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Original Research Article

Adverse drug reactions to antiseizure medications in pediatric epilepsy: a pharmacovigilance study from a tertiary care centre in India

Divya Chamariya[1]*, Kamlesh Garg[2], Rachna Sehgal[3], Hitesh Verma[4]

[1]Department of Pharmacology, Lady Hardinge Medical College, New Delhi, India
[2]Department of Pharmacology, Vardhman Mahavir Medical College, New Delhi, India
[3]Department of Paediatrics, Vardhman Mahavir Medical College, New Delhi, India
[4]Department of Anatomy, Lady Hardinge Medical College, New Delhi, India

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***Correspondence:**
Dr. Divya Chamariya,
Email: divya.chamaria1995@gmail.com

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ABSTRACT

Background: Epilepsy is a chronic neurological disorder requiring long term antiseizure drug (ASD) therapy, often associated with adverse drug reactions (ADRs). Understanding the frequency and nature of ADRs in pediatric patients is essential for optimizing treatment outcomes. Objectives of the study were to evaluate the prevalence, pattern, and causality of ADRs associated with antiseizure drugs in pediatric patients using the Naranjo scale and World Health Organization-Uppsala monitoring centre (WHO UMC) causality assessment system.

Methods: A descriptive cross-sectional study was conducted over 12 months in the Departments of Pharmacology and Paediatrics at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. Pediatric epilepsy patients (1–12 years) on antiseizure drugs for ≥1 month were enrolled. ADRs were recorded using the Central Drugs Standard Control Organization (CDSCO) ADR reporting form and assessed using Naranjo and WHO UMC scales. Descriptive statistics were used for data analysis.

Results: Among 196 enrolled patients, 39 (20%) experienced ADRs. The most common ADRs were sedation (10.2%), gum hypertrophy (5.1%), constipation (4.6%), vomiting (4.1%), nausea (4.1%), rash (3.6%), and abdominal pain (3.6%). Causality assessment showed 56.42% of ADRs were probable and 43.58% were possible using both the Naranjo and WHO UMC scales.

Conclusions: ADRs to antiseizure drugs are common in pediatric patients, with sedation being the most frequent. Most ADRs were of probable or possible causality. Regular monitoring and early recognition can improve treatment outcomes and quality of life.

Keywords: Antiseizure drug, Adverse drug reaction, Sedation, Valproate

INTRODUCTION

Epilepsy is characterized by recurrent unprovoked seizures resulting from abnormal, excessive neuronal discharges in the brain.[1] A chronic non communicable neurological disorder, epilepsy is associated with significant physical, psychological, and social consequences impacting quality of life.[2] Globally, epilepsy affects an estimated 50–70 million individuals, with nearly 80% residing in low-and middle-income countries. India alone accounts for nearly one sixth of the global epilepsy burden.[3,4] In childhood, epilepsy constitutes a major health concern, with approximately 6–7% of children experiencing at least one seizure. The prevalence of active epilepsy ranges from 4–5 per 1000 population globally and 4.15–7.03 per 1000 in India.[5] Antiseizure drugs (ASDs) remain the cornerstone of epilepsy management. While effective, ASDs are often associated with adverse drug reactions (ADRs), owing to their narrow therapeutic index and systemic effects. ADRs contribute to treatment failure in up to 40% of patients and

represent a major factor influencing drug selection and compliance.[6]

Given the chronic nature of epilepsy management, early identification and monitoring of ADRs are essential to improve outcomes. This study aims to assess the prevalence, pattern, and causality of ADRs among pediatric epilepsy patients receiving ASDs.

METHODS

This is a descriptive observational cross-sectional study at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi between the period of 12 months (January 2023 to February 2024).

The estimated sample size was calculated using the formula given with confidence interval (Z)=1.96, prevalence (P) of epilepsy in pediatric age group=0.5, precision (d)=0.05.[7] The estimated sample size (n) was 384.

$$n = (Z^2 P(1 - P))/d^2$$

Since, our study population is limited by size, we take finite population (T) as 400 and the adjusted sample size was 196.

$$Adjusted\ sample\ size = n/(1 + (n - 1)/T)$$

Inclusion criteria

All children aged 1–12 years of either gender who are diagnosed with epilepsy and receiving ASDs for ≥1 month are included in study.

Exclusion criteria

Children with major psychiatric illness (e.g., psychosis), seizure mimicking conditions such as breath holding spells are excluded from study.

Sociodemographic and clinical characteristics of patients were recorded in a predesigned proforma. ADRs were documented using the CDSCO ADR reporting form. Causality assessment of reporting ADR was done by 2 scales - Naranjo ADR scale: 10 item structured questionnaire, scores: definite (≥9), probable (5–8), possible (1–4), doubtful (≤0); and WHO UMC system: classifies ADRs as certain, probable, possible, unlikely, conditional, or unclassifiable.

