

Correlation between Breakthrough Seizures and Serum Level of Phenytoin and Valproate in Indian Patients

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Abstract

Objectives: To determine the optimum range of phenytoin (PHT) and valproate (VAP) levels and find out the critical drug levels below which chances of breakthrough seizures increase in North Indian population. **Methodology:** A cross-sectional, case-controlled, record-based study was conducted in a quaternary care hospital from September 2018–2019. The case group comprised epilepsy patients on monotherapy with PHT/VAP presenting with breakthrough seizures after at least 6 months of seizure control. Noncompliant, overdose, toxicity, no or partial response, any other psychiatric or neurological disorder, adverse effects, and patients taking two or more antiepileptic drugs were excluded. **Results:** Data of 100 patients in each group were analyzed. Significantly lower mean levels in cases were observed in PHT (5.74 ± 3.68 mg/L vs. 13.75 ± 4.27 mg/L control) and VAP (24.13 ± 27.39 mg/L vs. 76.37 ± 17.71 mg/L control). A negative correlation of drug levels was observed with age and weight in both the groups. The level/dose ratio in controls (0.05 ± 0.03 ; 0.09 ± 0.06) was significantly ($P < 0.0001$) higher than cases (0.02 ± 0.01 ; 0.02 ± 0.03) in PHT and VAP, respectively. **Conclusions:** This study identifies the critical levels and level/dose ratio at which the risk of breakthrough seizures increases. A wide level/dose ratio was found in controls, more so in the VAP group. A prospective study with larger group size along with genetic studies should be done to evaluate further.

Keywords: Breakthrough seizures, dose/drug level ratio, epilepsy, phenytoin, valproate

INTRODUCTION

Epilepsy is a chronic noncommunicable disease of the brain that affects people of every age group. It is the second most common neurological condition resulting in unpredictable, unprovoked recurrent seizures, and India contributes to one-sixth of the global burden.^[1] Antiepileptic drug (AED) therapy has shown promising results in controlling seizures for epileptic patients.^[2] However, these drugs have complex pharmacokinetic properties and narrow therapeutic indices resulting in wide fluctuations of their plasma concentration. These fluctuations lead to either loss of therapeutic efficacy or toxic effects. Consequently, monitoring of plasma drug concentrations is essential in AED therapy.^[3] Therapeutic drug monitoring (TDM) optimizes patient outcome by managing the treatment regimen with the assistance of information on the concentration of AEDs that are present in the blood at a specific time.^[4] The therapeutic range of two first-line AEDs commonly used in India is 10–20 mg/L of phenytoin (PHT) and 50–130 mg/L of valproate (VAP).^[5] Lack of seizure control

is influenced by epilepsy etiology, seizure type, comorbidities, and treatment nonadherence. The International League Against Epilepsy (ILAE) identifies breakthrough seizures as evidence of inadequate seizure control and hence treatment failure, after excluding poor treatment compliance and planned dose reductions.^[6] Two studies have defined the seizure control as seizure-free interval of at least 6 months.^[7,8]

Despite TDM, up to 37% of patients with controlled epilepsy continue to have breakthrough seizures. Due to ongoing epileptogenic processes, 20%–30% of the patients have the natural history of developing treatment refractoriness following a period of remission.^[9] Besides these, other factors

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that may lead to breakthrough seizures are watching television, playing video games, sleep deprivation, exertion, alcohol, and emotional stress.^[10] In view of these factors associated with breakthrough seizures, previous studies have shown that episodes are primarily due to missed doses or noncompliance, thereby causing serum drug levels to drop below the set therapeutic range.^[11]

In our experience, we observed that many patients reported no seizures even with drug levels in the subtherapeutic range, suggesting that there could be a critical level below which the possibility of breakthrough seizure increases significantly for our population. There are limited data in Indian patients correlating the serum drug level and breakthrough seizures. Hence, this study was conducted to evaluate the optimum levels for breakthrough seizures and the relationship of most commonly used first-line AEDs, i.e., PHT and VAP with patient-related factors, namely age, sex, weight, and dose in North Indian population.

METHODOLOGY

The prospective, cross-sectional, case-controlled, record-based study was conducted in a quaternary care hospital in Delhi from September 2018 to September 2019. Sample size ($n = 100$ each) was selected to have 80% power and $P < 0.05$.^[12]

The control group comprised confirmed idiopathic epilepsy patients of both sexes who were well controlled on monotherapy with PHT or VAP who came for follow-up. Inclusion criteria for cases were confirmed idiopathic epilepsy patients of either gender in the age group of 18–60 years presenting with breakthrough seizures occurring after a period (at least 6 months) of sustained seizure control on monotherapy with PHT or VAP. Noncompliant patients, irregular treatment, patients presenting with overdose or toxicity, patients having no or partial response to the drug, any other psychiatric or neurological disorder, adverse effects of drugs, and patients taking drugs interacting with the study drugs were excluded.

