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DRUG UTILIZATION PATTERN OF ANTIEPILEPTICS AND THEIR ADVERSE EFFECTS IN PEDIATRICS

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ABSTRACT

Objectives: The main objectives of the study are to describe the drug utilization pattern of anti-epileptic drugs (AEDs), to get an insight into drug use and/or prescribing patterns, to study the effects (beneficial and adverse) of anti-epileptic drugs, to promote appropriate drug use through patient counseling and pharmacist intervention and provision of results for the clinicians, to aid in selecting appropriate anti-epileptics. **Design:** Prospective study **Setting:** Department of Pediatrics, Sri Ramachandra Medical Centre, Chennai **Participants:** Children aged ≤18 years, of both sexes with seizure disorder who were on anti-epileptic drugs for more than 6 months in both outpatient and inpatient departments. **Main outcome measures:** Drug utilization pattern was studied by going through the medication chart. Adverse drug reactions were monitored by interviewing the patients and their parents and they were assessed using Naranjo ADR probability scale. Potential drug interactions were identified by using data bases like uptodate.com, drugs.com and micromedex. Accuracy of doses is assessed by the guidelines of Indian Academy of Pediatrics. **Results:** Among 170 patients, 235 AEDs was prescribed. Sodium valproate (n=87, 37.02) was the most commonly prescribed AED. The overall incidence of adverse drug reactions was low. We encountered use of phenytoin and carbamezapine in 33 patients with Idiopathic generalized seizures, phenyotin in 2 patients with focal seizures, which was

not in accordance with the guidelines for diagnosis and management of childhood epilepsy by Indian Academy of Pediatrics. **Conclusion:** Pharmacist plays an important role in monitoring adherence of drug usage to the guidelines, drug interactions, adverse drug reactions and this study helps to promote appropriate antiepileptics and to serve to the health care professionals.

KEYWORDS: Anti-epileptic drugs, Children, Seizure.

INTRODUCTION

Epilepsy is a chronic disorder characterized by recurrent seizures [1]. There are 55, 00,000 persons with epilepsy in India, 20, 00,000 in USA and 3, 00,000 in UK [2]. Epilepsy is the most common neurological disorder in children, and it is characterized by a spontaneous propensity for recurrent and unprovoked seizures. Epilepsy, in particular childhood epilepsy, remains a challenge to treat [3]. Around 4%–10% of children suffer at least one seizure in the first 16 years of life [4]. The incidence is highest in children below 3 years of age, with a decreasing frequency in older children [5].

Common types of seizures are [6, 7]: 1) Partial seizures - Simple partial seizures, Complex partial seizures 2) Febrile seizures 3) Generalized seizures 4) Unclassified seizures 5) Status epilepticus

Seizures result from excessive excitation or in the case of absence seizures from disordered inhibition of a large population of cortical neurons [8]. Control of abnormal neuronal activity with anti-epileptic drugs (AEDs) is accomplished by elevating the threshold of neurons to electrical or chemical stimuli or by limiting the propagation of the seizure discharge from its origin.

More number of drugs is currently available for the treatment of epilepsy. Older/conventional drugs used as first line agents include phenytoin, carbamazepine, valproic acid, phenobarbitone. They are relatively less expensive than the newer anti-epileptics. Newer anti-epileptics include gabapentin, clobazam, levetiracetam, lamotrigine, clonazepam, lorazepam, vigabatrine, topiramate, tiagabine, zonasimide. They have lesser adverse effects and few drug interactions, if any [9, 10].

The overall aim of AED treatment is to reduce epileptic seizure frequency and enhance patient's quality of life with as few adverse effects and as few co-medications as possible while minimizing long-term detrimental effects. In children, the outcome of AED therapy

depends on various factors, which include selection, dosing and monitoring of AEDs, the identification of underlying cause, the type of seizures and the pharmacokinetic parameters of AEDs. All these factors are essential for successful management of seizure, but there is a lack of properly conducted outcome-based studies in pediatrics. The current AED development system essentially renders children with epilepsy "therapeutic orphans", who can only benefit if the drugs developed for adults are also effective for children [11].