Ethical approval was obtained from Institutional Review Board (IRB) and Project Review Committee, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. Written informed consent was obtained from parents/caregivers; assent was obtained where required. Data were analyzed using STATA 17.0. Data were obtained in number and percentage. Descriptive statistics were used to present frequencies, percentages, means, and proportions.

RESULTS

In this study, majority of study participants (39.29%) were 9-12 years of age showing adverse drug reaction from antiseizure drugs, followed by 74 participants (37.69%) in the age group of 5-8 years. There were high proportion of males (69.9%) compared to females (30.10%) (Table 1).

Table 1: Demographic distribution of participants (n=196).

Age group (years)	Number of participants (N)	Percentage (%)
<4	45	22.96
5–8	74	37.76
>9	77	39.29
Total	196	100.00
Mean age±SD	6.85±3.45	
Median age	7	
Range (years)	1-12	
Gender		
Boy	137	69.90
Girl	59	30.10

Out of 196 patients, majority were getting primary education (62.76%). About 1.53 % had a history of drug allergy. Valproate was the most prescribed single antiseizure, comprising 61.76% of the total adverse drugs reaction followed by prescription of dual therapy of valproate and levetiracetam. Overall incidence rate of ADRs was 20%. Most encountered ADR was sedation (10.20%) followed by constipation (4.53%), gum hypertrophy and vomiting (4.09%) (Table 2).

Table 2: Side effects of antiseizure medication.

Side effects	Number of participants (N)	Percentage (%)
Sedation	10	5.10
Rash	7	3.57
Nausea	8	4.08
Vomiting	9	4.08
Abdominal pain	7	3.57
Constipation	9	4.59
Gum hypertrophy	9	5.10
Weight gain	5	2.55
Drowsiness	5	2.55

Organ system wise distribution of ADRs is shown in Table 3.

Majority (56.42%) of ADRs were found to be probable in nature and about 43.58% were possible according to WHO/UMC causality assessment system (Figure 1) and Naranjo algorithm scale (Table 4). In our study, we found

no certain cases as rechallenge was not attempted by the attending physician, once a drug was withdrawn because of safety precautions.

Table 3: Organ system–wise adverse drug reactions (ADRs) of antiseizure drug.

Organ system	Number of cases (N)	Percentage (%)
Central nervous system	10	5.10
Dermatological system	7	3.57
Gastrointestinal system	33	16.0
Oral/dental system	9	5.10
Metabolic system	5	2.55

Table 4: Causality assessment in PWE by Naranjo scale.

Naranjo scale	Number of cases (N)	Percentage (%)
Possible	17	43.58
Probable	22	56.42
Total	39	100

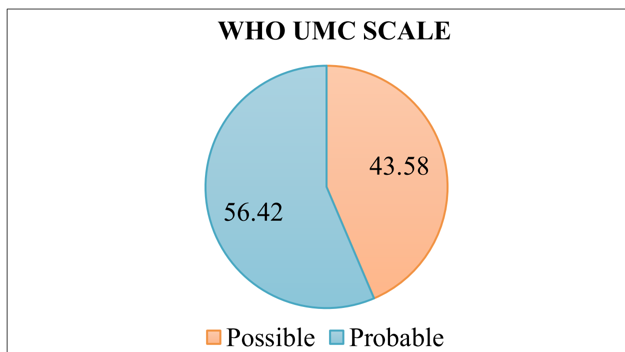

Figure 1: Causality assessment of ADR by WHO-UMC scale.