Quantification of serum level of PHT and valproate was done using PHT and valproate assay reagents (microgenics) on Indiko® mass photometric system of Thermo Fisher. Sensitivity and specificity quality control was maintained by running three-level control sera provided along with the CEDIA® kits. The range of assay of PHT is 0.6–40 mg/L and valproate is 3–150 mg/L. Coefficients of variation were 4.42% (PHT) and 2.29% (VAP). Drug levels were categorized into subtherapeutic, therapeutic, supratherapeutic, and toxic [Table 1].

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean $\pm$ standard deviation and median. Normality of data was tested by the Kolmogorov–Smirnov test. If the normality was rejected, the nonparametric test was used. Statistical tests were applied as follows:

Table 1: Categorization of the drug assay values of phenytoin and valproic acid

Categories	Phenytoin ^[13] (mg/L)	Valproate ^[14] (mg/L)
Subtherapeutic	<10	<50
Therapeutic	10–20	50–130
Supratherapeutic	>20	>130
Not detectable	<0.001	<0.001

1. Quantitative variables were compared using the independent *t*-test/Mann–Whitney test (as the data sets were not normally distributed) between the two groups
2. Qualitative variables were correlated using Chi-square test/Fisher's exact test.

$P < 0.05$ was considered statistically significant. The data were entered in MS Excel spreadsheet, and analysis was done using the Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21.0, IBM Corp., Armok, N.Y., USA.

RESULTS

One hundred patients in each group on monotherapy with PHT and VAP were analyzed. The demographics of cases and controls are given in Table 2. The groups were comparable as there was no significant difference in the age, gender, weight, dose, and duration of therapy.

Although there was no significant difference in the mean dose, the mean serum levels of PHT and VAP in cases were lower than controls, and the level/dose ratio was significantly higher among cases than controls for both the drugs [Figure 1 and 2] [Table 3].

In the present study, the mean PHT levels among cases (5.74 ± 3.68 mg/L) were significantly ($P < 0.0001$) lower compared to the control group (13.75 ± 4.27 mg/L). The median PHT levels among cases were found to be 5 mg/L with interquartile range (IQR) of 4–6.5 mg/L, whereas it was 13.15 mg/L with IQR of 11.95–14.6 mg/L in the control group. In the VAP group, the mean levels were significantly lower ($P < 0.0001$) in cases (24.13 ± 27.39 mg/L) compared to the control group (76.37 ± 17.71 mg/L). The median VAP levels among cases were found to be 10 mg/L (IQR = 5–38 mg/L), while for controls, it was 75 mg/L (IQR = 65–85.9 mg/L). The level/dose ratio was significantly low in controls (22.31 ± 11.46 L/kg) compared to cases (66.17 ± 45.54 L/kg) in the PHT group. Similarly, in VAP controls, the level/dose ratio was significantly low (15.12 ± 6.6 L/kg) compared to cases (122.9 ± 101.06 L/kg).

Although statistically not significant, there was a positive correlation with dose in both the groups, i.e., higher drug levels were observed with higher dose [Figure 1]. On correlation, age showed a negative correlation though not significant in both the groups, i.e., the more the age, the lesser were the PHT and VAP drug levels [Figure 3 and 4]. Weight showed a negative correlation with cases, i.e., the more the weight, the lesser

Table 2: Demographic distribution of the phenytoin and valproate groups

Demographic	Phenytoin control (n=100), n (%)	Case (n=100), n (%)	P	Valproate control (n=100), n (%)	Case (n=100), n (%)	P
Age (years)						
18-40	82 (82.00)	83 (83.00)	0.852	91 (91.00)	90 (90.00)	0.809
41-60	18 (18.00)	17 (17.00)		9 (9.00)	10 (10.00)	
Mean±SD	29.59±10.59	30.23±10.43	0.518	28.83±9.64	29.09±10.15	0.997
Median (IQR)	26 (20.50-36)	28.5 (23-35)		26 (21-36)	27 (21-35)	
Gender						
Male	80 (80.00)	70 (70.00)	0.102	74 (74.00)	77 (77.00)	0.622
Female	20 (20.00)	30 (30.00)		26 (26.00)	23 (23.00)	
Duration of therapy						
6 months	0 (0.00)	4 (4.00)	0.088	0 (0.00)	4 (4.00)	0.13
6 months-1 year	15 (15.00)	19 (19.00)		19 (19.00)	18 (18.00)	
>1 year	85 (85.00)	77 (77.00)		81 (81.00)	78 (78.00)	
Weight (kg)						
Mean±SD	55.49±8.86	58.37±13.93	0.254	57.14±11.66	58.33±14.09	0.537
Median (IQR)	55 (49.5-62)	55 (50-65.5)		55.7 (50-64.5)	56.5 (50-67.5)	