Drug utilization was defined by World Health Organization (WHO) in 1977 as the marketing, distribution, prescription, and use of drugs in the community, with special importance on the medical, social and economic consequences [12]. Epidemiological study is useful in providing proper services for epileptic patients and improving their quality of life. There is an urgent need for pharmacotherapy data from developing countries such as India.

Few economic studies have explored the cost-effectiveness of AEDs. The analyses under taken have focused more on the overall cost of epilepsy, the effect on mortality and the impact upon quality of life [13]. Studies focusing on the economics of childhood epilepsy are limited [14].

The main objectives of the study are to describe the drug utilization pattern of anti-epileptic drugs (AEDs), to get an insight into drug use and/or prescribing patterns, to study the effects (beneficial and adverse) of anti-epileptic drugs, to promote appropriate drug use through patient counseling and pharmacist intervention and provision of results for the clinicians, to aid in selecting appropriate anti-epileptics [15].

MATERIALS AND METHODS

This prospective study was conducted in the department of Pediatrics, Sri Ramachandra Medical Centre, Chennai, for a period of 9 months, after getting approval from the Research & Ethics Committee, Faculty of Pharmacy, Sri Ramachandra University. Children aged ≤18 years, of both sexes with seizure disorder who were on anti-epileptic drugs for more than 6 months in both outpatient and inpatient departments were included in the study. Informed consent was obtained from the children's parent. Children having seizures associated with acute conditions like CVA, poisoning, fever, meningitis were excluded from the study. The demographic data, type of seizures, antiepileptic drugs, its dose, dosage form, frequency, duration, and co-morbidities were recorded in a specially designed proforma. Adverse drug reactions were monitored by interviewing the patients and their parents and they were

assessed using Naranjo ADR probability scale. Potential drug interactions were identified by using data bases like uptodate.com, drugs.com and micromedex. Accuracy of doses is assessed by the guidelines of Indian Academy of Pediatrics. Results were analyzed statistically.

RESULTS

A total of 170 patients were included in the study. Among them 93(54.71%) were males and 77(45.29%) were females. Majority of the patients were in the age group of 0-3 yrs (n=45, 26.47%). Among 170 patients, 100(58.82%) were out patients and 70 (41.18%) were inpatients. Majority of the children were diagnosed with Idiopathic generalized seizures (n=136, 80%), followed by complex partial seizures (n=16, 9.41%).

Among 170 children, 38 were with co-morbidities. The co-morbidities associated with seizures are depicted in table 1.

Table 1: Co-Morbidities of The Patients Associated With Seizures.

Co-morbidity	Number (38)	Percentage (%)	Type of seizure
Attention deficit hyperactivity disorder (ADHD)	2	5.26	Idiopathic generalized seizures(2)
Atrial septal defect (ASD)	1	2.63	Idiopathic generalized seizures(1)
Developmental delay	29	76.32	Idiopathic generalized seizures(23) Neonatal seizures(1) Absence seizures(2) Status epilepticus(1) Complex partial seizures (2)
Down's syndrome	1	2.63	Status epilepticus
Headache	5	13.16	Idiopathic generalized seizures(3) Status epilepticus(1) Absence seizures(1)

Among 170 patients, 235 AEDs was prescribed. Sodium valproate (n=87, 37.02) was the most commonly prescribed AED irrespective of the type of seizures, second commonly prescribed AED was phenytoin (n=56, 23.83%), followed by clobazam (n=28, 11.91%) and carbamazepine (n=22, 9.36%). Monotherapy was prescribed for 120 children (70.5%), dual therapy for 37 children (21.7%0, triple therapy to 11 children (6.4%) and four AEDs was prescribed for 2 children (1.1%). Among monotherapy, sodium valproate (n=57, 48.31%)

was the most commonly prescribed drug followed by phenytoin (n=25, 21.19%). The most frequently used combination for dual therapy was sodium valproate + phenytoin (n=7, 18.92%) and phenytoin + clobazam (n=7, 18.92%). Of the triple therapy, most frequently used combination was sodium valproate + phenytoin + levetiracetam (n=3, 27.27%) followed by sodium valproate + phenytoin + clobazam (n=2, 18.18%).

