ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 3, 2022

Online - 2455-3891
Print - 0974-2441

Case Report

ADVERSE DRUG REACTIONS OF ANTI-EPILEPTIC DRUGS IN PEDIATRIC AGE GROUP IN A TERTIARY CARE TEACHING HOSPITAL; A CROSS-SECTIONAL STUDY

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Received: 23 October 2021, Revised and Accepted: 08 February 2022

ABSTRACT

Objectives: In this cross-sectional study, the aims were to analyze the incidence and pattern of adverse drug reactions (ADRs) of antiepileptic drugs in pediatric patient. Most common adverse effect and most common drug causing adverse effect were evaluated.

Methods: Study was conducted over 60 Patients for 6 months in out-patient basis pediatric department in Rajindra Hospital associated with GMC, Patiala, a tertiary care teaching hospital in Punjab. The patient diagnosed by the Pediatrician with epilepsy who fulfilling inclusion and exclusion criteria was enrolled after taking informed consent. ADRs were noted using Pediatric Epilepsy Side Effect Questionnaire at clinic visit and any other adverse effects reported by patients.

Results: In this study, a total of 60 children were enrolled**.** The mean age was 10.26±3.70, median were 11.00. 41 (68.33%) patients were boys and 19 (31.67%) were girls. In Cognitive ADRs with anti-epileptic drugs, there were total 17 ADRs reported. Valproate was causing most cognitive ADRs (32.43%). Among all cognitive ADRs, attention difficulty was the commonest complains. There were no motor and behavioral ADRs reported. Total 27 general neurological ADRs reported, which was highest reported ADRs. Among general neurological, Clobazam was causing highest ADRs (55.56%). 10 patients also reported tremor as another ADR and Clobazam causing most (22.22%).

Conclusion: In the present study, boys were developing more epilepsy than girls. Valproate was causing most ADRs. Among all cognitive ADRs, attention difficulty was the most common ADR. General neurological ADRs were highest reported ADRs.

Keywords: Epilepsy, Antiepileptic drugs, Pediatric epilepsy side effect questionnaire, Adverse drug reactions.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i3.43425. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Epilepsy is one of the most common serious neurological disorders [1]. Seizures often cause transient impairment of awareness, leaving the individual at risk of bodily harm and often interfering with education and employment [2].

In the mid-1800 s, the first effective anti-seizures medication, Bromide, was introduced. The first modern treatment, Phenobarbital, was developed in 1912, with Phenytoin coming into use in 1938.

5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late childhood [3]. In the world, the prevalence of epilepsy has been estimated at 5–30 persons per 1000 [4]. The median incidence for children aged 0–14 years is 0.822/1000 children. It has also been estimated that 70% of all epilepsy syndrome start between the age of 0 and 19 years and 30% of the children with seizure will have their first episode before the age of 4 years, and more than half of the children with epilepsy will have more than one type of seizure [5]. Crude prevalence rate for active epilepsy was 7.44/1000 population in Punjab [6].

The mainstay treatment of epilepsy is anticonvulsant medications, possibly for the patient's entire life. Seizures are controllable with medication in about 70% of cases, inexpensive AEDs are often available [7]. There are a number of medications available including Phenytoin, Carbamazepine, Valproate. We have a lot of new drugs in the past 10 years such as Felbamate, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Tiagabine, Topiramate, and Zonisamide.

Adverse effects can contribute to treatment failure in up to 40% of patients and can affect the ultimate quality of life independent of seizure control [8]. The adverse effects may be dose dependent and also reversible. Only a few epidemiological studies are available, which have explored the AED safety profile in pediatric patients [9].

The present study was conducted to determine the nature and rate of adverse effects of anti-epileptic drugs in children with epilepsy in our institute. This study will be helpful to analyze the therapeutic benefit for the patient.

METHODS

Study design

This cross-sectional study was conducted in out-patient in pediatric department in Rajindra Hospital associated with GMC, Patiala, a tertiary care teaching hospital in Punjab. All epileptic patients who fulfill all inclusion and exclusion criteria were registered for the study. Duration of the study is 6 months. The study was approved by the institutional Ethical Committee, the Government Medical College, Patiala Ethical Committee for Human Research(Approval no. Trg.9 (310)2020/2601).

