Research Article

Monitoring of Prescriptions and Pharmacovigilance Evaluation of Antiepileptic Drugs in a Tertiary Care Teaching Hospital

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ABSTRACT

Amongst the neurological conditions, epilepsy is one of the most common & serious condition. Seizure is one of the common causes of childhood hospitalization with significant mortality and morbidity. It represents a global problem affecting all ages, social classes, groups and countries. There is limited data regarding the prescribing pattern and observed side effects of various anti epileptic drugs (AEDs) form the developing countries. To know about epidemiological profile, prescribing patterns of AEDs and adverse drug reaction profile and outcome in both adult and pediatric patients. This was a cross-sectional clinico-epidemiological observational study of epilepsy patients over 1 year in neurology & pediatrics outpatient departments. The prescriptions from 820 patients containing AEDs were analyzed. Tonic clonic seizures were most common followed by partial seizures. Most of patients are in pediatric age group and were more common in male. Dual therapy (45.4%) was the most common regimen followed by polytherapy and monotherapy (26.5%). Valproic acid (43.1%) was the most frequently prescribed AED followed by Phenytoin (38.04%). No of adverse drugs reactions were reported was 122. Phenytoin and valproic acid were the major drugs implicated for adverse drugs reactions. Newer drugs like Levetiracetam, Lamotrigine, and Topiramate etc are less used in our cohort, most probably due to the cost factor. The choice of an AED depends on the type of seizure, drug's efficacy, availability, accessibility, ADR profile and patient factors. This study strongly highlights the need for therapeutic drug monitoring of epileptic patients.

Keywords: Adverse drug reaction, AED's, Childhood seizure, Epilepsy.

INTRODUCTION

Epilepsy is the second most common chronic neurological disorders encountered next to stroke & dementia which is characterized by recurrent unprovoked seizure.[1,2] Worldwide prevalence of the active epilepsy ranges from 4 to 5 per 1000 population[3] and in India, the prevalence rate of epilepsy ranges between 4.15 and 7.03 per 1000 population.[4] Seizures are the most common pediatric neurological disorder. Four to ten percent of children suffer at least one episode of seizure in the first 16 years of life. The incidence is highest in children less than 3 years of age, with a decreasing frequency in older children.[5] The incidence of epilepsy (recurrent unprovoked seizures) in children and adolescents seems relatively consistent across all populations studied, ranging from 50 to 100/l00, 000 person/years.[6]

Almost any type of brain pathology can cause seizures/epilepsy. It is multifactorial & may be due to an interaction between genetically determined seizures thresholds, underlying predisposing pathologies or metabolic derangements and acute precipitating factors.[7]

Epileptic seizures have many causes, including a genetic predisposition for certain seizures, head trauma, stroke, brain tumors, alcohol or drug withdrawal, and other conditions.[8,9] In children central nervous system (CNS) infections are the main cause of seizures and acquired epilepsy in the developing world. [10, 11] Acute seizures are common in meningitis, viral encephalitis and neurocysticercosis and in most cases are associated with increased mortality and morbidity, including subsequent epilepsy.[12-15] Epileptic seizures are divided into two main patho physiologic groups—partial seizures and generalized seizures—by EEG recordings and clinical symptomatology.[16] Geographical variations are also a determinant for knowing the common causes of seizure and epilepsy in a particular region.

The incidence of seizure is highest in childhood and old age. The principle of management of seizure include an accurate diagnosis and characterization of seizure type, choosing the most effective antiepileptic drug (AED) for the seizure type, and exhausting monotherapy before using polytherapy or nonmedical therapies. Achieving a seizure free state should be the ultimate goal of antiepileptic therapy.

Amongst the various factors affecting AEDs usage, the major determinants are type of epilepsy, age and gender of patient, side effect profile and availability of medicines, affordability of the patient, and preference of the treating physician as well as the practice setting. Due to the long duration of treatment, various adverse reactions (ADRs) are seen, which require change of medication and monitoring.