AEDs were given in dosage forms of syrup, tablet and injection. Table 2 indicates the dosage forms of various AEDs prescribed.

Table 2: Dosage Forms of Various AEDs Prescribed.

Type of dosage form	Number	Percentage	Drugs
Syrup	55	22.73%	Sodium valproate (38) Phenytoin (10) Levetiracetam (3) Phenobarbitone (2) Clonazam(10
Tablet	164	67.77%	All AEDs
Injection	19	7.85%	Phenytoin (12) Sodium valproate (12) Clobazam (3) Levetiracetam (10)

Prescribing pattern of AEDs along with the compliance guidelines is given in table 3.

Table 3: Type of Seizure And Drugs Prescribed Along With Compliance Rate.

Type of seizure	Commonest drug prescribed alone or in combination	Second commonest drug prescribed alone or in combination	Other drugs	Compliance with guidelines		
				Good (%)	Average (%)	Poor (%)
Idiopathic generalized seizures	Sodium valproate (65)	Phenytoin (46)	Clobazam(19) Lamotrigine(2) Levetiracetam(15) Lorazepam(2) Carbamezapine(15) Clonazepam(1) Phenobarbitone (6)	56.63	19.11	24.26
Complex partial seizures	Sodium valproate (9)	Clobazam (4)	Carbamezapine(2) Clobazam(4) Phenytoin (2) Phenobarbitone (3)	62.5	37.5	---
Focal seizures	Phenytoin (2)	Carbamezapine(1), sodium valproate(1).	---	25	25	50
Absence seizures	Sodium valproate (4)	---	Phenytoin (1) Carbamezapine(1)	100	---	---
Neonatal	Phenobarbitone (1)	---	---	50	50	---

seizures	Sodium valproate (1)					
Rolandic epilepsy	Oxy carbamezapine	---	---	100	---	---
Status epilepticus	Phenytoin (5)	Sodium valproate (4)	Clobazam (1)	100	---	---

30 prescriptions were found to have potential drug interactions. Among those, 18 prescriptions were found with drug interaction between AEDs in which 6 were mild and 22 were moderate. 12 prescriptions were found with interaction between AEDs and other drugs in which 12 were mild and 7 were moderate.

Adverse drug reactions were observed in 9 patients. The ADR along with the causality assessment is denoted in table 4.

Table 4: Adverse Drug Reaction Along With Causality Assessment.

No. of patients	ADR reported	Suspected drug	Causality relationship	Whether treatment with AED continued/stopped
2	Drowsiness	Phenytoin	Probable	Continued
1	Drowsiness, weight loss	Sodium valproate	Probable	Continued
1	Drowsiness	Sodium valproate	Possible	Continued
1	Gum swelling	Phenytoin	Probable	Continued
1	Hyperactive	Sodium valproate	Possible	Continued
1	Skin rashes	Lamotrigine	Probable	Stopped
1	Weight gain	Sodium valproate	Possible	Continued
1	Weight loss	Sodium valproate	Possible	Continued

DISCUSSION

This study described the utilization pattern of anti-epileptics (AEDs) in 170 patients in the Department of pediatrics of a tertiary care University teaching hospital. Unlike the subjects included in other pharmacoepidemiologic study population, our study focused on children aged 1-18 years. Maximum number of cases (n =45, 26.47%) was observed between age group of 0-3 years. It is in contrast to the previous studies, in which majority of children fall in 6-10 years age group[16]. Consistent with earlier studies, epileptic seizures were found to be more common in boys (n =93, 54.70%) than in girls (n = 77, 45.29%) in our study [15, 17. 18, 19]. More number of patients were out patients (n =100, 58.82%). Out of 170 patients, 6 patients were under weight, 16 patients had a family history of seizures.

Idiopathic generalized seizures were the commonest type of seizure, contributing to 80% which is similar to the study conducted by Mathur S et al [20]. In our study, sodium valproate was the commonest drug used for seizure, followed by phenytoin, which is in contrast to the previous study conducted by Nandhakumar et al [21], which reports that phenytoin was the commonest drug followed by sodium valproate.