Sample size

60 Patients.

Inclusion criteria

1. Both male and female patients
2. Age group 1–12 years
3. Diagnosed as epilepsy patient.

Exclusion criteria

1. Patient with secondary epilepsy due to head injury, cerebral palsy, stroke, metabolic disorder.
2. Parent not willing to participate in the study
3. Patients with uncertain diagnosis.

Study sequence
In the OPD, all patients were screened according to inclusion and exclusion criteria. All patients were informed about the study in their own preferable language (English/Hindi/Punjabi).Written informed consent was obtained from each patient. All the adverse effects were recorded in a prestructured data entry form.

Data collection
Patient age, gender, present and past medical history, drug report, type of seizures, the anti-epileptic drug prescribed, and adverse drug reactions (ADRs) were recorded in a prestructured data entry form.

Adverse effects measurement
In this cross-sectional study ADRs were noted using Pediatric Epilepsy Side Effect Questionnaire (PESQ) at clinic visit and any other adverse effects reported by patients.

Data analysis
All data were statistically analyzed using appropriate tests.

RESULTS

Demographic profile of patients enrolled
In this study, a total of 60 children were enrolled**.** The mean age was 10.26±3.70; median was 11.00. Out of total 60 children, 41 (68.33%) patients were male and 19 (31.67%) were female patients. The Distribution of epilepsy patients according to age groups presented in Table 1 and Fig. 1. The Distribution of epilepsy patients according to sex also presented in Table 1 and Fig. 2.

Patients with ADR
Out-patient of pediatric department in Rajindra Hospital, there was found that Valproate, Clobazam, Phenobarbitone, and Phenytoin used as antiepileptic drugs mostly. Among the four antiepileptic drugs, Valproate was most commonly used drug.

In this study, total 64 ADRs occurred in 60 patients. ADRs were noted using PESQ at clinic visit and any other adverse effects reported by patients.

In Cognitive ADRs with anti-epileptic drugs, there were total 17 ADRs reported by patients. Valproate was causing most cognitive ADRs (32.43%) among drugs. Among all cognitive ADRs, attention difficulties were the most common complain. There were no motor and behavioral ADRs with antiepileptic drugs reported.

In the study, total 27 general neurological ADRs reported by the patients, which were highest reported ADRs. Among general neurological, Clobazam was causing highest ADRs (55.56%). Out of 27 general neurological ADRs, drowsiness and sleepiness were reported by total 23 patients. Clobazam was causing drowsiness and sleepiness in most of the patients as ADR. Increase in appetite also reported by patients and Valproate causing the most (24.3%). One patient was reported increase in appetite by Clobazam, but no case reported in Phenobarbitone and Phenytoin. Total 10 patients also reported tremor as another ADR and Clobazam causing most (22.22%).

A total of 64 suspected ADRs reported in this study by total 60 patients. Among all four antiepileptic drugs, Valproate causing most ADRs (68.33%) followed by Clobazam (30%). Phenytoin was prescribed in one patients and tremor was reported as an ADR. In comparison, Clobazam was causing less ADR than Valproate.

Tables 2-6 representing ADRs as per PESQ reported by the patients. Fig. 3 showing comparison studies of ADRs among all four drugs.

Table 1: Distribution of epileptic patients according to age and sex

Characteristic (n=60)	Percentage
Age groups	
<5 years	8 (13.33)
6–10 years	18 (30)
More than 10 years	34 (56.67)
Sex	
Male	41 (68.33)
Female	19 (31.67)