P<0.05 Statistically significant. IQR: Interquartile range, SD=Standard deviation

Table 3: Drug dose and levels in the phenytoin and valproate groups

	Phenytoin control (n=100)	Case (n=100)	P	Valproate control (n=100)	Case (n=100)	P
Dose (mg/kg)						
Mean±SD	274.5±58.39	282±59.68	0.414	1104.5±380.26	1206.5±363.39	0.222
Median (IQR)	300 (200-300)	300 (250-300)		1200 (750-1500)	1200 (1000-1400)	
Drug level (mg/L)						
Below range, n (%)	7 (7.00)	95 (95.00)	<0.0001	5 (5.00)	87 (87.00)	<0.0001
Within range, n (%)	85 (85.00)	3 (3.00)		85 (85.00)	8 (8.00)	
Beyond range, n (%)	8 (8.00)	2 (2.00)		10 (10.00)	5 (5.00)	
Mean±SD	13.75±4.27	5.74±3.68	<0.0001	76.37±17.71	24.13±27.39	<0.0001
Median (IQR)	13.15 (11.95-14.6)	5 (4-6.5)		75 (65-85.9)	10 (5-38)	
Level/dose ratio						
Mean±SD	0.05±0.03	0.02±0.01	<0.0001	0.09±0.06	0.02±0.03	<0.0001

P<0.05 statistically significant. IQR=Interquartile range, SD=Standard deviation

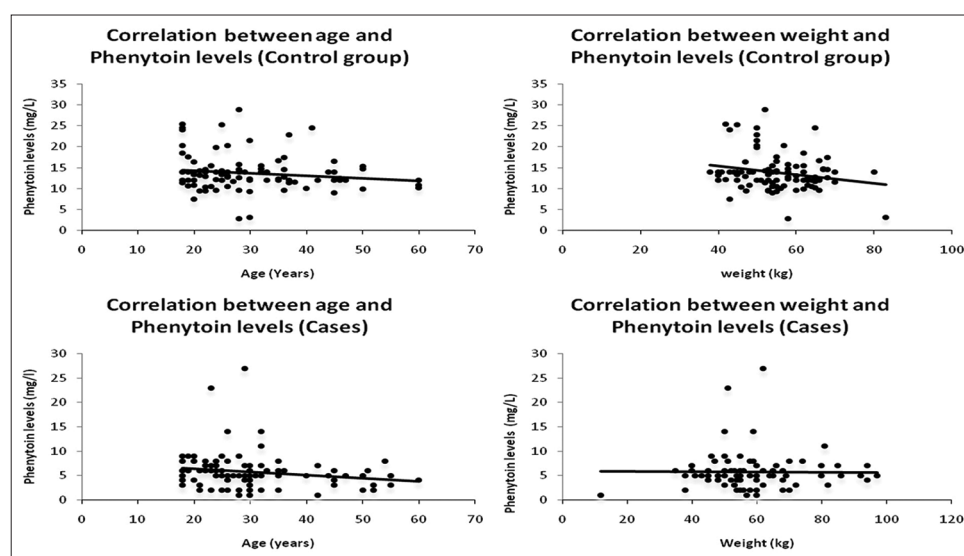


Figure 1: Correlation between phenytoin and valproate dose and drug levels in case and control groups

were the PHT and VAP drug levels, but it was not significant, however, there was a significant negative correlation in control patients who were on PHT [Figures 3 and 4].

DISCUSSION

This comparative case-controlled study was done to determine the optimum drug levels at which breakthrough seizure occurs in patients on first-line AED (PHT and VAP) in otherwise well-controlled patients. In the present study, almost all cases had VAP levels below the reference range, while in controls, the levels were within the reference range, but the range was narrower compared to standard reference range. On the contrary, Harivenkatesh *et al.* reported that only 38% of patients with breakthrough seizures had VAP levels below the reference range.^[11] According to our study, based on the reported median level of the serum, VAP levels of 38 mg/L

could be considered as a critical level, below which the risk of breakthrough seizures increases significantly.

