RESEARCH PAPER

Antiseizure Drug Levels in Children Aged 2-12 Years Presenting With Breakthrough Seizures: A Single Center Cross-sectional Study

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Objective: To study the antiseizure drug levels and associated factors in children with breakthrough seizures. **Methods:** This cross-sectional study conducted at a public hospital from November, 2017 to April, 2019, included 145 children with epilepsy aged 2 to 12 years presenting with breakthrough seizure. Antiseizure drug levels were measured, and the levels were categorized as within, below, and above the reference range. **Results:** Children with epilepsy receiving sodium valproate, phenytoin and carbamazepine were 111 (73%), 31 (20.4%) and 10 (6.6%), respectively, of which 7 were receiving multiple antiseizure drugs. Drug levels below the reference range were found in 64 (44.1%), within the reference range in 70 (48.3%), and the above reference range in 11 (7.6%) children. **Conclusion:** Nearly half the children with breakthrough seizures had sub-therapeutic levels, especially those on phenytoin therapy. Drug levels in below therapeutic range were not associated with occurrence of breakthrough seizures.

Keywords: *Precipitating factors, Reference range, Therapeutic drug monitoring*.

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In children with well-controlled epilepsy, a breakthrough seizure may occur in up to 40% [1]. International League Against Epilepsy (ILAE) recommends that plasma levels of antiseizure drugs should be interpreted as within, below, and above the reference range [2]. Therapeutic drug monitoring (TDM) helps in dosage individualization based on clinical response [3]. Therefore, a therapeutic range is introduced, which defines drug concentration associated with the best achievable response in a given person. The benefits of TDM are in case of status epilepticus, polypharmacy, change in drug dose/formulation, and clinical toxicity. It also helps to assess compliance, and guide dosage adjustment in children with associated liver and kidney diseases [2,4,5]. Well-delineated precipitating factors precede epileptic attack and commonly include fever, sleep deprivation, and stress [1,6,7]. Non-compliance to the treatment is another common cause [6,7].

There is a relative lack of literature on an antiseizure drug levels in children with a breakthrough seizure. Therefore, this study was planned to describe the association between the occurrence of a breakthrough seizure and anti-seizure drug levels.

METHODS

A cross-sectional study was conducted at the pediatrics department of a public tertiary care hospital from November, 2017 to April, 2019, after obtaining clearance from the institutional ethics committee. A written informed consent was obtained from the parents/ guardians/caregivers.

Children aged 2 to 12 years either having an active breakthrough seizure or those who had a breakthrough seizure within the last 24 hours and receiving either one or two anti-seizure drug (phenytoin, carbamazepine, sodium valproate) were enrolled from the emergency room or the outpatient department. Patient's demographic, clinical, and investigation details (serum sodium and potassium, blood glucose, and total leukocyte count) were recorded in a pre-designed case record form. Compliance with the drugs was ensured after taking a detailed history. For this study, a breakthrough seizure was defined as seizures in a child with epilepsy on one or two anti-seizure drugs, who did not have any seizure activity in the last one month. Generic form of anti-seizure drugs were available free of cost to the patients from the hospital formulary. The dose of antiseizure drug and treatment for epilepsy was given as per the guidelines followed in the hospital. Children who had received a loading dose of any antiseizure drug before presentation, those with deranged blood glucose/serum electrolyte levels, history of myoclonic or absence seizure, and known patients of chronic liver disease/chronic renal disease, meningitis, syndromic epilepsies, and known

non-compliance (missed >3 doses of anti-seizure drug) were excluded.

A venous blood sample (3 mL) was collected aseptically in serum vial before the loading dose of the antiseizure drug. Serum was separated within 30 min and stored at 0-8 ºC. Drug level estimation was done using CEDIA II kits (Thermofisher Scientific/2018) based on recombinant DNA technology to create a homogenous immunoassay system. The minimum detectable concentration of CEDIA Phenytoin II, Carbamazepine II, and Valproic acid II assays was 0.6 mg/L, 0.5 mg/L and 3.0 mg/L. The reference range for serum levels of phenytoin, carbamazepine, and sodium valproate was considered between 10-20 mg/L, 4-12 mg/L, and 50 to 100 mg/L, respectively, as per laboratory and kit specifications.

According to a previous study [8], serum levels of first-line antiseizure drug were in the below reference range in 40% of cases with breakthrough seizures. Using the formula for hospital-based population proportion with confidence interval 95%, estimated prevalence of 40%, power of 80%, a error of 5%, and acceptable absolute precision of ±8% (acceptable relative precision of 20%), the sample size was calculated as 144. Thus, 145 children were planned to be enrolled.

Statistical analysis: Analysis was performed using SPSS version 20 software. Pearson Chi-square / Fisher exact test was used to assess the association between demographic and clinical variables with below and normal reference range of antiseizure drug; the above range subjects were not included in the comparison. The 95% confidence level of below reference range proportion was determined using the binomial Wald method. *P* value of <0.05 was taken as significant.