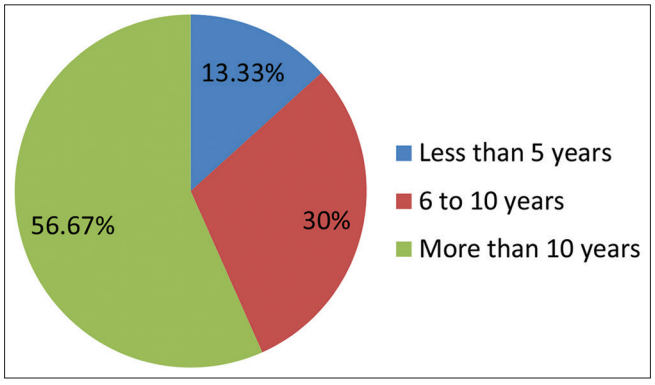

Fig. 1: Distribution of epilepsy patients according to age group

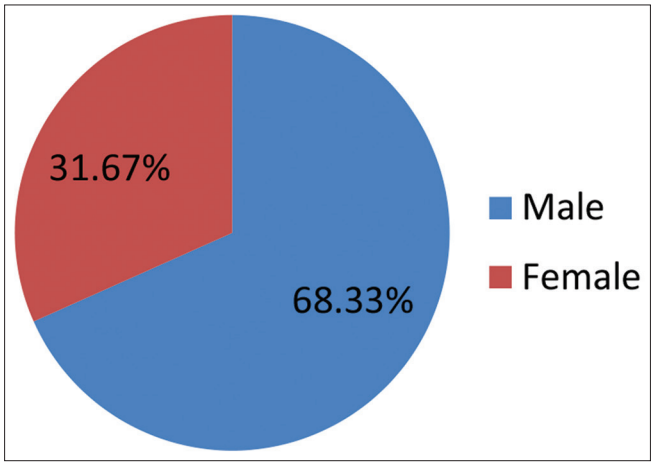

Fig. 2: Distribution of epilepsy patients according to sex

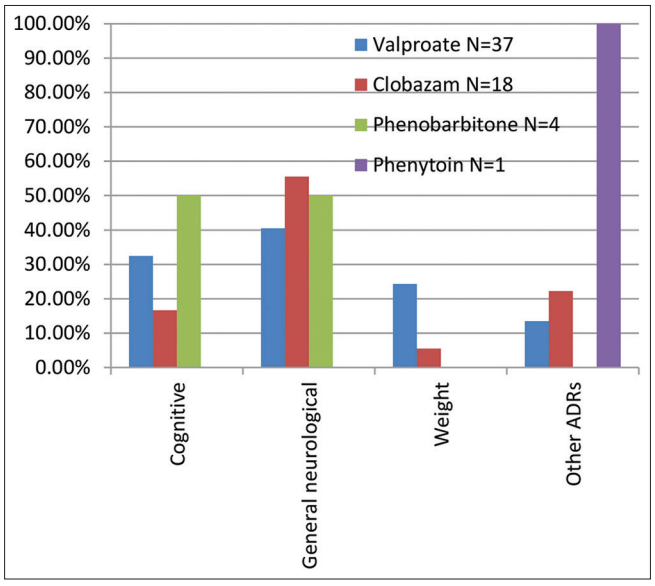

Fig. 3: Comparison study of ADRs among drugs

Table 2: Cognitive ADRs with anti-epileptic drugs (PESQ)

ADR Related ONLY to seizure medicine	Valproate n=37	Clobazam n=18	Phenobarbitone n=4	Phenytoin n=1
A Cognitive				
1. Slow thinking	0	0	0	0
2. Memory problems	0	0	0	0
3. Confusion	0	0	0	0
4. Poor school results	4 (10.8%)	0	1 (25%)	0
5. Decreased concentration	0	0	0	0
6. Attention difficulties	8 (21.6%)	3 (16.67%)	1 (25%)	0
Total	12 (32.43%)	3 (16.67%)	2 (50%)	0

ADR: Adverse drug reactions, PESQ: Pediatric Epilepsy Side Effect Questionnaire

Table 3: Motor and behavioral ADRs with anti epileptic drugs (PESQ)

ADR related ONLY to seizure medicine	Valproate n=37	Clobazam n=18	Phenobarbitone n=4	Phenytoin n=1
B. Motor				
7. Unstable walking	0	0	0	0
8. Poor coordination, clumsiness	0	0	0	0
9. Falling (not seizure)	0	0	0	0
10. Speech difficulties	0	0	0	0
Total	0	0	0	0
C. Behavioral				
11. Aggression	0	0	0	0
12. Hyperactivity	0	0	0	0
13. Personality change	0	0	0	0
Total	0	0	0	0

ADR: Adverse drug reactions, PESQ: Pediatric epilepsy side effect questionnaire

Table 4: General neurological and weight related AD11s with AEDs (PESQ)