The interest in drug utilization studies began in the early 1960s, and its importance has increased since then because of increase in marketing of new drugs, wide

variation in the pattern of drug prescribing and consumption, growing concern about delayed adverse effects and the increasing concern regarding the cost of drugs.[17-19]

There are limited studies on causes and treatment modalities & outcome of acute episode of seizure in developing countries. It was found from various epidemiological studies, the management of pediatric epilepsy is a serious problem due to various factors like lack of education, poor financial status, limited access of services, lack of knowledge about the disease in developing countries. [20] Thus, it is important to study the utilization pattern of anti seizure drugs and ADRs for treatment, and control of epilepsy in pediatric patients. Purpose of the study is to investigate the use of AEDs in epilepsy, changes in prescription patterns, combination of drugs, and ADR profile of AEDs in a tertiary care hospital.

MATERIALS AND METHODS

This study was carried out over one year period (from April 2013 to March 2014) in the outpatient Department of Neurology & Pediatrics in collaboration with the department of Pharmacology. This was a retrospective hospital-based study conducted in the Department of Neurology & Pediatrics of IMS & SUM HOSPITAL, BBSR. All the prescriptions issued during this period were recorded on case record forms. Our study was conducted on a patient pool of 820 no of people. Only patients with seizure and treated with an AED were included in this study. The criteria for including a subject in the study were that he/she has been diagnosed to have epilepsy by a Consultant Neurologist or a Physician with a clinical history, examination and relevant investigations including an EEG, has been on AED/s for more than eight weeks, not on any other medication and consented to take part in this study. Demographic profile of the patient (age and gender), type and etiology of epileptic seizure, AED data (name of the AEDs, mono or polytherapy, no of AEDs per prescription, formulation) and associated adverse drug reactions with the prescribed AED were recorded during this study period.

The epileptic seizures were grouped according to the classification of the International League against Epilepsy. [21] Statistical analysis was done by calculating the Frequencies, mean values and percentages.

RESULTS AND DISCUSSION

820 patients were included in this study over one year period (from April 2013 to March 2014). Seizures were more common in males. In our study population, 59.3% were males and 40.7% were females (Table 1). The age ranged from 2 months of age to 78 years (Table 1) with 601(73.2%) % patients being younger than 30 years of age. Out of all the study population no of patients 551 (67.1%) are of pediatric age groups that is from 2 months of age to 14 years of age.

Table 1: Demographic profile of the population on AEDs treatment (n=820)

Demographic profile		Number patients with percentage
Sex	Male	486(59.3)
	Female	334(40.7)
Age In years	Less than one year	154(18.7)
	1-5	282(34.3)
	6 – 14	115(14.02)
	15 – 34	101(12.3)
	35 – 65	102(12.4)
	> 65	66(8.04)

Table 2: Types of epileptic seizure in adults more than 14 years of age (n= 269) & in pediatric group(less than14 years of age) (n=551)

Types of seizure in adults (n= 269)	Number patients with %	Types of seizure in paediatric group (n=551)	Number patients with %
Tonic-clonic seizure	132(49.07)	Tonic-clonic seizure	196(35.5)
Complex Partial seizure	60(22.3)	Complex partial seizure	150(27.2)
Simple partial seizure	34(12.6)	Simple Partial seizure	98(17.7)
Myoclonic seizure	24(8.9)	Myoclonic seizure	52(9.4)
Tonic seizure	10(3.7)	Absence seizure	34(6.1)
Atonic seizure	6(2.2)	Tonic Seizure	18(3.2)
Absence seizure	3(1.1)	Atonic Seizure	3(0.54)
		Status	5(0.9)

Table 3: Causes of epileptic seizures in adults (n= 269) & in children (n= 551)

Causes in adults	Number patients with %	Causes in children	Number patients with %
Idiopathic	123(45.7)	Idiopathic seizure	213(38.65)
Infection	43(15.9)	Febrile Seizure	172(30.96)
Vascular-Stroke	33(12.2)	Infection	115(20.8)
Post trauma	24(8.9)	Metabolic/toxic	22(3.9)
Tumour	15(5.5)	Tumor	14(2.5)
Metabolic/toxic	20(7.4)	Vascular-Stroke etc	9(1.62)
Systemic disease	8(2.9)	Post trauma	6(1.08)
Degenerative	3(1.1)		

Generalized tonic-clonic seizures were the most prevalent of all types of epileptic seizures which accounted in 49.07% of patients followed by partial seizure 34.9% in adult patients (Table 2). Status epilepticus presentation was seen as initial presentation in 14(5.2%) patients.

