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Original Research Article

Plasma phenytoin concentration in epileptic patients with adequate seizure control in a North-Eastern tertiary care hospital in India

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ABSTRACT

Background: In this study, estimation of plasma phenytoin level was done on epileptic patients with adequate seizure control. Since, no such study reporting on phenytoin estimation on seizure-free period in the north-eastern part of India was undertaken; hence rationale of adequate seizure control with phenytoin is yet to be ascertained. This retrospective study is being done to obtain a satisfactory clinical outcome with minimal adverse effects in our setting regarding the target plasma level of phenytoin.
Methods: The patients from the Neurology Department were enrolled for this study. Blood samples were taken and the plasma extracted was used for the phenytoin estimation using HPLC.
Results: Results showed that the majority of the study population exhibited total plasma phenytoin levels within the recommended therapeutic range (10-20 µg/ml).
Conclusions: The study findings showed that patients with adequate seizure control exhibited plasma phenytoin concentration within the recommended therapeutic level, which is the safe level of the drug in blood. However, some variations in the plasma phenytoin level are suggestive of the inter-individual differences in pharmacokinetics after phenytoin therapy. Hence, monitoring of phenytoin treatment is necessary to ensure dosage delivery is at therapeutic levels and to avoid any untoward toxicity.

Keywords: Anti-epileptics, Epilepsy, HPLC, Phenytoin

INTRODUCTION

Epilepsy is defined by the presence of nerve cells clustering, which signals the brain differently.[1] About 1% of the world's population is affected by epilepsy, making it one of the leading disabling disorders worldwide and causing great disability.[2] According to the WHO, around 50 million people in the world suffer from this disorder, making it a global health concern. In India, the prevalence of epilepsy ranges from 3.0 to 11.9 cases per 1,000 population and the incidence varies from 0.2 to 0.6 cases per 1,000 population annually.[3] Phenytoin is a commonly used anti-epileptic drug (AED) for treating primary or secondary generalized convulsions, partial or complex partial seizures and status epilepticus.[4] Its low cost and easy availability make it a well-sought-after AED medication.[5]

However, due to its narrow therapeutic index, non-linear pharmacokinetics and activity being highly influenced by the presence of other compounds, administration of phenytoin can lead to neurotoxicity and may aggravate the intensity of seizures.[6] The therapeutic drug monitoring (TDM) principle and high performance liquid chromatography (HPLC) analytical method have been used for the estimation of phenytoin levels in the plasma.[7-

[9] Seizure-free period refers to the duration of time during which an epileptic patient has not experienced any kind of seizures. This duration is an important predictor for risk assessment for these patients pertaining to their daily activities. In the United States, the required seizure-free interval varies from 18 months to three months.

Other countries have formulated a three-month seizure-free restriction and a three-month seizure-free interval as the standard, recommended by American Academy of Neurology, American Epilepsy Society and Epilepsy Foundation.[10] In the study, seizure-free period of three months or more have been taken into consideration. Less studies reporting on phenytoin estimation, especially on seizure-free period, are being done in India. Moreover, no such studies have been undertaken in this part of the region to date, so the rationale of adequate seizure control with phenytoin is yet to be ascertained. This study provides the target plasma level of phenytoin that is required for obtaining a satisfactory clinical outcome with minimal adverse effects in our setting.

METHODS

Study design

This retrospective study was conducted for a period of one year by the department of Pharmacology in association with the department of Neurology (November 2018-November 2019). In this study, patients under follow-up in the Department of Neurology and having a seizure-free period of at least three months were included. Institutional ethics committee approval was taken and written informed consent from all the participants was obtained.

Inclusion criteria

All patients of both genders with age>=18 years on phenytoin therapy. Patients with a seizure-free period of at least three months.

Exclusion criteria

Patients without phenytoin therapy. Patients on phenytoin but exhibiting seizures. Patients on phenytoin but treated with another AED

Study procedure

5 ml of the patient's blood was collected in an EDTA vial and the plasma extracted was used to estimate the total phenytoin level in the blood. Total plasma phenytoin estimation was done by using the agilent technologies HPLC system (1260 Infinity).