Average number of AED per patient was 1.42 which is slightly lesser compared with the study conducted by Nandhakumar et al [21] in which an average of 1.69 AED was prescribed per patient.

A total of 235 AEDs were prescribed to 170 patients. Monotherapy (n=120, 70.5%) was the commonly used therapeutic approach followed by dual (37, 21.7%), triple (11, 6.4%) therapy and four drugs (n = 2, 1.1 %), which were similar to the previous studies conducted by Palanisami S et al, Hyuing et al and Nanadhakumar et al [15, 17, 21]. Polytherapy offers no advantage over monotherapy. It increases the potential for drug-drug interactions, results in failure to evaluate the individual drugs, can increase the risk of chronic toxicity [15]. In our study, the commonly prescribed AED as monotherapy was valproic acid, whereas in the previous study by Hassan SS et al [16], carbamazepine was the most commonly used monotherapy. The commonly prescribed AED combination was phenytoin + clobazam.The present study showed that older AEDs (78.9%) were most widely used for epilepsy treatment, which is similar to the study conducted by Hassan SS et al [16]. Commonest prescribed dosage form was tablet followed by syrup. Potential drug interactions were noted in 30 prescriptions. Interactions within AEDs observed were mainly between oxycarbazepine & clobazam in which concomitant administration can potentially increase CNS effects. When phenytoin and valproic acid are given together, the dose of phenytoin should be monitored as valproic acid increases the level of phenytoin. Patient should be informed about sedation when combinations of phenobarbitone and lorazepam, phenobarbital and clonazepam are prescribed. Valproic acid, carbamezapine and phenobarbitol decreases the level of phenytoin by affecting hepatic enzyme CYP2C9/10.

In interaction between AEDs and other drugs, when valproic acid is prescribed with paracetamol, valproic acid decreases the levels of paracetamol by increasing the liver metabolism. Ranitidine increases the levels of phenytoin by decreasing the metabolism of phenytoin. Concomitant administration of either cetrizine or triprolidin with clobazam may increase potential CNS effects. Administration of either risperidone or triclofos with

clonazepam increases sedation. Phenytoin levels should be monitored when given with ondansetron as it decreases the level of phenytoin. Levels of clobazam will be increased when given along with promethazine.

The overall incidence of adverse drug reactions was not very high. They were observed in 9 patients. Drowsiness was the commonest of the reported ADRs. Sodium valproate accounted for most of the ADRs. Treatment with AEDs was continued in all cases expect one due to rashes, as remaining ADRs were not considered serious. It is similar to the study conducted by Nandhakumar et al[21] and Mathur S et al [20]. Gingival enlargement was observed with phenytoin. In a study conducted by Huseiyn et al [22] gingival enlargement was observed with sodium valproate. Lamotrigine caused skin rashes, which was similar to the study conducted by Levit N et al [23].

We encountered use of phenytoin and carbamezapine in 33 patients with Idiopathic generalized seizures, phenyotin in 2 patients with focal seizures, which was not in accordance with the guidelines for diagnosis and management of childhood epilepsy by Indian Academy of Pediatrics [24].

For idiopathic generalized seizures, sodium valproate, lamotrigine and phenobarbitone are the drug of choice. Phenobarbitone tablets are cheaper compared to sodium valproate, where as sodium valpraote syrup is cheaper than phenobarbitone syrup.

For complex partial seizures, carbamazepine, phenytoin, oxcarbamezapine and clobazam can be given. Phenytoin is cheaper compared to all other drugs. For focal seizures, carbamezapine should be given. For absence seizures, sodium valproate can be given. For neonatal seizures, phenobarbitone is the drug of choice. For rolandic epilepsy, oxcarbamazepine should be prescribed. For status epilepticus, phenytoin is the drug of choice.

CONCLUSION

Majority of children with epilepsy had Idiopathic generalized seizures. Sodium valproate was the most commonly prescribed drug for Idiopathic generalized seizures. The overall incidence of adverse drug reactions was low. Pharmacist plays an important role in monitoring adherence of drug usage to the guidelines, drug interactions, adverse drug reactions and this study helps to promote appropriate antiepileptics and to serve to the health care professionals.

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