Among total 551pediatric patients, 150(27.2%) patients were having focal seizure, 401(72.7%) patients were having generalized seizure.

Generalized tonic clonic seizures were the commonest seizure type in children (Table 2) in this study. Status epilepticus presentation initially was present in 44 (7.9%) children.

Idiopathic epilepsy was the most common cause of epileptic seizures (45.7%) in adults followed by infections (15.9%).(Table 3)

Childhood seizure disorder was commonest diagnosis 213(38.6) followed by febrile seizures 172(30.9). The idiopathic seizures include various epileptic syndromes like West syndrome, Lennoux gastaut Syndrome etc. The Infective causes include various bacterial, virus, atypical organisms out of which tubercular was most common. (Table 3)

Table 4: Percentage of mono, dual and polytherapy in different types of seizure in total study population

Types of seizure	Monotherapy	Dual therapy	Polytherapy
Tonic clonic	102	208	81
Partial seizure (both complex & simple)	98	104	102
Myoclonic seizure	0	34	21
Tonic seizure	1	4	2
Atonic seizure	2	5	0
Absence seizure	15	6	0
Status	0	12	23
Total	218(26.5)	373(45.4)	229(27.9)

Table 5: Types of AED prescribed in the study population (n=820)

Name of the drugs	No of prescriptions with percentages
Valproic acid	354(43.1)
Phenytoin	312(38.04)
Carbamazepine	288(35.1)
Diazepam	21(2.5)
Clonazepam	185(22.5)
Topiramate	22(2.6)
Clobazam	264(32.1)
Lamotrigine	34(4.1)
Levitracetam	154(18.7)
Lacosamide	8(0.97)
Phenobarbitone	81(9.8)

In this study population, 218 (26.5%) were prescribed an AED as monotherapy and 373 (45.4%) needed dual therapy. 229(27.9%) patients were managed with Polytherapy (≥3 AEDs). Most of the polytherapy prescriptions consisted of triple therapy. Only nine patients were administered with 4 AEDs. (Table 4)

Total Number of AEDs prescribed to the study population was 1723. Number of AEDs per prescription was 2.1. Independent of the AED use profile (either monotherapy or combination therapy, Sodium Valproate (43.1%) was the most frequently prescribed AED followed by Phenytion sodium (38.04%) and Carbamazepine (35.1%) (Table 5). The most frequently used combination therapy of AEDs consisted of Sodium Valproate/ Carbamazepine (32%) followed by Sodium Valproate/ Phenytoin (22%). 82.4% of the prescribed drugs are from the Essential drug list (EDL).

Table 6: Spectrum of suspected ADRs noted with AEDs: n 122

Types of ADRs	No (% of all ADRs, n=122)
Sedation	46(37.7)
Gum hyperplasia	12(9.8)
Other CNS side effects(tiredness, fatigue, dizziness, ataxia, tremor, slurred speech, confusion, decreased coordination)	22(18.03)
Dry mouth, nausea, diarrhoea, GI disturbance	18(14.7)
Allergic rash	8(6.5)
Weight loss(decreased appetite)	1(0.08)
Weight gain	2(1.6)
Stevens-Johnson syndrome and toxic epidermal necrolysis	4(3.2)
Haematological reactions including thrombocytopenia, aplastic anaemia, agranulocytosis and leucopenia	7(5.7)
Hepatic failure	2(1.6)

Table 7: AEDs responsible for ADRs noted

Name of the drugs	(% of all ADRs, n=122)
Phenytoin	63(51.6)
Valproic acid	30(24.5)
Diazepam	1(0.8)
Carbamazepine	19(15.5)
Clonazepam	2(1.6)
Topiramate	1(0.8)
Clobazam	2(1.6)
Lamotrigine	1(0.8)
Levitiracetam	1(0.8)
Phenobarbitone	2(1.6)

In our study group 103 patients developed 122 ADRs of various types. (Table 6).Some patients developed more than one ADR (11 patients developed 2 ADRs and 4 patients developed 3 ADRs). In most of the ADRs, the

organ system affected was gastrointestinal system and central nervous system. The most common drugs implicated for ADRs were phenytoin (51.6%), valproic acid (24.5%), and carbamazepine (15.5%) (Table 7). There were 63 ADRs with phenytoin. They were: Gum hyperplasia (12), rash (23), somnolence (19), 3 each for ataxia, dizziness and; two for asthenia, and one fixed drug eruption (Figure 1) .There were 30 ADRs with valproic acid. They were: weight increase (2), sedation (12), fatigue (5) abnormal behavior (5) and two each for, menstrual disorder, dizziness, and liver function test abnormality. There were 19 ADRs with carbamazepine. They were sedation (12), ataxia (3), and two each for dizziness and lethargy. There were 2 ADRs with phenobarbitone, one each for sedation and abnormal behavior. Tremor was seen in four patients while increasing the dose of valproate.

