

Trends in Utilization of Antiepileptic Drugs Among Pediatric Patients in a Tertiary Care Hospital

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Abstract

The primary purpose of this study was to evaluate the utilization pattern and seizure outcome of newer and older antiepileptic drugs in pediatric clinical practice in a tertiary care hospital setting. The study was a retrospective observational study carried out, among pediatric epilepsy patients who were diagnosed according to the classification of the International League Against Epilepsy and the information was gathered with the help of a validated data collection form. There was a relative male preponderance (56%) seen among epileptic patients. Of the total 210 patients analyzed, 110 (52.4%) were having partial seizure and 100 (47.6%) had generalized seizures. Out of 210 patients 134 (63.8%) were on monotherapy and 76 patients (36.2%) were on polytherapy. Mean daily doses of carbamazepine were 492.69 ± 51.8 and 320.97 ± 42.09 in polytherapy and monotherapy respectively. The number of patients on newer anticonvulsants was much smaller. The serum levels were monitored for commonly used antiepileptics like phenytoin, carbamazepine, phenobarbitone and Valproate in 43 (20.5%) patients. Among 210 patients, antiepileptic drugs were changed for 96 (45.71%) and the reasons for changing prescriptions were uncontrolled seizures (67.7%), recurrence (22.9%) and adverse effects (9.3%). A nationally based study and guidelines may bring a more rational approach for antiepileptic drug. Though most of the cases can be effectively managed with conventional antiepileptics, an increase in experience with the use of newer medications can offer an additional advantage to patients.

Key Words: antiepileptic drugs, drug utilization, generalized seizure, partial seizure, monotherapy, polytherapy, mean daily dose

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Introduction

The development of twin concept of therapeutic formularies and essential drug list is one of the main reasons for studying drug utilization. In establishing a selected list of drugs, one will after all, need to be guided to an important extent not only by epidemiological statistics and scientific considerations of efficacy and safety, but also by current patterns of usage, which are likely to reflect what a community wants and needs.[1] The mainstay of management of epilepsy is antiepileptics. The beneficial effects of new generation antiepileptic drugs (AED) compared with traditional AEDs in the control of seizure attacks is still a matter of debate. The most commonly used antiepileptic drugs reported in various studies include carbamazepine, Valproate, phenytoin and phenobarbitone. [2] Different combinations of AEDs and monotherapy are used for the treatment of different forms of childhood epilepsy. Treatment should be aimed at controlling seizures associated with the lowest possible occurrence of adverse ef-

fects, thus allowing the child to become an active member of the community at the lowest possible overall cost. Data on the efficacy, potency, safety and tolerability of AEDs are critical in choosing the optimal AED, but monotherapy data specific to children is often not available. The ultimate outcome of AED treatment in pediatric epilepsy is to attain no seizures and no side effects. [3]

Objectives

1. To analyze the current drug utilization pattern of different antiepileptics used in various types of epilepsy in pediatric population in a tertiary health care set up.
2. To evaluate the use of antiepileptics in different pediatric age groups, gender and to know the importance of drug monitoring for optimization of drug therapy.
3. To study the extent of use of newer antiepileptic drugs in the study population.

Methodology

The study was conducted at a 1050 bedded tertiary care hospital.

Ethical clearance was obtained from the Institutional Ethics Committee. A retrospective observational study was carried out for a total duration of six months. Around 210 pediatric epileptics aged between 3 months to 18 years who were prescribed with at least one AED were included in the study. The patients were further classified into different age groups of <6, 6–10 and 11–18 years.

Code wise list of patients classified according to International classification of disease (ICD – 10) maintained at MRD was retrieved from medical records section. Demography of the patients i.e. age, sex, and locality and clinical profiles i.e. types of epilepsy, its subtypes and presumptive etiological diagnosis were collected in a semi structured proforma i.e. Case Record Form. The treatment related facts like current drugs, dosages, previous drugs, reason for change and adverse effects were also noted in the same semi structured proforma.

Results

A. Clinical and Demographic Profile

There is a relative male preponderance (56%) seen among epileptic patients. (Table 1).

