (2%) with sodium valproate. After induction of polytherapy, there was a good control of seizures. Only one child with GTCS type required Clobazam as an adjuvant to sodium valproate and phenytoin sodium to achieve remission of seizures during this study.

Table – 3: Types of seizure and treatment prescribed.

Type of seizure seizure	**No. of children affected/ Total children**	**One drug therapy used / Drug used**	**Two drug therapy/ Drugs used**	**Three drug therapy/ Drugs used**
Generalised Tonic-clonic	35/41 (85%)	Sodium valproate 26 (74%) Carbamazepine 2 (6%)	Sodium valproate+ Phenytoin sodium 2 (6%) Sodium valproate+ Carbamazepine 2 (6%) Sodium valproate+ topiramate 1 (3%) Phenytoin sodium +Phenobarbitone 1 (3%)	Sodium valproate +clobazam +Phenytoin Sodium 1(3%)
Generalised myoclonic	2/41 (5%)	Sodium valproate 1(50%) Carbamazepine 1 (50%)	-	-
Generalised Absence	2/41 (5%)	Sodium valproate 2 (100%)	-	-
Partial simple type	2/41 (5%)	Oxcarbamazepine 2 (100%)	-	-

Table - 4: Observed Adverse reactions.

No. of patient	**ADR reported**	**Suspected drug**	**Casuality relationship**	**Whether treatment with AED continued/ stopped**
2	Hyperactivity	Sodium Valprovate	Possible	Stopped
1	Behavioural disturbances/ Hyperactivity	Phenytoin /Phenobarbitone	Possible	Continued
1	Weight gain	Sodium Valproate	Possible	Continued
1	Sedation	Sodium Valprovate	Possible	Continued
1	Oral ulcers	Sodium Valprovate	Possible	Continued

Table - 5: Effectiveness of a therapy.

End points	Monotherapy (n/N)%	Polytherapy (n/N)%
Efficacy (Seizure free period)	32/34(94%)	7/7 (100%)
Compliance	Good	Good
Tolerability	5/34 (14.70%)	1/7 (14.28%)

Monotherapy is desirable because using one drug controls seizure in most patients with fewer side effects [20]. Advantages of monotherapy are:

- Lower cost
- Reduced potential for adverse reaction
- Undesirable drug interactions
- Improved medicine compliance with a more simplified drug administration schedule [21].

These factors carry greater significance as our study population is children and adolescents. AED monotherapy may fail for a variety of reasons [22] including inaccurate diagnosis of seizure leading to ineffective AED choice, intolerable adverse effects (e.g. sedation, cognitionproblems), idiosyncratic reactions (e.g. rash, aplastic anaemia), non-compliance, overtreatment [23] and pharmacogenetic factors [24].

There are no randomized trials to suggest the superior efficacy of polytherapy over monotherapy. The main pharmacokinetic interactions in polytherapy are CYP 450 metabolism competition and a high percentage of protein binding those results in drug displacement. Co-administration of enzyme inducing AEDs like phenobarbitone, phenytoin or carbamazepine with inducible AEDs such as lamotrigine, topiramate hastens the metabolism of the later, reducing drug concentration and efficacy. The concept of “Rational polytherapy” has held that AED combination with differing MOA is more effective than polytherapy with similar MOA [25]. Several preclinical experiments suggest synergistic efficacy between a specific combination of AEDs, including phenytoin and phenobarbital [26]; valproate with phenytoin, carbamazepine or ethosuximide [27]. In our present study also valproate was combined phenytoin sodium/carbamazepine and phenytoin sodium with phenobarbitone in the treatment of GTCS not controlled with monotherapy. As per IAP Expert Committee Guidelines, Clobazam is used as add-on therapy in uncontrolled GTCS. In our study also Clobazam was used as an add-on therapy with sodium valproate and phenytoin sodium in one child with GTCS.

Table - 4 shows the adverse reactions noted during this study and assessed as per Naranjo scale [13]. Adverse reactions were noted in only 15% of study population. Five children (15%) on monotherapy with Sodium valproate developed adverse reactions like hyperactivity, weight gain, and sedation. The behavioral disturbance was observed in one child treated with phenytoin sodium + phenobarbitone. All the reactions were not serious warranting treatment and the relationship were possible to the drugs in all cases. No serious drug specific adverse reactions were noted during this study. For example, Hepatotoxicity of Sodium valproate was assessed by the pediatrician by conducting Liver function tests in the regular interval in all children receiving this drug. Alterations in the values of the liver function tests could not be appreciated during the study period.

Controlling seizures with minimal adverse effects and maintaining the patient's ability to perform daily activities are the critical measures of treatment outcome [28]. In our study, 95% of children had complete control of seizures during the study period and adverse reactions were noted in only 15% of study population. The effectiveness of monotherapy is shown a good efficacy (94%), good compliance and reduced adverse reactions (14.7%) in this clinical study. 2 children on monotherapy with incomplete seizure control improved with an increase in dosage of

same AED. ILAP guidelines were thus exactly followed by our pediatrician during this study period. Though polytherapy shows a good compliance and effectivity, the risk of adverse effects in long term treatment should not be forgotten. Monotherapy is most likely to be effective if the clinician develops a personalized treatment plan that is appropriately customized for the individual child, provides the child's attendant with suitable education regarding the AED chosen and surveillance with evolution of any adverse effects to enable prompt feedback and modification of the titration scheme or target dose [29].

Conclusion

Monotherapy still remains the mainstay of treatment among paediatric seizures. Monotherapy is efficacious in most children with better tolerability than polytherapy. Monotherapy facilitates compliance among children, who are usually aversive in taking drugs. Last, but not the least, monotherapy avoids the problem of adverse drug interactions. On the physician's part, monotherapy enables him to adjust the dosage more easily to suit the patient. Although it is acknowledged that a small group of refractory cases may require combination therapy, the paediatrician should fully exploit the possibilities of single AED therapy before adding another AED.

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