RESEARCH ARTICLE

Utilization pattern of antiepileptic drugs and their adverse effects, in a teaching hospital

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The overall aim in treating epilepsy should be complete control of seizures, without causing any untoward reaction due to the medication. Many of the drugs currently available for epilepsy cause side effects. This study attempts to get an insight into the utilization pattern of anti-epileptic drugs (AEDs) in different types of epilepsy, to identify the extent of poly-pharmacy and to evaluate the adverse drug reactions reported. In a prospective study spanning 8 months (January to August 2008) we analyzed the prescription data of 278 patients of seizures from neurology out patient department (OPD) of Owaisi hospital, general medicine and pediatric O.P.D.s of Princess Esra hospital, Hyderabad. The demographic data, type of seizures, anti-epileptic drugs prescribed and adverse drug reactions (ADRs) reported by the patients were recorded. A total of 278 prescriptions were analyzed and adverse drug reactions reported by the patients were recorded. Idiopathic generalized epilepsy was the commonest type of epilepsy (34.53%) and Phenytoin was the commonest drug prescribed (60.41%) for it's treatment, followed by Sodium Valproate (20.83%). Symptomatic epilepsy comprised the second commonest category of seizures (26.25%). Phenytoin (57.53%) followed by Sodium Valproate (27.39%) were the most commonly prescribed drugs to treat it. Monotherapy was given in 53.95% of patients. The overall incidence of adverse drug reactions (ADRs) was 4.67%. Unlike previous studies Phenytoin was the most frequently prescribed AED followed by Sodium Valproate. In contrast to other studies, our study revealed frequent use of Topiramate as an adjuvant. Carbamazepine and Phenytoin accounted for most of the ADRs. Drowsiness was the commonest ADR reported.

Keywords: *Antiepileptic drugs, Drug utilization, Epilepsy, Adverse drug reactions.*

INTRODUCTION

Epilepsy is a common neurological disorder which demands immediate medical attention and often long term therapy. The incidence is approximately 0.3 – 0.5% in different world populations with a prevalence rate of five to ten per thousand people. The overall aim in treating epilepsy should be complete control of seizures, without causing any untoward reaction due to the medication. A large number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like phenytoin, carbamazepine, valproic acid and ethosuximide are commonly used as first line drugs. They are relatively less expensive than the newer anti-epileptics. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide are the newer ones and currently used as add-on or alternative therapy.They have lesser adverse effects and have few, if any, drug interactions [1, 2].

Some side effects may be common with the above mentioned drugs and include sedation and ataxia. They can be diverse as well, ranging from idiosyncratic reactions like bone marrow depression (carbamazepine) to acute myopia and glaucoma (topiramate). Monotherapy is the usual dictum, but polytherapy is needed for patients with multiple seizure types or refractory disease [3, 4, 5]. The current study attempts to analyze the pattern of drug utilization in different types of epilepsy. The extent of polytherapy is also looked into. The adverse drug reactions reported by the patients and their impact on the continuation of anti-epileptic therapy are evaluated.

Objectives of the study

Get an insight into the utilization pattern of anti-epileptic drugs (AEDs) in different types of epilepsy and to identify the extent of poly-pharmacy.

Evaluate the adverse drug reactions caused by the anti-epileptic drugs.

MATERIALS AND METHODS

In a prospective study spanning eight months (January to August 2008) we analyzed the prescription data of 278 patients of seizures from neurology out patient department (OPD) of Owaisi hospital and the general medicine and pediatric OPDs of Princess Esra hospital, Hyderabad. Current diagnosis was made by the doctor in charge of the patient.

Inclusion criteria: Patients with seizures, of both sex and all age groups, who are prescribed an anti-epileptic drug, are included in the study.

Exclusion criteria: Patients with status epilepticus and seizures associated with acute conditions like paralytic stroke are excluded. The demographic data, type of seizures, the anti-epileptic drugs prescribed and the adverse drug reactions (ADRs) reported by the patients were recorded.

The data thus obtained was analyzed to arrive at prescribing indicators, patient indicators and adverse drug reaction profile [6].

Prescribing indicators include

1) Average number of anti-epileptic drugs (AEDs) prescribed per patient. This is calculated as:

$$\text{Avg. no. of AEDs/patient} = \frac{\text{Total no. of AEDs prescribed for all patients}}{\text{Total no. of patients}}$$

2) Most commonly prescribed anti-epileptic drug(s) in this study and the commonest drug(s) prescribed for each seizure type.
3) Number of AEDs prescribed using generic names.

Patient indicators include

1) Total number of male and female patients.
2) Average age of male and female patients.
3) Number of patients receiving monotherapy and multiple anti-epileptic drugs respectively.

