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A prospective observational study on drug utilization pattern of anti epileptic drugs: A pharmacoepidemiologic and pharmacovigilance study in RMMCH

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Abstract

Objective: Neurologists see epilepsy as the second most common chronic neurological condition. The incidence of epilepsy is estimated to be 5 per 1000 in India. The aim of this study is therefore to obtain an insight into the type of epileptic seizures prevalent in a tertiary teaching hospital in India, to describe the pattern of drug use of antiepileptic drugs (AEDs) for the management of different forms of epileptic seizures over a period of six months and to investigate the pattern and extent of adverse drug reactions (ADRs) with AEDs.

Methods: According to a detailed semi-structured questionnaire, data were collected from 85 patients with epilepsy in the Department of Medicine, RMMCH, and Chidambaram. The data comprises demographic data, data from AEDs and data from ADRs.

Results and Discussion: Tonic clonic seizures have been the most prominent followed by complex partial seizures. The majority of patients are young and epileptic seizures are more common in men. Poly therapy was most commonly used in all epileptic seizures. Sodium Valproate was the most commonly prescribed AED followed by Phenyton and levetiracetam. The prescribed drugs are primarily from the list of essential drugs. The ADRs in females are found to be mild and predominant.

Conclusion: This study highlights epileptic patient's need for therapeutic drug monitoring. Measures to improve the rational use of antiepileptic drugs should be taken to minimize the number of epileptic refractory cases. The use of new AEDs is underway. It is recommended that new AEDs such as Lamotrigine, Topiramate etc. it can also be included in the Essential Drug List. Special care is needed for female patients because some of the anti-epileptic drugs may cause teratogenic effect.

Keywords: AEDs; pharmacoepidemiology; pharmacovigilance; teaching hospital.

Introduction

Epilepsy is one of the most frequent neurological disorders with recurrent and unprovoked seizures. The incidence and prevalence of epilepsy is substantially heterogeneous in geographic location [1]. While the incidence of this disorder is between 50 to 100 cases per 100,000 population per year in most developed countries and the prevalence is about 5-8 cases per 1000 population [2], the prevalence has been reported to be more than 40 per 1000 population in developing countries [3]. There is also a lack of uniform distribution of epilepsy across age groups in the population [4]. Neurologists see epilepsy as the second most common chronic neurological condition. In India, there are estimated to be 55, 00,000 people with epilepsy [5].

Available anti- epileptic drugs aim to inhibit the abnormal neuronal discharge rather than to correct the underlying cause. There are three mechanism of action appear to be important:

1. Enhancement of GABA action.
2. Inhibition of sodium channel function.
3. Inhibition of calcium channel function.

Later to 1993 some new drugs have entered the worldwide market such as Levetiracetam, Felbamate, Gabapentin, Lamotrigine, Vigabatrin, Topiramate, Zonisamide etc. The growing no of newly approved drugs have contributed to the increased adverse drug reactions. Adverse effects in the treatment of epilepsy drugs are highly prevalent. Despite a significant increase in side effects, poly therapy is a common practice for epilepsy management.

Materials & Methods

Study Place: The study was conducted in the Department of Medicine, RMMCH, Annamalai

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University, Tamil Nadu which is a 1400 bedded super speciality, tertiary care teaching hospital located in rural South India.

Study Type: Prospective observational study.

Study Period: The study was carried out for duration of Six months (JAN 2019 – JUN 2019) all prescriptions issued during this period immediately following each day's consultation with the physician was copied out and recorded on case record forms. Our study was conducted on a patient pool of 85 people. Only people with epilepsy and treated with a AEDs were included in this study. The following data are collected from the patient and their attender: demographic data (age and gender), known or newly diagnosed epileptic patient, epileptic seizure type and aetiology, AED data (i.e. drug type and formulation and availability), and drug selection from Essential Drug List (EDL) and ADR data. A detailed semi-structured questionnaire collected the type of reaction, causality, onset, severity and outcomes of ADRs⁶. If an ADR was detected it was subjected to WHO probability scale to assess the causal relation between the medication and the adverse reaction with the help of a physician. Afterwards, the severity of the reaction was determined mild, moderate or serious. When an ADR was associated with more than one medication, the agent most likely to be responsible for the adverse reaction was included in the final analysis. The epileptic seizures were grouped by the International League classification against Epilepsy: partial complex, partial simple, tonic-clonic, absence, myoclonic, clonic, tonic, atonic and epileptic status⁷. The following aetiologies have been considered: idiopathic, trauma, infection, tumor, induced drug, systemic, metabolic / toxic and degenerative disease.

Result

Table 1.A: Demographic characteristics of the study population being treated with AEDs based on gender (n=85)

Gender	No. of patients	Percentage
Male	52	61.17%
Female	33	38.82%

Table 1.B: Demographic characteristics of Age wise distribution of patients treated with AEDs

Age	No. of patients	Percentage
13-20	23	27.05%
21-30	12	14.11%
31-40	15	17.64%
41-50	6	7.05%
51-60	11	12.94%
60-70	10	11.76%
≥ 70	8	9.41%

Table 2: Types of seizure and aetiology in study population (n=85)

Classification	No. of patients	Percentage
Simple partial seizure	9	10.58%
Complex partial seizure	16	18.82%
Absence seizure	7	8.23%
Atonic seizure	7	8.23%
Tonic-clonic seizure	46	54.11%

Etiology	No. of patients	Percentage
Idiopathic	53	62.35%
Infection	9	10.58%
Systemic disease	3	3.52%
Trauma	4	4.70%
Metabolic/toxic	10	11.76%
Degenerative	6	7.05%