Of the total 210 patients analyzed, 110 (52.4%) were having partial seizures and 100 (47.6%) had generalized seizures. (Table 2) Among partial seizures, 'complex partial' was more common (31.9%) as compared to simple partial seizure (7.6%). Tonic-clonic seizure was

Table 1. Demographic characteristics

Characteristics		Number (n=210)	Percentage
<i>Age (years)</i>			
<6		93	44.3
6-10		57	27.1
11-18		60	28.6
<i>Gender</i>			
<6	M	53	
	F	40	25.3
6-10	M	32	19
	F	25	15.23
11-18	M	33	11.9
	F	27	15.7
			12.85

the most common (20.5%) generalized seizure followed by myoclonic (17.6%), absence (3.3%) and atonic type (1.9%). One hundred eighty four (87.6%) cases were idiopathic and 26 (12.4%) cases had epilepsy due to secondary causes. Around 163 patients (77.6%) showed abnormal EEG (Electroencephalogram) pattern and 18 patients (8.6%) had normal EEG (Table 2)

B. Drug Utilization

Out of total 210 patients, 134 (63.8%) were on monotherapy and 76 patients (36.2%) were on polytherapy.

Majority of patients were on conventional antiepileptic drugs. Carbamazepine (52.8%), Valproate (37%), phenytoin (19%) and phenobarbitone (10.9%) were the most commonly used drugs. The newer antiepileptic drugs were used less frequently, of which lamotrigine the most commonly used (8.5%) was followed by topiramate (3.3%). (Table 3).

In polytherapy, most commonly used two drug combinations were "Valproate and carbamazepine", "Valproate and clonazepam" followed by "phenytoin and carbamazepine". The most common three drug combinations were that of "carbamazepine, phenytoin and lamotrigine", followed by "carbamazepine, Valproate and clonazepam".

Mean daily dose of phenytoin when used as polytherapy was 175.97 ± 31.37 and in monotherapy was 126 ± 27.18 , mean daily dose of phenobarbitone was 51.5 ± 6.24 in polytherapy and 55.3 ± 14.38 in monotherapy, and that of Valproate in polytherapy was 521.36 ± 54.8 and in monotherapy 443.82 ± 42 . Mean daily doses of carbamazepine were 492.69 ± 51.8 and 320.97 ± 42.09 in poly therapy and monotherapy respectively (Table 4) On comparison of mean dosage of antiepileptic drugs used in generalized and partial seizures, statistical significance was noted only with carbamazepine. (Table 4)

The number of patients on newer anticonvulsants was much smaller. Thereby the calculation of mean dose in certain age groups was not possible.

Plasma monitoring was done for 43 (20.5%) patients (Table 2). The serum levels were monitored for the commonly used antiepileptics like phenytoin, carbamazepine, phenobarbitone and Valproate. Among 210 patients, antiepileptic drugs were changed for 96 (45.71%) and the reasons for changing were uncontrolled seizures (67.7%), recurrence (22.9%) and adverse effects (9.3%) (Table 5).

Around 51 patients experienced seizures while on therapy and were categorized based on the number of seizures

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Table 2. Clinical variables

Characteristics	Number (n=210)	Percentage
<i>Types- generalized</i>		
<6	53	25.23
6-10	23	10.95
11-18	24	11.4
<i>Partial</i>		
<6	40	19
6-10	34	16.19
11-18	36	17.14
<i>Etiology: idiopathic</i>		
<6	81	} Total no-184 87.62
6-10	49	
11-18	54	
<i>Secondary</i>		
<6	12	} Total no- 26 12.38
6-10	6	
11-18	8	
<i>Treatment: Monotherapy</i>		
<6	60	} Total no-134 63.8
6-10	40	
11-18	34	
<i>Polytherapy</i>		
<6	33	} Total no-76 36.2
6-10	17	
11-18	26	
<i>ECG</i>		
Abnormal	163	77.61
Normal	18	8.57
Not done	29	13.8
<i>Therapeutic drug monitoring</i>		
Done	43	20.5
Not done	167	79.5

Table 3. Antiepileptic Drug Utilization

DRUGS	PATIENTS (n=210)		PERCENTAGE
	Polytherapy	Monotherapy	
<i>Conventional</i>			
Phenytoin	18	12	19
Phenobarbitone	15	8	10.9
Valproate	44	34	37
Carbamazepine	39	2	52.8
Benzodiazepines (Clobazam, Lorazepam, Nitrazepam, Clonazepam, Diazepam)	34	4	18
<i>Newer</i>			
Lamotrigine	18	-	8.57
Topiramate	7	-	3.3
Levetiracetam	2	-	0.9
Tiagabine	3	-	1.4
Gabapentin	2	-	0.9
Oxcarbazepine	3	-	1.4