Adverse drug reaction (ADR) profile includes

1) The incidence and type of adverse drug reaction.
2) The causality relationship of the ADR with suspected drug according to Naranjo ADR probability scale.
3) Whether the suspected drug was stopped after the ADR.
4) Whether any treatment was given for the ADR.
5) The drug(s) most commonly causing ADRs.

RESULTS

Prescribing indicators

1) Average number of anti-epileptic drugs (AEDs) prescribed per patient. This is calculated as:

$$\text{Avg. no. of AEDs/patient} = \frac{436}{278} = 1.56$$

2) The types of seizures encountered in this study and their frequency are shown in Table 1.

Table 1. Seizure types and their frequency

Seizure type	Cases out of 278	%
Idiopathic generalized epilepsy	96	34.53
Symptomatic epilepsy *	73	26.25
Simple Febrile seizures	48	17.26
Complex partial seizures	18	6.47
Seizures with mental retardation (cerebral palsy)	16	5.75
Complex febrile seizures	9	3.23
Simple partial seizures	8	2.87
Absence seizures	6	2.15
Juvenile myoclonic seizures	1	0.35
Post partum epilepsy	1	0.35
Benign Rolandic epilepsy	1	0.35
Eating (reflex) epilepsy	1	0.35

*Seizures due to structural lesions of brain such as stroke, cerebral bleed trauma, granuloma, cerebral atrophy, cyst, tumor etc.

The most commonly prescribed anti-epileptic drugs (AEDs) in our study were Phenytoin 42.44% followed by Sodium Valproate 23.74%. The drug(s) prescribed in each type of seizure is shown in table 2.

3) Number of AEDs prescribed in generic name: Diazepam – 72 cases, Midazolam – 26 cases.

Patient indicators

1) Total number of patients in the study = 278
   a) Number of male patients = 173 (62.23%)
   b) Number of female patients = 105 (37.77%)

$$\text{Ratio} = \frac{\text{Male}}{\text{Female}} = \frac{173}{105} = 1.64$$

Table 2. Types of seizures and drugs prescribed

Seizure type	Commonest drug prescribed alone or in combination (% of cases)	Second commonest drug prescribed alone or in combination (% of cases)	Other drugs prescribed
Idiopathic generalized epilepsy	Phenytoin (60.41)	Sodium valproate (20.83)	Clobazam Topiramate Midazolam Carbamazepine Phenobarbitone Clonazepam Oxcarbazepine
Symptomatic epilepsy	Phenytoin (57.53)	Sodium valproate (27.39)	Topiramate Midazolam Carbamazepine Oxcarbazepine Clonazepam
Simple febrile seizures	Clobazam (79.16)	Diazepam (66.66)	Phenytoin Midazolam Phenobarbitone Lorazepam
Complex partial seizures	Carbamazepine (55.55)	Sodium valproate (27.77)	Topiramate Oxcarbazepine Clonazepam Phenytoin
Seizures with mental retardation (cerebral palsy)	Phenytoin (50)	Sodium valproate (25) Midazolam (25)	Topiramate Carbamazepine Clobazam Diazepam
Complex febrile seizures	Phenytoin (44.44) Diazepam (44.44)	Sodium valproate (33.33) Clobazam (33.33)	---
Simple partial seizures	Carbamazepine (50)	Phenytoin (25) Sodium valproate (25) Diazepam (25)	---
Absence seizures	Topiramate (83.33) (as adjuvant drug)	Carbamazepine (33) Sodium valproate (33) Phenytoin (33)	---
Juvenile myoclonic seizures	Sodium valproate (100)	---	---
Post partum epilepsy	Carbamazepine (100)	---	---
Benign Rolandic epilepsy	Carbamazepine (100)	---	---
Eating (reflex) epilepsy	Oxcarbazepine (100)	---	---

2) Age range of patients = 7 months to 70 years.
   a) Average age of male patients = 22.21 years.
   b) Average age of female patients = 22.98 years.
3) Incidence of mono and polytherapy (Table 3).

Table3. Incidence of mono and polytherapy

Type of therapy	Percentage
No. of patients receiving single AED	150(53.95 %)
No. of patients receiving two AEDs	114 (41.00 %)
No. of patients receiving three AEDs	14 (5.03 %)

Adverse drug reaction (ADR) profile

13 patients out of a total of 278 reported ADRs (incidence = 4.67%) as shown in the Table 4. Phenytoin and Carbamazepine contributed equally to the occurrence of adverse effects (six cases each). None of the patients received any treatment for adverse effects.