In our study, the serum PHT levels in most cases (95%) were below the reference range while Taur *et al.*^[15] and Garg *et al.* reported two-third patients having levels below the reference range.^[3] In contrast, Harivenkatesh *et al.*^[3], reported less than half of the patients with their drug levels below the reference range.^[11] On the contrary, controls had a reference range almost similar to standard reference range in our study. The critical level of serum PHT was found to be 6.5 mg/L (median), below which the risk of breakthrough seizure surges significantly.

Reasons for these differences in the drug level range among cases and controls could be the narrow therapeutic index of the drug, inadequate dosing, and faster drug metabolism due to genetic polymorphism, despite adequate dosing and compliance.^[16] Although inter-individual variation in

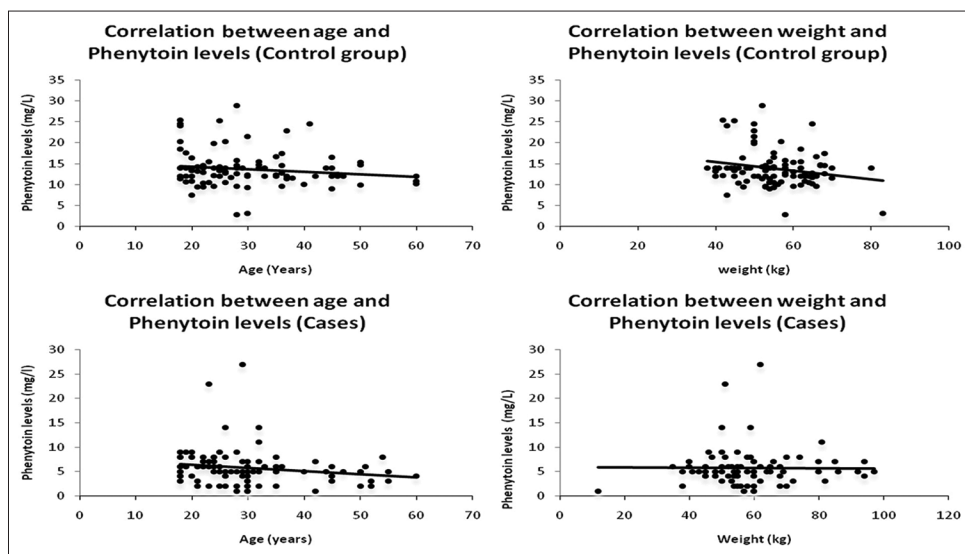


Figure 3: Correlation phenytoin levels in case and control groups with age and weight

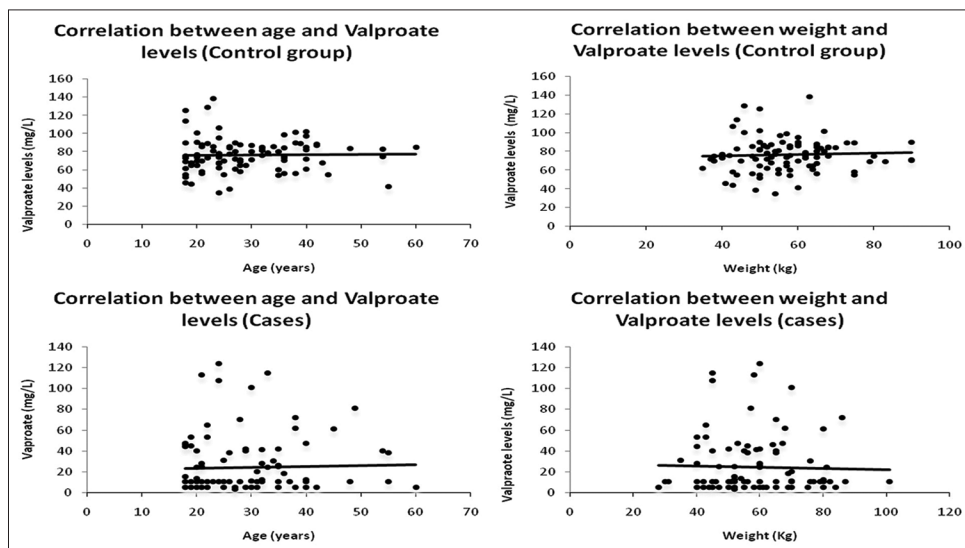


Figure 4: Correlation valproate levels in case and control groups with age and weight