Table 4. Dosage of antiepileptic drugs in monotherapy and polytherapy

Antiepileptics	Mean dose (SD) mg	Significance
<i>Phenytoin</i>		
Monotherapy (N=18)	126.08 (94.17)	0.271 NS
Polytherapy (N=12)	175.97 (133.09)	
<i>Phenobarbitone</i>		
Monotherapy (N=15)	55.31(40.67)	0.779
Polytherapy (N=8)	51.5(24.19)	
<i>Valproate</i>		
Monotherapy (N=34)	443.82(245.46)	0.288
Polytherapy (N=44)	521.36(363.50)	
<i>Carbamazepine*</i>		
Monotherapy (N=72)	320.97(158.85)	0.000
Polytherapy (N=39)	492.69(320.16)	
<i>Clonazepam</i>		
Monotherapy (N=3)	0.83 (0.57)	0.293
Polytherapy (N=28)	1.58 (1.19)	

* $p < 0.001$

Lamotrigine, Levetiracetam, Clobazam, Topiramate, Tiagabine do not have enough sample for comparison

Table 5. Reasons for Change to Current medications

Reasons For Change	Number (n=210)	Percentage
Uncontrolled seizure	65	67.7
Recurrence	22	22.9
Adverse effects	9	9.4
Total	96	100

experienced per month as (1-5 seizures) (76.47%), (6-10 seizures) (19.6%) and (>10 seizures) (3.92%)

Discussion

Epilepsy usually begins in childhood, potentially impeding education, social relationships and development of a sense of worthlessness. Prompt, accurate diagnosis with

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appropriate social and medical management will optimize the situation.

Drug therapy is the mainstay of epilepsy treatment. The therapeutic goals of antiepileptic drugs are to reduce the frequency of recurrent seizure and to minimize the adverse effects. Specific treatment end points must be individualized for each patient. The selection of an antiepileptic drug is primarily dictated by efficacy in attaining full control of seizures. The goal for every patient should be the use of only one drug with the fewest possible side effects. The drug is increased slowly until seizure control is accomplished or until undesirable side effects develop. The child's serum anticonvulsant level should be monitored during this stage, and the dose should be altered accordingly. [4] In addition, type and severity of side effects produced by the various antiepileptic drugs are a major consideration in selection of a drug.

In our study majority of the patients receiving AED therapy were males as compared to females which were similar to earlier reports. [5, 6] This was in contrast to a community based study in UK where there was slight preponderance of females. [7]

There was almost equal number of patients suffering from generalized and partial seizure (48% and 52%) in our study. A hospital based study had shown 54.45% of patients having generalized epilepsy (generalized tonic-clonic 36.76%, absence 9.19%, myoclonic 8.50%) as compared to 28.4% of partial seizure patients.[6] More than three fourth (87%) of seizures were idiopathic in our study compared to 42% in a study conducted in Europe.[8]

Carbamazepine was the most commonly prescribed drug (52.8%), which is in accordance with previous studies which suggest Carbamazepine as the most frequently used drug (39%).[9,10,11,12] In this study Valproate was the second most commonly used drug in 37% of patients. A study done in Bulgaria also showed Valproate as second most commonly used drug.[9] In most of the European and Asian studies, Valproate was not a commonly prescribed antiepileptic.[8,12]

Recent studies from UK have reported Valproate (22%) followed by carbamazepine (21.3%) as most commonly used antiepileptic drug. [7]

The current NICE (National Institute of Clinical Excellence) guidelines and other guidelines advise either carbamazepine (focal seizures) or sodium Valproate (focal or generalized seizures) as first line of therapy for epilepsy. If there is no control of seizure with one drug, alternative monotherapy should be tried before considering polytherapy. [13]

The recent trend of shifting prescription pattern toward these drugs (carbamazepine or Valproate) from that of phenobarbitone or phenytoin is most likely due to better safety profile of former agents.

The use of newer antiepileptics was not reported in many studies as these drugs are made available recently in the market. In some countries it had to be procured from overseas due to non-availability. [5] The NICE guidelines report that the role of the newer drugs (gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate) will become clearer after randomized controlled studies comparing their efficacy as first line monotherapy with conventional AEDs. [13] At this point the consensus is that traditional (conventional) antiepileptic drugs may be as effective as newer ones.