ADR related ONLY to seizure medicine	Valproate n=37	Clobazam n=18	Phenobarbitone n=4	Phenytoin n=1
D. General neurological				
14. Drowsiness, sleepiness	13 (35.1%)	8 (44.44%)	2 (50%)	0
15. Fatigue, tiredness	2 (5.4%)	2 (11.11%)	0	0
16. Dizziness, lightheadedness	0	0	0	0
17. Headaches	0	0	0	0
Total	15 (40.54%)	10 (55.56%)	2 (50%)	0
E. Weight				
18. Increase in appetite	9 (24.3%)	1 (5.56%)	0	0
19 Weight	0	0	0	0
Total	9 (24.3%)	1 (5.56%)	0	0

ADR: Adverse drug reactions, PESQ: Pediatric epilepsy side effect questionnaire

Table 5: Other ADRs with anti-epileptic drugs

ADR related ONLY to seizure medicine	Valproate n=37	Clobazam n=18	Phenobarbitone n=4	Phenytoin n=1
1. Nocturnal Enuresis	0	0	0	0
2. Alopecia	0	0	0	0
3. flirsutism	0	0	0	0
4. Tremor	5 (13.5%)	4 (22.22%)	0	1 (100%)
5. Gum Hypertrophy	0	0	0	0
6. Loss of Appetite	0	0	0	0
7. Toxicity (ataxia, nystagmus, etc.)	0	0	0	0
Total	5 (13.5%)	4 (22.22%)	0	1 (100%)

ADR: Adverse drug reactions

Table 6: ADRs (total) by antiepileptic drugs

ADR related ONLY to seizure medicine	Valproate n=37 (%)	Cloobazam n=18 (%)	Phenobarbitone n=4 (%)	Phenytoin n=1 (%)
A. Cognitive	12 (32.43)	3 (16.67)	2 (50)	0
B. Motor	0	0	0	0
C. Behavioral	0	0	0	0
D. General neurological	15 (40.54)	10 (55.56)	2 (50)	0
B. Weight	9 (24.32)	1 (5.56)	0	0
F. Other ADRs	5 (13.5)	4 (22.22)	0	1 (100)
Total	41 (110.8)	18 (100)	4 (100)	1 (100)
Percentage of total (n=60)	68.33	30	6.67	1.67

ADR: Adverse drug reactions

DISCUSSION

Epilepsy is a chronic disease so treatment required for long time. Sometimes treatment is continued for life long. However, long-term seizure control in patients with chronic epilepsy can be obtained with skillful treatment. The frequency or severity of seizures may not possible to complete control. Some patients are developing epilepsy seizures remain severe, frequent, or intractable. Although small in number, these patients require a high level of medical treatment. Older drugs such as Valproate, Phenytoin, and Carbamazepine are relatively less expensive and commonly used as first-line drugs. Gabapentin, Lamotrigine, Vigabatrin, Topiramate, Tiagabine, and Zonisamide are newer drug with lesser side effects.

A prospective longitudinal study was conducted by Daniel Raj *et al.*, for 8 months in 2016 among children attending Pediatric outpatient Department of RMMCH, Chidambaram. Sodium valproate was the mainstay of treatment in pediatric seizures. Side effects were minimal (10). In the present study, the most commonly used Antiepileptic drug was also Sodium valproate. Hence, the finding of study by Henry Raj *et al*. is similar with the current study. However, another cross-sectional study by Kaushik *et al*., on 2019 was conducted in the Department of Pediatrics, Kalawati Saran Children's Hospital for a period of 1 year. Two hundred consecutive eligible patients (aged 2–17 years with epilepsy on AED) were enrolled. A total of 139 ADRs occurred in 97 patients. One hundred and nine ADRs were reported by use of PESQ, in addition, 30 ADRs were reported by parents [9]. The study was similar with the present study as they found the most commonly used AED was Sodium Valproate [9]. Furthermore, Anderson *et al*. found Valporate followed by Carbamazepine as the most common used Antiepileptic in their study [11].

In the present study, majority of children with ADRs were in the age group more than 10 years, similarly Bansal and Coworkers also found that children developing ADRs with AED therapy were significantly older [12].

In the present study, out of total 60 children, 41 (68.33%) patients were boy and 19 (31.67%) were girl patients so boys were more developing ADRs than girls which was in contrast with the study done by Kaushik *et al*. as well as Bansal *et al*.