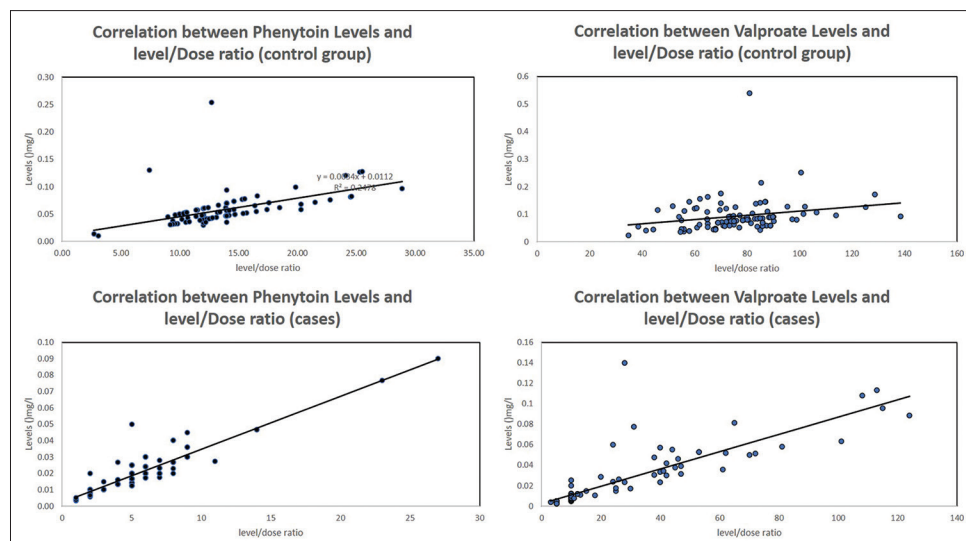


Figure 2: Correlation between phenytoin, and valproate levels and level/dose ratio in case and control groups

pharmacokinetics has been described as one of the reasons for breakthrough seizures, the same reference ranges had been defined for all ages. Hence, the concept of individual therapeutic concentration, as described by ILAE, should be considered.^[4]

There was a significant difference in level/dose ratio between the groups. A significantly low mean level/dose ratio was observed in PHT controls (0.05 ± 0.03) compared to cases (0.02 ± 0.01) and VAP controls (0.09 ± 0.06) compared to cases (0.02 ± 0.03). 0.05 can be considered as the changing point below which the chances of breakthrough seizures surge. Higher level/dose ratios, indicating lower clearance, are associated with nonsmokers, Asians, genetic poor metabolizers, inhibitors, obesity, inflammation, and possibly with renal impairment and pregnancy. Lower level/dose ratios indicate lack of adherence or higher clearance associated with males, smokers, non-Asians, and inducers.^[17]

In this study, most patients were in the age groups of 18–40 years, with the majority being males, but gender was not found to be a significant factor associated with drug levels. Reason for male preponderance found in the present study could be due to preference given to the males in bringing them to the health care facilities. A similar patient pattern was reported in a study done by Harivenkatesh *et al.*^[11] Demographic profile (age, gender, and weight) of patients with breakthrough seizures has been correlated with reference levels of AED in our study. Most of the previous studies did not take these correlations into consideration.

Limitation of the record-based study was overcome by the case-control design. Many factors contribute to the control of seizures or the occurrence of it such as compliance of patients and regular/irregular treatment. Although noncompliance was ruled out, other precipitating factors for seizures or comorbidities or genetic polymorphism should be studied further.

In the present study, PHT levels of 6.5 mg/L and VAP levels of 38 mg/L or below are significantly associated with high probabilities of breakthrough seizures. There is a need to determine the individual therapeutic concentration, and drug levels must be maintained within the reference range but should not be allowed to go below critical levels. The drug/level ratio was significantly higher and wider in cases in both the groups but was much broader in the VAP group. In the PHT group, the level/dose ratio was three times higher, while in the VAP group, it was almost five times higher in controls; therefore, genetic studies are required for finding the reason for the difference in the drug/level ratio between cases and controls.

CONCLUSIONS

This study identifies the critical levels and level/dose ratio of phenytoin and valproate at which the risk of breakthrough seizures increases. A wide level/dose ratio was found in controls, and in the VAP group. A negative correlation of drug levels was observed with age and weight in both drug groups. A prospective study with larger group size along with genetic studies should be done to evaluate further.

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Conflicts of interest

There are no conflicts of interest.

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