RESULTS

A total of 145 children (97 males) were enrolled with a mean (SD) age of 6.9 (3.0) years. Generalized seizures were seen in 93 (64.1%) children, and normal development was seen in 90 (62.1%) children. Microcephaly was found in 26 (17.9%) children. All children had baseline laboratory parameters within the normal range. A single drug was being used by 138 children (sodium valproate-104, phenytoin-26, and carbamazepine-8). Two drugs were prescribed in 7 children (5-phenytoin/sodium valproate and 2-carbamazepine/sodium valproate).

Drug levels in the below reference range were found in 64 (44.1%), within the reference range in 70 (48.3%), and above reference range in 11 (7.6%) children. Children with polytherapy had drug levels in below reference range in five children on phenytoin, one on carbamazepine and three on sodium valproate therapy. The proportion of children and the serum level of different drugs is shown in **Table I**. The associated clinical and demographic variables were comparable across the various drug levels of different anti-seizure drugs (**Table II**). Children with focal seizures had twice the number of children in the reference range group as compared with the below reference range group ($P<0.05$). Precipitating factors were fever in 19 (13.1%) and sleep deprivation in 4 (2.8%) children. Precipitating factors were not significantly associated with anti-seizure drug levels (**Table II**).

Table I Antiseizure Drug levels in Children With Breakthrough Seizures

Anti-seizure drug[a]	*Below reference range, n=64*	*Within reference range, n=70*	*Above reference range, n=11*
Valproate	38 (34.2)	62 (55.9)	11 (09.9)
Phenytoin	29 (93.6)	1 (3.2)	1 (3.2)
Carbamazepine	3 (30.0)	7 (70.0)	0

Data in no. (% of row total).[a]*Single drug was received by 138 children, and two drugs were prescribed in 7 children.*

DISCUSSION

The antiseizure drug levels were comparable among the children on monotherapy or polytherapy with sodium valproate, phenytoin and carbamazepine who presented

Table II Demographic and Clinical Characteristics and Serum Drug Levels in Children With Breakthrough Seizures

Characteristics	*Below reference range n=64*	*In the reference range n=70*	*Above reference range n=11*
Mother's education			
Iliterate	22 (15.2)	21 (14.5)	3 (2.1)
Primary	35 (24.1)	31 (21.4)	7 (4.8)
Secondary	5 (3.4)	8 (5.5)	1 (0.7)
Graduate and beyond	2 (1.4)	10 (6.9)	0
Socioeconomic status			
Upper lower	39 (26.9)	39 (26.9)	4 (2.8)
Lower middle	23 (15.9)	25 (17.2)	7 (4.8)
Upper middle	2 (1.4)	6 (4.1)	0
Normal development	41 (28.3)	43 (29.7)	6 (4.1)
Seizure type[a]			
Generalized	48 (33.1)	39 (26.9)	6 (4.1)
Focal	16 (11.0)	31 (21.4)	5 (3.4)
Precipitating factor present	10 (6.9)	12 (8.3)	1 (0.7)

Data in no. (%). For comparison between below reference vs reference range groups, all P>0.05 except [a]*P=0.02.*

WHAT THIS STUDY ADDS?

- No association was found between serum antiseizure drug levels and breakthrough seizures in children compliant to antiseizure drugs.

with breakthrough seizures. Of the total children receiving sodium valproate and carbamazepine, 34.2% and 30% of children had levels below the reference range. However, on phenytoin therapy, 93.6% of children had serum levels below the reference range.

The results of the valproate and carbamazepine group were comparable with two previous Indian studies [8,9]. While in case of phenytoin, previous Indian studies [8,10] reported 43% and 68% patients had drug levels below the reference range, which was quite high as compared to the other antiseizure drugs. The difference in the phenytoin group could be due to narrow therapeutic index, suspension form of syrup, and variable pharmacokinetics in different individuals and age groups [9]. Kumar, et al. [1] reported precipitating factors in 37% of children; though many factors reported by them were not elicited in our study.

Limitations of our study include a cross-sectional study design with no longitudinal follow-up. It is a hospital-based study with only single-center results and a mixed population of children with varied diagnosis. Comparison with a group of children with a well-controlled epilepsy would have increased the validity of the study. The strength of this study includes a large sample size, with breakthrough seizure as the sole indication for TDM, which was done in an accredited lab.

Drug levels within reference range are more important in controlling generalized seizures than focal seizures where other factors may have a greater role. A greater number of children compliant on phenytoin drug had levels below reference range in both groups of with and without precipitating factors. Antiseizure drug levels should not be blindly followed for seizure control in children with breakthrough seizures, and specific indication should be kept in mind before obtaining the drug levels. The concept of therapeutic range should be considered [2]. There is a need for study in a larger sample and a homogenous population to determine critical levels at which breakthrough seizures are likely to occur.

Ethics clearance: Institutional ethics committee of University College of Medical Sciences; No. IEC-HR/2017/32/93, dated October 17, 2017.
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