DISCUSSION

Epilepsy is a disorder of major public health concern, in terms of its prevalence, suffering, dysfunction and morbidity. Current treatment for epilepsy is suboptimal, and it takes weeks to months to achieve their antiseizure effects, also a significant number of patients do not have adequate improvement even after months of treatment. Although antiseizures have been found beneficial in treating many neurological disorders, their association with a wide range of potential ADRs is a matter of great concern. Several studies from literature showed that antiseizure are most frequently associated with ADRs. Benign and transient side effects are more common than dangerous or irreversible effects. In Our study, we evaluated adverse drug reactions due to antiseizures among epileptic patients. Overall incidence rate of ADR was 20 % as out of 196 participants, 39 reported a ADRs. In our study, most encountered ADR was sedation (10.20%) followed by gum hypertrophy, constipation (4.53%) and vomiting (5.09%). The other ADRs reported were nausea (4.7%), rash (3.57%), abdominal pain (3.57%), weight gain (2.4%), drowsiness (2.4%). Assessment of causality of recorded adverse events was done by WHO-UMC and Naranjo scale. Out of 39 ADR, majority (56%) were probable in nature and 43% were found to be of possible in causality on both WHO/UMC causality assessment system and Naranjo algorithm scale. In our study, we found no certain 'cases as rechallenge was not attempted by the attending physician, once a drug was withdrawn. This finding is like the study conducted by Gajjar et al, total 112 ADEs were reported from 58 (36.25%) patients in 6-month follow-up. Sedation and drowsiness were most frequently found with 68 (60.71%) patients followed by the nausea, vomiting, abdominal pain. Phenytoin was most suspected AEDs (with 39 cases) followed by carbamazepine (in 23 cases). Causality assessment by the WHO-UMC criteria most common association was possible in 75 (66.96%) cases, probable 21 (18.75%), certain 6 (5.36%), and conditional/unclassified 10 (8.93%). Similar result was obtained by Naranjo's criteria as possible 84 (75.00%), probable 22 (19.64%), and definite 6 (5.36%). 91 (80.36%).[8] Common ADRs of these drugs are mentioned in many studies such as: neurocognitive- tiredness, drowsiness, and sedation vertigo, diplopia, and ataxia, tremor, slow thinking and difficulty finding words, hyperactivity, inattention, insomnia, irritability, and behavioral issues, shifts in mood and despair. All of them, although most frequently with Benzodiazepines, Topiramate, Phenobarbital, and Zonisamide. Gastrointestinal: increased appetite, vomiting, nausea, anorexia with Rufinamide, Zonisamide, Felbamate, and Topiramate, Pregabalin, Clobazam, and Valproic acid. Hyponatremia and metabolic acidosis; Carbamazepine, Oxcarbazepine, Zonisamide, Topiramate decreased density of bone minerals; Primidone, Phenytoin, Carbamazepine, and Valproate.[9]

In a study on the use of antiepileptic drugs by Gunshaw et al, 100 pediatrics patients with epilepsy experienced adverse medication reactions associated with their antiepileptic treatment. The main goal of study was assessing the ADR of phenobarbitone, phenytoin, carbamazepine and valproic acid drugs. Headache, epigastric discomfort, disorientation, memory loss, skin rash, depression, and gingival hypertrophy are side effects encountered by patients, whereas in our study sedation was the most common reported ADR.[10] The observed ADR incidence in our study was lower than that reported by Y.B. et al, who documented 110 ADRs among 98 patients, with an average of 1.12 reactions per patient. Their higher ADR burden was largely attributed to the predominant use of older anti-seizure medication (ASMs), particularly phenobarbital and phenytoin, and the frequent use of polytherapy—both of which were significantly associated with ADR occurrence.

In comparison, the lower frequency of polytherapy in our study may partly explain the reduced incidence of ADRs. Sedation emerged as the most common ADR in our study

(10.20%), followed by constipation, gum hypertrophy, and vomiting. These findings agree with earlier reports describing central nervous system–related adverse effects as the most frequently encountered reactions with valproate and other conventional ASMs. Bayane et al similarly identified CNS drowsiness as a major ADR, although gastrointestinal symptoms such as epigastric pain were more prominent in their cohort, highlighting differences in drug utilization patterns and patient characteristics.[11]

Data from pharmacovigilance studies further support these observations. Mukhyaprana et al reported that skin and subcutaneous tissue disorders, particularly maculopapular rash associated with phenytoin, were the most reported ADRs. The lower prevalence of cutaneous reactions in our study likely reflects the comparatively limited use of phenytoin.[12]

At a population level, Girgis et al, using the surveillance database, demonstrated that older ASMs are more frequently associated with serious ADR outcomes, including hospitalization, disability, and mortality, whereas newer ASMs are predominantly linked to less severe but clinically important events. In the present study, most ADRs were non-serious and manageable, which is consistent with findings from large pharmacovigilance datasets.[13]

Overall, our findings corroborate existing evidence that ADRs remain a significant challenge in epilepsy management, particularly with conventional ASMs. The predominance of central nervous system and gastrointestinal adverse effects emphasizes the importance of close monitoring, patient counseling, and rational drug selection. Where feasible, the use of newer ASMs and avoidance of unnecessary polytherapy may help reduce the burden of ADRs and improve long-term treatment outcomes in patients with epilepsy.[14]

Limitations

The limitation of our study is lower rate of ADR that could be because of ADRs being transient or too mild to have inconvenienced the patient to an extent sufficient to report to the next hospital visit or due to underreporting of already known ADRs by physician.

CONCLUSION

ADR incidence among pediatric epilepsy patients receiving ASDs was 20%. The most common ADRs were sedation, constipation, gum hypertrophy, nausea, and vomiting. Most ADRs were of probable (56.42%) or possible (43.58%) causality as per both WHO UMC and Naranjo scales. Overall, these findings reinforce the importance of routine ADR monitoring can facilitate early detection and optimize epilepsy management, thereby improving the safety and effectiveness of antiseizure therapy in children.

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