Adverse Drug Reactions of Antiepileptic Drugs in Neurology Department of M.Y.H Indore, India: An Observational, Prospective Study

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Abstract

Background: Epilepsy is the second most common neurological disorder that affects 1 percent of global population. Since antiepileptics have narrow therapeutic index having multiple adverse drug reactions (ADRs) thus have significant safety concerns. The aim of this study was to observe adverse drug reactions due to antiepileptics in neurology department M.Y.H. Indore, India.

Methods: An observational prospective study was done from November 2021 to January 2022. Patients having history of seizures attending neurology outpatient department at MYH Hospital, who were on antiepileptic drugs were recruited. Suspected adverse drug reaction forms were recorded and their causality assessment was done by Naranjo's scale.

Results: Data of total 70 patients were recorded. Males reporting ADRs due to antiepileptics were 67.1% and females 32.8%. Using Naranjo's scale, we noted 93.3% ADRs as "probable" and 6.7% as "possible". Common causes of prescribing antiepileptic drugs were known case of epilepsy (78.5%),old case of neurocysticercosis (11.4%),post traumatic(4.3%),gliosis (2.8%) and tuberculoma (2.8%). Most ADRs were dermatological 76% (rashes),central nervous system (16%) (nocturnal enuresis, poor school performance, dizziness, headache, sleep disturbances, personality changes) ,Gastrointestinal (8%) (gastric irritation, nausea, vomiting and hepatotoxicity) .Most common drug for causing ADRs were sodium valproate(58.5%),carbamazepine(17.14%),phenytoin(14.2%),leviteracetam(7.1%),and lamotrigine(2.8%).

Conclusion: Our study aimed us to know the incidence and patterns of adverse drug reactions due to antiepileptics in a tertiary care institute of central India. Despite of recent advances and novel therapies used for the treatment of epilepsy, conventional drugs like sodium valproate, phenytoin and carbamazepine still are the first choice for the management and treatment of seizures and their ADRs are very common.
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Keywords: Adverse Drug Reactions; Antiepileptic Drugs; Epilepsy; Pharmacovigilance

Introduction

Epilepsy is a common neurological disorder which demands immediate medical attention. It is the second leading neurological cause of reduced disability adjusted life years and affects 1 percent of global population (1,2). The main stay of treatment in epilepsy is the use of antiepileptic medications for a longer time.

The use of drugs in the management of epilepsy is accompanied by adverse effects such as idiosyncratic reactions, dose-related neurocognitive effects and complications of long-term use (2). The overall cost of treating epilepsy is impacted by Antiepileptic drugs related adverse Event (3,4).

The last two decades observed large increase in new antiepileptic drugs (AEDs) discovery and approval. Since antiepileptics have narrow therapeutic index having multiple adverse drug reactions (ADRs) thus have significant safety concerns they cause treatment failures and affect quality of life, independent of seizures.

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The overall cost of treating epilepsy is impacted by Antiepileptic drugs related adverse Events (5). Therefore, ADRs are among the most in which most crucial factor for deciding the choice of AED in patients of seizures. Also if two drugs have same efficacy, the frequency and type of expected drug toxicity are essential drug elements to decide which drug to use (6-8).

Long term administration of AEDs causes behavioral abnormalities, diminution of intelligence, impairment of learning memory, hyperactivity in children, mental confusion in older people. Rashes, megaloblastic anemia, gastric irritation, vomiting, hepatotoxicity and osteomalacia occur in some patients on prolonged use of AEDs (9).

The goal of epilepsy treatment is to achieve adequate seizure control and improve quality of life without adverse events from the medication. However, adverse events due to AEDs occur frequently and are the main reasons that limit doses to be used for achieving adequate seizure control. Adverse events may also cause impaired treatment adherence.

Therefore, current study was done to see and analyze various ADR's due to antiepileptics in patients attending MYH neurology Outpatient Department.

Methods

This was an observational study conducted in the Department of Neurology at Mahatma Gandhi Medical college, Indore Madhya Pradesh from November 2021 to January 2022.

We conducted an observational, prospective study in which 70 patients of both sex having seizures attending neurology Out Patient Department (OPD) at M.Y.H Hospital were included, in them those reporting adverse drug reactions (ADRs) after antiepileptic medications were recorded and follow up was done. Institutional Ethics Committee permission was obtained before conducting the study and informed consent was taken from patients. In case of pediatric population consent were from parents or guardians. The duration of study was from November 2021 to January 2022.

Patients reporting ADRs due to AEDs were recruited in study after applying inclusion and exclusion criteria. All Patients reporting ADR after consuming antiepileptic drugs were included in study. suspected ADR reporting form were filled for recording general patient information, reaction with treatment details, suspected medications, relevant medical history and laboratory test, seriousness of reaction and outcome was recorded and Causality assessment of all the ADRs was done by Naranjo's scale to know whether the ADR is possible, probable or certain (10). Relevant tests/laboratory data/medical/personal/family/allergy history was also obtained. For recording the details of Patients treated with antiepileptic drugs, suspected ADR forms for voluntary reporting of ADR by IPC, PVPI Ghaziabad, MOHFW INDIA were filled.11Data was entered in MS excel sheet, analyzed by SPSS software version 20.0 and results were interpreted in graphs and tables. Descriptive statistics (mean/standard deviation/percentages) were used to describe the characteristics. Our Primary objective was to observe adverse drug reactions due to anti epileptics and Secondary objective was to observe various indications for prescribing AEDs and the implicated drug.

Results

An observational study was conducted in the Department of Neurology at Mahatma Gandhi Medical College, Indore Madhya Pradesh. After excluding 10 patients that didn't applied for the inclusion criteria, data of total 70 patients was analyzed. Males (67.4%) outnumbered females (32.8%) in our study (Table 1). The most common age group range was 0-15 years.