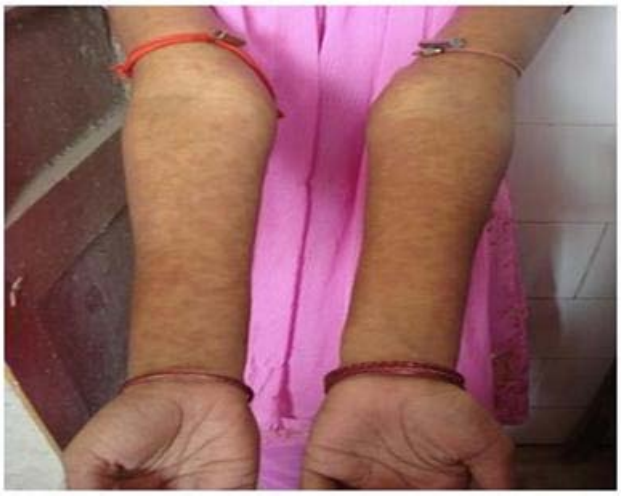

Figure 1: Fixed drug eruption

Causality association between drug and reaction was probable in 62.2.4% (n=76) and 45.08% (n=55) as assessed by using WHO probability scale and Naranjo's algorithm respectively. Medications were discontinued in 22 cases and the dose was altered in 18 cases. No change was made in 69.6% (n=85) of cases, as these ADRs were mild.

Among 820 patients with epilepsy 122 (14.8%) ADR were recorded. Most of the ADRs belonged to possible (82.8%) followed by probable (62.2%) categories. Highest percentage of patients showed mild ADR (85%). The ADRs were predominant in female (57.2%). The ADRs with AED monotherapy was 14.6% and with polytherapy it was 22.4 %. Central Nervous system related ADRs (sedation, memory impairment, depression, dizziness, ataxia etc) were maximum in number. Sedation was the most common side effect.

Of the enrolled population of 551 children, 38.6% children had idiopathic generalized tonic clonic epilepsy. More than two-thirds of children were on monotherapy, with Valprote (n=254, 46.01%) and phenytoin (n=202, 36.6%) being the most common AED. 72 AED-related ADRs were recorded in 551 children (13.06%). Sedation was most common side effect (32.1%). Decreased memory with poor scholastic performance (19.2%), followed by drug rash, SJS (8.3%), gum hypertrophy (4.2%) and behavioral problems (3.7%). There are 55 ADRs were probable, and 17 ADRs were possible. Severe ADRs were noted in 24 children. Monotherapy was the preferred treatment. Phenytoin was the most common ADR causative agent.

DISCUSSION

There is increase interest in the development of newer AEDs in pharma industries due to increase incidence in refractory epilepsy and also increase side effects related to the older AEDs. Data available regarding the therapeutic efficacy of these drugs and monotherapy versus combination therapy for management of seizure disorders are scant. But there are no significant advances & extensive studies regarding the therapeutic monitoring and proper pharmacovigilance for AEDs.

In our current study of utilization pattern of AEDs, a total of 820 epileptic patients were included. In our cohort 73.2% patients are younger than 30 years of age. This contradicts the studies from western countries. [22-24]According to the western literatures, the incidence of epilepsy has a bimodal distribution with a peak in the first decade and a second peak in the elderly [25 – 27], the possible explanation being the lower life expectancy in developing countries.