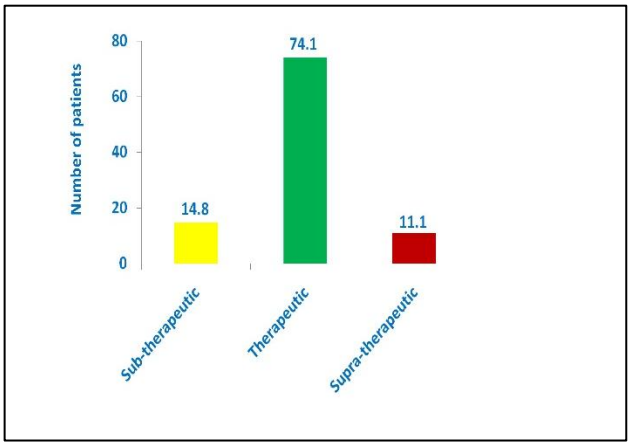
Statistical analysis

The data are represented by frequency, percentage, mean and standard deviation. Data was analysis was done using Microsoft excel 2007.

RESULTS

Demographic profile and clinical details (n=27)

A total of 27 patients consented to their enrolment in this study. Majority (33.0 %) of the study population falls between 18-35 years and mean age was found to be 30.9 years with SD of 16.6. Male participants were larger in number accounting for 62.3 % of the total study population. All patients were on tablet phenytoin 100 mg BD except three patients who were on intravenous phenytoin 100 mg BD. 70.4 % of the patients included in this study have undergone phenytoin therapy for more than 24 months and seizure seizure-free period was reported to be highest (59.2 %) at 12-24 months (Table 1).



Data are represented as %. Y-axis denotes the number of patients (%). X-axis denotes the therapeutic levels of phenytoin. Sub-therapeutic level: <10 µg/ml, Therapeutic: 1- 20 µg/ml; Supra-therapeutic: >20 µg/ml.

Figure 1: Total plasma phenytoin concentrations according to therapeutic levels.

Total plasma phenytoin concentration

Total phenytoin concentration in the plasma is classified into three different categories, i.e., sub-therapeutic level, therapeutic level and supra-therapeutic level. Plasma phenytoin concentration falling below 10 µg/ml is considered a sub-therapeutic level, plasma concentration within 10-20 µg/ml is the desired therapeutic level and plasma concentration greater than 20 µg/ml is taken as the supra-therapeutic level. In this study, 74.1 % of the patients exhibited therapeutic levels of phenytoin, 14.8 % of the patients had sub-therapeutic levels and 11.1 % of the study population showed phenytoin levels above the therapeutic range (Figure 1). It is to be noted that, although 88.9 % of the patients received the same dose of phenytoin 300 mg BD, their total plasma concentration of phenytoin differs. Mean value of the plasma phenytoin levels was 15.2 µg/ml with a standard deviation of 4.3. 15.9 µg/ml was the median plasma phenytoin level with a minimum plasma level of 9.2 µg/ml and a maximum plasma phenytoin level of 22.8 µg/ml (Table 2).

Table 1: Demographic profile and clinical details.

Parameter	N	%
Age (in years)		
18-35	17	33
36-45	6	22.2
46-60	2	7.4
>60	2	7.4
Mean	30.9	
SD	16.6	
Gender		
Male	17	63
Female	10	37
Dosage form		
Tablet	24	88.9
I.V	3	11.1
Duration of phenytoin therapy (in months)		
0-12	1	3.7
13-24	7	25.9
>24	19	70.4
Seizure free period (Months)		
03-December	7	25.9
December-24	16	59.2
>24	4	14.8

N: Number of patients, SD: Standard deviation, I.V: Intra-venous.

Table 2: Frequency distribution of total plasma phenytoin concentration.