Majority of patients were known case of epilepsy (78.5%) and old cases of neurocysticercosis (11.4%), while rest were having post traumatic (4.3%), gliosis (2.8%) and tuberculoma (2.8%) (Table 1). When we performed Fisher's exact test these results are not found statistically significant (P=0.65).

Table 1. Indications for prescribing antiepileptics.

Etiology	Total	Male	Female
Known case of epilepsy	78.5%(55)	42.8%(30)	35.7%(25)
Old case of neurocysticercosis	11.42%(08)	8.5%(06)	2.85%(02)
Post traumatic	4.28%(03)	2.85%(02)	1.42%(01)
Gliosis	2.80%(02)	1.42%(01)	1.42%(01)
Tuberculoma	2.80%(02)	2.80%(02)	0%(00)
TOTAL	70	41	29

Distribution of patients according to the system involved shows that majority of ADRs were dermatological (76%), while rest were involving central nervous system (16%) and gastrointestinal (8%).

Drugs implicated for causing ADRs shows that most common drug involved is sodium valproate (58.5%) followed by carbamazepine (17.1%), phenytoin (14.2%), levetiracetam (5%) and lamotrigine (2%). These results are statistically insignificant when Fischer's test was applied (P value=0.98) (Table 2).

Causality assessment of all the ADRs done by using Naranjo's probability scale, that shows 93.3% ADRs as "probable" and 6.7% as "possible" and none were certain.

Table 2. Drugs implicated for causing ADRs.

Drugs	Total	Male	Female
Sodium valproate	41(58.5%)	28(40%)	13(18.57%)
Carbamazepine	12(17.14%)	8(11.42%)	4(5.71%)
Levetiracetam	5(7.14%)	3(4.28%)	2(2.85%)
Phenytoin	10(14.2%)	7(10%)	3(4.28%)
Lamotrigine	2(2.85%)	2(2.85%)	0(0%)

Discussion

ADRs due to AEDs are very common, variety of drugs are currently available for treatment or control of seizures or epilepsy. Older or first line drugs like phenytoin, carbamazepine, sodium valproate and ethosuximide are commonly used as first line conventional drugs. They are less expensive than the newer or second like antiepileptics and easily available in hospital pharmacy free of cost. Newer drugs like lamotrigine, levetiracetam, vigabatrin, gabapentin, pregabalin, zonisamide and tiagabine are used as add on or alternative therapy they have lesser side effects and drug interactions. Usually monotherapy is common but in multiple seizure type or refractory disease, polytherapy is commonly used by physicians.

In our study the most common age group in which ADRs due to AED are seen in 0-15 years of age and 35-45 years of age we observed ADRs commonly in male patients, some previous studies also reported male preponderance (11). Adults (35-45 years) as the common group followed by the elderly (aged ≥ 65 years). And they also noted more ADRs due to antiepileptics among males as compared to female patients (12). Some other studies found that majority of children with ADRs in the age group of more than 10 years and they found high frequency of ADRs in girls as compared to boys (13). While other studies found boys developing more ADRs than girls (14-18). In our study we noted most common drug for causing ADRs were sodium valproate followed by carbamazepine, phenytoin and ethosuximide. Some other studies also reported sodium valporate followed by phenytoin as the most common drugs for causing ADRs (7). The findings of the present study were in conformity with the findings of Kousalya et al., who found the most common drug for causing ADR's to be sodium valporate followed by phenytoin (7,14). In contrast to the present study, Bansal et al. and Mathur et al., found phenytoin as the most common drug (13,15). Clobazam followed by phenytoin was found as the commonest drug used in a study by George et al., (16). In our study we found that the most common type of ADRs are dermatological followed by central nervous system and GI involvement. Most ADRs were dermatological which included maculopapular rashes. Central nervous system involvement manifested as nocturnal enuresis, poor school performance, dizziness, headache, sleep disturbances, personality changes, while gastrointestinal adverse effects manifested as gastric irritation, nausea, vomiting and hepatotoxicity. Some previous studies show that the most frequently encountered adverse events were fatigue (5.08%), gastrointestinal disturbance (4.24%) and sedation/depression (4.24%) (18,19). Common causes of prescribing antiepileptic drugs are mostly known case of epilepsy. These are also prescribed for neurocysticercosis, post traumatic epilepsy cases, gliosis, tuberculomas and others. Other studies also found these as the common indications for prescribing various antiepileptic drugs (20). Causality assessment of all the ADRs was done by Naranjo's scale to know whether the ADR is possible, probable or certain. Using Naranjo's probability scale, we noted 93.3% ADRs as "probable" and 6.7% as "possible". None of the ADRs is certain as re-challenge was not done in our study.

Our study aimed us to know the incidence and patterns of adverse drug reactions due to antiepiletics in a tertiary care institute of central India. Despite of recent advances and novel therapies used for the treatment of epilepsy, conventional drugs like sodium valproate, phenytoin and carbamazepine still are the first choice for the management and treatment of seizures and their adverse drug reactions are very common. Drug interactions of antiepileptics may occur with various enzyme inducers that can cause treatment failures like in oral contraceptives, anticoagulants, antibiotics etc. Similarly, enzyme inhibitors can interact with antiepileptic drugs and can cause toxicity. In pregnant and lactating females' timely management is obligatory to prevent the hazardous consequences like congenital malformations, neural tube defects, hirsutism etc. Our study findings may help physicians for early detection and withdrawal of the drug causing adverse drug reaction and substituting it with other safer alternatives. Also this will help to improve patient safety and decreases mortality and morbidity due to adverse drug reactions. However much larger studies are required for a better understanding.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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