Among four antiepileptic drugs Valproate causing most ADRs (68.33%). Among all cognitive ADRs, attention difficulty (21.6%) was the most common ADR. There were no motor and behavioral ADRs with antiepileptic drugs reported. But in Bansal *et al*. study, they found poor school results (19%) as the most prevalent ADR followed by gum swelling (13%) and drowsiness (5.7%). On the other hand, Kaushik *et al*. in their study, poor school result (33.8%) was the commonest ADR followed by drowsiness (25.9%). Whereas in contrast to the present study, Anderson *et al*. showed that behavioral problems (19.3%) as the most common ADR of antiepileptic drugs followed by somnolence (15.8%). Furthermore, in contrast to the present study, Mistry *et al*. [13] in their study, irritability was the most prevalent ADR(32.2%) followed by drowsiness (18.6%).

CONCLUSION

In the present study, boys were more developing epilepsy than girls. Valproate was causing most ADRs. Among all cognitive ADRs, attention difficulty was the commonest ADR. There were no motor and behavioral ADRs with antiepileptic drugs reported. In the study, total 27 general neurological ADRs reported by the patients, which were highest reported ADRs. Among general neurological, Clobazam was causing highest ADRs.

ACKNOWLEDGEMENTS

We also give special thanks to Dr. Anjleen Kaur, Associate Professor, Dept. Of Pharmacology, Govt. Medical College and Rajindra Hospital, Patiala for reviewing the manuscript. We are also thankful to the consultant physicians for their supporting help.

AUTHORS CONTRIBUTION

All authors revise it critically for important intellectual content. All authors approved the final version.

CONFLICTS OF INTERESTS

No potential conflicts of interests were disclosed.

AUTHORS FUNDING

The authors received no specific funding for this work.

REFERENCES

1. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology 2007;68:326-37.
2. Smith DM, Metcalf SC, Wilcox SK. Pharmacotherapy of the epilepsies. In: Brunton L, Chabner B, Knollman B, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 13th ed. United States: McGraw-Hills; 2018. p. 303-26.
3. Lowenstein DH. Seizures and epilepsy. In: Jameson LJ, Fauci SA, Kasper LD, Hauser LS, Longo LD, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th ed. United States: McGraw-Hill; 2018. p. 3050-67.
4. Van de Vrie-Hoekstra NW, De Vries TW, Van den Berg PB, Brouwer OF, de Jong-van den Berg LT. Antiepileptic drug utilization in children from 1997-2005 a study from the Netherlands. Eur J Clin Pharmacol 2008;64:1013-20.
5. Hara HS, Gupta A, Singh M, Raj R, Singh H, Pawar G, *et al*. Epilepsy in Punjab (India): A population based epidemiologic Study. Neuroepidemiology 2015;45:273-81.
6. Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Sen F, *et al*. Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia 2010;51:789-96.
7. World Health Organization. Epilepsy Fact Sheet. Geneva: World Health Organization; 2019. Available from: https://web.archive.org/web/20160311001129/http:/www.who.int/mediacentre/factsheets/fs999/en
8. Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. Acta Neurol Scand Suppl 2005;181:30-5.
9. Kaushik S, Chopra D, Sharma S, Aneja S. Adverse drug reactions of anti-epileptic drugs in children with epilepsy: A cross-sectional study. Curr Drug Saf 2019;14:217-24.
10. Daniel Raj T, Sylvia A, Chidambaranathan S, Nirmala P. A prospective study of drug utilization pattern of anti-epileptic drugs and their adverse effects in a tertiary care Hospital. Henry. Int J Curr Pharm Res 2016;9:42-5.
11. Anderson M, Egunsola O, Cherrill J, Millward C, Fakis A, Choonara I. A prospective study of adverse drug reactions to antiepileptic drugs in children. BMJ Open 2015;5:e008298.
12. Bansal D, Azad C, Kaur M, Rudroju N, Vepa P, Guglani V. Adverse effects of antiepileptic drugs in North Indian pediatric outpatients. Clin Neuropharmacol 2013;36:107-13.
13. Mistry RA, Solanki KC, Prajapati HK, Doshi TM, Trivedi HR. Drugutilizasion pattern of antiseizure drugs and their adverse effects in the pediatric population, in a tertiary care hospital attached to a medical college. Int J Basic Clin Pharmacol 2014;3:336-42.