DISCUSSION

In this study, idiopathic generalized epilepsy was the commonest type of epilepsy 34.53% and phenytoin was the commonest drug prescribed 60.41% for it's treatment, followed by sodium valproate 20.83%. Symptomatic epilepsy comprised the second commonest category of seizures 26.25%. It included seizures due to structural lesions of the brain such as stroke, cerebral

Table 4. Adverse drug reactions

No. of patients	ADR reported	Suspected drug	Causality relationship	Whether treatment with AED continued / stopped
3	Drowsiness, subtle imbalance	Phenytoin	Possible	Continued
2	Gum swelling	Phenytoin	Possible	Continued
1	Decreased memory and learning	Phenytoin	Possible	Continued
7	Drowsiness	Carbamazepine (6 cases)	Possible	Continued (5 cases) Stopped (1 case)
		Topiramate (1 case)	Possible	Continued

bleed, trauma, granuloma, cerebral atrophy, cyst, tumour etc. Phenytoin 57.53% followed by Sodium Valproate 27.39% was the most commonly prescribed drugs. Phenytoin was widely prescribed in our study, unlike another South Indian study by Radhakrishnan et al. where it was underutilized, inspite of being less expensive [4]. Simple febrile seizures were treated with diazepam in the acute stage and therapy was maintained with Clobazam. The latter drug is preferred as maintenance therapy to prevent recurrence. It has fewer side effects like ataxia and drowsiness compared to Diazepam and also ensures better patient compliance [7]. In cases of complex febrile seizures Diazepam/ Phenytoin/ Sodium Valproate were used in the acute stage and Clobazam was used for maintenance therapy.

Among the newer AEDs Topiramate was most commonly used as an adjuvant drug. It was most often combined with Sodium Valproate (18 cases) followed by combination with Carbamazepine (four cases), Oxcarbazepine (four cases) and Phenytoin (two cases). Topiramate was the commonest adjuvant drug and recorded maximal use in absence seizures. Though the efficacy of Topiramate is similar to the conventional drugs, it was preferred because of lesser incidence of adverse effects [8].

We encountered use of Phenytoin and Carbamazepine in two cases each of absence seizures, which is not in accordance with the standard treatment protocol. In case of partial seizures (both simple and complex) Carbamazepine was the commonest first line drug, which conforms with standard treatment guidelines.

We came across one case of benign rolandic epilepsy. A typical attack involves twitching, numbness or tingling of the child's face or tongue (partial seizure) which often interferes with speech and may cause drooling. These seizures last less than two minutes and the child remains fully conscious. Sometimes the child may also have tonic-clonic seizures, usually during sleep. This case was treated with carbamazepine which is commonly used for this seizure type [9].

We recorded one case of eating epilepsy which is a type of reflex epilepsy. In this condition, seizures can be provoked habitually by an external stimulus (like eating) or internal mentalprocesses. Reflex epilepsies may manifest as either focal onset or primary generalized seizures [10]. Among the prescribed AEDs, Diazepam (72 cases) and Midazolam (26 cases) were the only drugs prescribed by generic names.

Diazepam, lorazepam and midazolam were the drugs used for acute control of different types of seizures. Single AED was prescribed in 53.95% of patients. The remaining patients required polytherapy. A combination of two AEDs was prescribed in 41% of patients while 5.03% were on a combination of three AEDs.

The overall incidence of adverse drug reactions (ADRs) was not very high in our study (13 patients out of 278 i.e. 4.67%). Phenytoin and Carbamazepine contributed equally to the occurrence of ADRs (six patients each).Drowsiness, imbalance, gum swelling, decreased memory and learning were the ADRs reported by patients on Phenytoin. Most of these correspond well with the known adverse effect profile of Phenytoin [11]. Since Phenytoin was the only AED in the prescriptions of these patients, the reported adverse effects can be attributed to it. Drowsiness was reported by six patients taking Carbamazepine as monotherapy. In one case, drowsiness was possibly due to Topiramate as the patient reported it only after it was added to Carbamazepine. The patient did not report drowsiness with the use of Carbamazepine as a single drug previously. Overall, drowsiness was the most frequent adverse effect in our study which is similar to the finding in a previous study [4].

The causality relationship between the ADRs and the respective drugs comes under "possible" category as per Naranjo ADR probability scale.

Except one, the treatment with AED was continued in all the patients who reported adverse effects because the seizures were well controlled and the adverse effects did not significantly disrupt the normal activities of the patient. In one case treatment with Carbamazepine was stopped as it caused significant drowsiness which disrupted the patient's normal activities.

CONCLUSIONS

Idiopathic generalized epilepsy was the commonest type of epilepsy recorded. Monotherapy was preferred in most cases. Unlike previous studies Phenytoin was the most frequently prescribed AED followed by Sodium Valproate.[12] In contrast to other studies, our study revealed frequent use of newer AED namely Topiramate as an adjuvant [12, 13].

The overall incidence of adverse drug reactions was not very high. Drowsiness was the commonest ADR reported. Carbamazepine and Phenytoin accounted for most of the ADRs. Treatment with antiepileptic drugs was continued in all cases except one, as the nature of adverse reaction was not considered serious. None of the patients received any treatment for adverse effects.

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