In our study we found the incidence of epilepsy in males (59.3%) were greater than the females (40.7%) which is in accordance with some previous findings.[28,29] The incidence of epilepsy was found to be higher in male supported by some studies.[30] The poor literacy rate, the fear of social stigma, poor understanding of disease& treatment and need for male relative for consent may be some factors related to the decrease in the number of female patients attending the hospital in developing countries. Previously some epidemiological studies on epilepsy which were failed to explain the differences between the incidence of epilepsy on gender basis[31, 32] and but in some other studies, they described the female predominance over male. [31, 33]

The most common type of seizure in adult was generalized tonic clonic seizure (49.07%), the findings being similar to Shaireen Usman et al.[34] study in which 43% of the subjects were suffering from GTCS. Idiopathic epilepsy was the most common cause of epileptic seizures (45.7%) in adults. Pediatric patients are different from an adult as the physiological systems are in growing phase which is responsible for differences in the pharmacokinetic & pharmacodynamic profile of the AEDs. In the current study, the incidence of generalized tonic-clonic seizure (35.5%) which was most common, followed by complex partial seizure (27.2%) in children. Most studies show generalized seizures are much more common compared to partial seizure.[10,11,13] Febrile seizures observed in 30.9% of cases. Febrile seizures have been reported to be one of the most common causes of

seizure attack in children.[6,10,35] We found that febrile seizures (19.2%) were the main etiology of a first attack of seizure in children.

Majority of patients 38.65% had no specific cause of seizure (Idiopathic seizure) which is in accordance with pharmaco-epidemiological study from Oman.[26] Central nervous system (CNS) infections have been documented as the main cause of seizures and acquired epilepsy in the developing world.[36] In our study population we found that infection was the second most common cause (15.9%) in adult and third most common cause (20.8%) in childhood epilepsy.

Our data indicated that dual therapy followed by polytherapy was the therapy of choice in majority of patient with partial or generalized seizure. This finding contradicts the finding in other studies.[37 – 39] Polytherapy increases the potential for drug-drug interaction, can increase the risk of chronic toxicity and is associated with a higher cost of medication.

Most of the epileptic patients were effectively managed with conventional AEDs like carbamazepine, phenytoin, phenobarbitone and valproic acid, as observed in the earlier studies.[6, 15-19, 22] Valproic acid (43.1%) was the most frequently prescribed AED followed by Phenytoin (38.04%). Valproic acid was widely used in this study population because of its broad spectrum of activity, particularly because many of our patients' seizure type could not be clearly determined. In most of the prescriptions the physicians prefer classical AEDs. Newer drugs like levitiraccetam, Lamotrigine, Topiramate etc are less used in our cohort, most probably due to the cost factor. Another cause may be that the drugs are selected from the EDL.

122 no of adverse drugs reactions were reported during the study period. Most of the ADRs belonged to possible (82.8%) followed by probable (62.2%) categories which contradicts the earlier findings.[40] Mild ADR were observed in 85% of cases.. Most common organ system affected due to adverse drug reactions was gastro intestinal tract which was comparable to other studies. [41] Our study showed that, the ADRs were predominant in female (57.2%) in comparison to male which was similar to the previous literatures. 42 Phenytoin (51.6%) and valproic acid (24.5%) were the major drugs implicated for adverse drugs reactions.[43] Most commonly the ADRs are mild. The incidence of ADRs increases with polypharmacy.

CONCLUSION

There is lack of data, at our setup and also in India, about utilization of AEDs in pediatric patients suffering from different types of seizure. Our study throws some light about the utilization pattern and ADR profile of AED in pediatric population. The choice of an AED depends on the type of seizure, drug's efficacy, availability, accessibility, ADR profile and patient factors. Thus availability and accessibility was guided by the free availability of medicines from the hospital pharmacy. Potential AED ADRs affect not only the choice of the physician but also acceptance of the drug by the patient. However not all patients develop ADRs and not all of them are unacceptable.

In our study tonic clonic seizures were most prominent followed by partial seizures. Most of patients are young and epileptic seizures are more common in male. Dual therapy followed by polytherapy was most frequently used in all type of epileptic seizures. The drugs prescribed are mainly from the Essential drug list. The ADRs are found to be mild and predominant in female.

This study strongly highlights the need for therapeutic drug monitoring of epileptic patients. Measures should be taken to improve rational use of antiepileptic drugs to minimize the number of refractory cases of epilepsy. There is under utilization of newer AEDs. Inclusion of newer AEDs like Lamotrigine, Topiramate etc in the Essential Drug List is recommended. Female patients need special attention during medication.

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