Table 3: Level of severity, type of ADR and gender wise distribution (n=85) in patient receiving AEDs

Level of severity	No. of reaction	Percentage
Mild	8	61.53%
Moderate	5	38.46%
Severe	-	-

Causality analysis	No. of reaction	Percentage
Probable	6	46.15%
Possible	7	53.84%
Definite	-	-
Unlikely	-	-

Gender	No. of reaction	Percentage
Male	5	38.46%
Female	8	61.53%

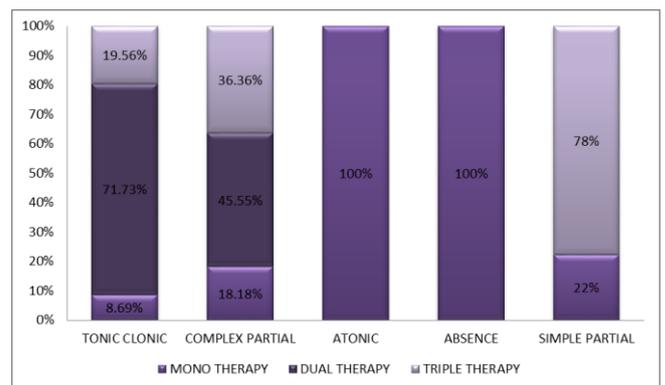


Fig 1: Mono / dual / triple therapy percentage for various types of seizures (n=85)

Prescription was collected over a period of six months from 85 patients with a confirmed seizure diagnosis and treated with AEDs. Table 1 A & B shows the demographic characteristics of these patients. The age ranged between 13 and ≥70 years with 59% patients being younger than 35 years of age (young adults). More than 64% of patients are males.

Type and aetiology of seizures are presented in Table 2. Out of all patients, 54.11% cases are found to be generalized tonic-clonic seizures and it is also the most prevalent type of seizure. Out of all cases, the most common cause of seizure was idiopathic epilepsy (62.35%).

In this study population, an AED was prescribed as mono therapy for 27 (31.76%) and 36 (42.35%) patients needed dual therapy (Figure.1) and triple therapy for 22 (25.88%) patients.

Among 85 patients with epilepsy 13(15.29%) had ADR. Table – 3 lists the level of severity, type of ADR and gender wise distribution in patients receiving AEDs. Most of the ADRs belonging to possible (53.84%) followed by probable (46.15%) categories. Highest percentage of patients showed mild ADRs (61.53%). The ADRs are predominant in female. Mono therapy has fewer ADRs while comparing poly therapy. There were ADRs related to the central nervous system (depression, dizziness, ataxia, etc.).

Discussion

In our study almost 59% of patients were younger than 35years of age. This contradicts the studies from western countries where the onset of epileptic seizures is more frequent at the age extremes of life. However, our study's gender distribution is similar to previous findings that men are more likely to experience epileptic seizures than women⁸⁻¹⁰.

Perhaps the most common type of epileptic seizure as previous studies was tonic-clonic seizures followed by complex partial seizures. Appropriate classification of the type of seizure or epileptic syndrome is a key determinant of AED choice. Valproic acid was the first line drug in tonic-clonic seizures prescribed in our study. In complex partial seizures, carbamazepine was the AED of choice. Our data indicated that in most patients with partial or generalized seizure, poly therapy was the therapy of choice. This finding contradicts the finding in other studies¹¹⁻¹⁴. Our study may attribute the reason for poly therapy to a higher incidence of refractory epilepsy. Poly therapy increases the potential for interaction between drugs, can increase the risk of chronic toxicity, and is associated with higher drug costs. However, there is improved seizure control in poly therapy. The most commonly prescribed AED was valproic acid. The medical professionals prefer classical AEDs in most prescriptions. New drugs such as Lamotrigine, Topiramate, etc. are not preferred, unlike other studies. The newer AEDs are used less commonly. Another limitation may be the selection of the drugs from the EDL. Interestingly, Phenobarbitone was also not prescribed in any of the prescriptions because of its neurological side effects. While it is important to have effective pharmacological treatment of epilepsy, it is equally important to consider whether potential adverse events outweigh patient benefits. There are few outpatient ADR studies that may be due to the challenges of identifying these ADRs and their associated risk factors. The demographic reports from different ADR epidemiological studies cited female over male predominance. In our study observation is similar to previous studies. The assessment revealed that most ADRs are possible followed by probable categories. This study contradicts previous findings. The evaluation showed the highest percentage of mild reactions. Most of the previous studies showed a higher percentage of geriatric populations reporting on ADR. Most of the patients are young in the current study. This may be the reason why AEDs are related to mild ADRs. Cognitive deficits and depressive disorder are associated with pharmaco resistant epilepsy or refractory epilepsy. This could be the reason for our study's maximum number of ADRs related to the central nervous system. Recently, a concerted effort has been made to ensure rational drug use. The WHO and other official bodies have identified specific drug use indicators for standardization that include drug no. and cost, use of generic names of prescribed drugs, and adherence to the essential drug list.¹⁵ Our study reveals that doctors adhere to the EDL while prescribing AEDs. As per this study, it will be beneficial if new AEDs are included in the EDL.

Conclusion

Most prevalent type of seizure in our study was tonic-clonic seizures followed by complex partial seizures. Etiology report shows that idiopathic causes were more in seizure patients. Most patients were young, and males were more likely to experience epileptic seizures. In all kinds of seizures, poly therapy was mostly used. The prescribed drugs were predominantly from the list of essential drugs. More ADRs were reported in female patients but those ADRs were mild. Special care is needed for female patients because some of the anti-epileptic drugs may cause teratogenic effect.

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