The first line use of newer antiepileptic drug cannot be recommended in many situations because of limited clinical experience and cost wherein the use of these drugs should be reserved for epileptics not responding to conventional drugs. [12]

In our study Lamotrigine was the commonly used antiepileptic (8.57%) which is in accordance with study in United Kingdom in 2004 where the usage was 3.3%. The use of Topiramate was 3.3% in our study and was similar to another study in Croatia (2.93%). [14]

The present study indicated that monotherapy is the modality of treatment frequently used in all types of seizures. This trend is as per the recommended treatment paradigm for epilepsy.[15] Monotherapy is preferred to polytherapy because of lower cost associated with medication and blood level monitoring, reduced potential for adverse reactions and undesirable drug interactions.

In addition, monotherapy with antiepileptic drug contributes to an improved medication compliance with a more simplified drug administration schedule. Furthermore, a growing body of evidence indicates that polytherapy offers no advantage over monotherapy for 90% of patients with epilepsy. [16] For patients in whom single drug therapy does not provide sufficient seizure control, polytherapy may be necessary to achieve the goal of treatment.

In this study majority (63.8%) of patients were on monotherapy and 36.2% were on polytherapy, which is in accordance with the studies that suggest monotherapy to be the gold standard for treatment of epilepsy being initially effective for 44-79% of patients.[6,17,18] Studies from Indian subcontinent had reported monotherapy in the range of 62.5% to 75.5%. [12,5] Studies from West reported 69% of the patients in the community on monotherapy.[20,7] In patients taking two antiepileptic drugs in our study, the most frequent combinations were Valproate + carbamazepine and phenytoin + carbamazepine which

is in accordance with a study where the most common regimens were carbamazepine + Valproate and carbamazepine + phenytoin respectively.[7] Among carbamazepine users, 60.4% were on monotherapy which was similar to previous studies where 85% Carbamazepine users were on monotherapy.[8] Among newer antiepileptic drugs, almost all were used as adjuvants to other drugs which is similar to other studies.[7] In our study the mean dose of phenytoin was 175.97mg which varies between 25mg to 600mg/day and the dose of phenobarbitone was 51.5 mg which varies between 22.5 to 120 mg/day, which is in accordance with other study. [12] The reason for variation might be due to different age groups included in the sample and the selection of dose of antiepileptics is based on the weight of the patient. There were no comparable studies on the dosage of other antiepileptics.

The doses of most of drugs in our study are towards lower side of Minimal Maintenance Dose (MMD) although it falls in the therapeutic range. [18] This finding was in accordance with similar study where around 32% patients were on smaller dose than expected MMD. [8]

In our study, monotherapy had been most commonly used for both generalized (57.3%) and partial seizure (60%) which is in accordance with similar studies. Carbamazepine was considered first line in partial epilepsy and Valproate for generalized epilepsy.[6, 8, 21] These preferences are in line with the results of the other studies and the randomized control trials and are therefore evidence based.[21,22,23] Results from our study showed that the order of drug preference in generalized epilepsy was Valproate, phenytoin and carbamazepine respectively.

Routine monitoring of the serum drug concentration has traditionally been used to guide dosage adjustment in patients taking antiepileptic drugs. [24]In our study plasma monitoring was done in 20.5% of patients with inadequate seizure control and toxicity, which is lower than expected.

A study done in Italy has shown that there were no significant differences between the epileptics managed with monitoring of serum levels of antiepileptic drugs and on clinical ground level with regard to achieving epileptic control and frequency of adverse effects.[25] Considering this some researchers have advocated the serum drug level measurement only in special situations and not for routine clinical practice.[5] So routine checking of drug levels is seldom indicated but planned checking of level to guide changes in therapy has an important role in management of epilepsy in a developing country like India.

In conclusion, a nationally based study and guidelines may bring a more rational approach for antiepileptic drug

prescriptions. Very few of the available clinical trials for the common childhood epilepsies have compared different treatments with each other or provide guidance concerning an treatment strategy.[26].

Though most epilepsy can be effectively managed with conventional antiepileptic, an increase in experience with the use of newer medications can offer an additional advantage to patients.

Conflict of interest: none

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