Parameters	Values
Mean	15.2
Standard deviation (SD)	4.3
Median	15.9
Minimum	9.2
Maximum	22.8

DISCUSSION

Phenytoin is a commonly used drug for treating generalized convulsions, status epilepticus, tonic-clonic seizures, focal seizures and seizures transpiring due to any neurosurgical intervention or head injury.[5] Its low cost and easy availability make it a well-known AED drug in developing countries. However, its narrow therapeutic range and non-linear pharmacokinetics are some of the factors contributing to the complications in phenytoin therapy. The blood concentration of patients on phenytoin therapy needs to be closely monitored and examined to avoid any adverse or toxic effects.[11] The estimation of the plasma phenytoin concentration is therefore important for better understanding by clinicians in treating epileptic patients.

In the study, 27 patients consented to be enrolled for the estimation of phenytoin level. This is similar to a study on TDM of phenytoin in eastern Nepal where 21 samples were taken for phenytoin estimation.[12] The majority (33.0 %) of the participants in our study fall in the age group of 18-35 years of age and the mean age of our study population was found to be 30.9 years with a standard deviation of 16.6. This is somewhat similar to a study conducted where the mean age of the study population was found to be 38.2 years and a standard deviation of 15.4.[13] Male patients (63.0 %) consenting to the study was more in number as compared to their female (37.0 %) counterparts. This could be due to female patients' unwillingness to get diagnosed and treated, fearing the social stigma surrounding epilepsy in India.[14]

The measurement of the plasma drug level has become an important tool to determine drug exposure, thereby helping in dose management as well as managing the possibility of any toxic events.[15] It has been established that a plasma phenytoin level of 10-20 µg/ml is the recommended therapeutic range and is considered the safe level for the drug in blood.[16] In our study, 74.1 % of the patients had phenytoin levels within the therapeutic range, similar to a study conducted in Eastern Nepal, where the phenytoin

estimation showed the majority of the patients falling within the therapeutic range.[12] Plasma phenytoin level of less than 50 % of the lower reference range is defined as the sub-therapeutic level.[17] 14.8 % of our study population showed phenytoin levels falling under the sub-therapeutic range, i.e., lower than 10 µg/ml and around 11.1 % showed phenytoin concentrations higher than 20 µg/ml, which is considered the supra-therapeutic level. It is interesting to note from the findings that 88.9 % of the patients had received the same dose of phenytoin, but exhibited different total plasma concentrations of this drug.

Some patients showed sub-therapeutic plasma levels, some exhibited therapeutic levels and some showed plasma phenytoin concentrations above the therapeutic range. This can be due to the non-linear pharmacokinetic profile of phenytoin displaying a high degree of pharmacogenetic differences, thereby resulting in poor correlation between the dose and patient plasma concentration. Further analysis of our study data displayed a mean plasma phenytoin level to be 15.2 µg/ml and a standard deviation of 4.3.

A similar study was conducted, which showed a mean phenytoin level of 23.8 µg/ml and a standard deviation of 20.4 µg/ml.[5] This study displayed a wide scatter of phenytoin levels, whereas our study data showed a small variation of plasma phenytoin levels within the study population. This might be due to the smaller patient population of our study, as well as the seizure-free factor. The selection of an accurate and proper analytical method for the estimation of phenytoin level is equally important.

In the study, the conventional HPLC method was used for the estimation of total plasma phenytoin concentration. HPLC method offers a safe and reliable procedure for the estimation of drugs with no chances of contamination from other components.[18] Another advantage that HPLC offers is the simple sample preparation and instrumentation, which facilitates fast and accurate routine monitoring and therefore it is found to be suitable for the analysis of various AEDs.[19]

CONCLUSION

The study findings showed that patients with adequate seizure control exhibited total plasma phenytoin concentration within the recommended therapeutic level, which is the safe level of the drug in blood. The variations in the phenytoin level between individuals demonstrated non-linear pharmacokinetics of phenytoin, thereby resulting in poor correlation between dose and plasma level. Hence, it is crucial for the patients undergoing phenytoin treatment to be monitored and studied for proper dosage delivery at therapeutic levels and to avoid any untoward adverse effects.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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