

## **A CLINICAL EVALUATION OF THERAPEUTIC DRUG MONITORING OF PHENYTOIN IN EPILEPTIC PATIENTS IN A TERTIARY CARE TEACHING HOSPITAL, CHENNAI, TAMILNADU: A RANDOMIZED, OPEN LABEL COMPARATIVE STUDY**

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### **ABSTRACT**

Phenytoin is effective for treatment of generalized tonic-clonic seizures and partial seizures. Therapeutic drug monitoring of phenytoin is useful as it has narrow therapeutic index, saturable kinetics and inter-individual variations. A randomized, open label, comparative study was done in 60 epileptic patients to assess the clinical impact of therapeutic drug monitoring of phenytoin. Patients of age 18 to 50 years on phenytoin monotherapy with subtherapeutic concentration ( $<10\mu\text{g/ml}$ ) were included and allocated into two groups. In group I, dosage was adjusted by using therapeutic drug monitoring, whereas in group II, dosage was adjusted on clinical grounds. Serum levels of phenytoin were determined by High Performance Liquid Chromatography. The results were analyzed. There was a significant increase in mean serum phenytoin concentration with reduction in the seizure frequency in group I ( $p=0.001$ ). To conclude, therapeutic drug monitoring assisted dosage modification provides better seizure control with fewer adverse effects than group II patients.

## KEYWORDS

Therapeutic drug monitoring, epileptic patients, phenytoin, seizures

## INTRODUCTION

Epilepsy is the second most common neurological disorder after stroke<sup>1</sup>. It affects about 50 million people in the world<sup>2</sup>. In India approximately 5.5 million people are suffering from epilepsy<sup>3</sup>. Epilepsy is a chronic disorder characterized by recurrent seizures or convulsions<sup>4</sup>. The chronicity of the disease, the drug therapy and associated psychosocial impact significantly affects the quality of life of epileptic patients<sup>5</sup>. The factors influencing the quality of life include seizure severity, unpredictability, stigma, fear, anxiety, cognitive and psychiatric problems<sup>6</sup>. The success of antiepileptic therapy depends on careful dosage titration based on pharmacokinetic principles to a desired patient response, the patient's ability to tolerate side effects and long term patient monitoring to ensure compliance, prevent drug interaction and minimize toxicity<sup>5</sup>.

Antiepileptic drugs are ideal candidates for therapeutic drug monitoring (TDM) because they have narrow therapeutic index and the clinical responses correlate better with serum concentration of the drug than with the prescribed daily dose regimen<sup>7</sup>. Monitoring of serum levels of phenytoin and other antiepileptic drugs plays an important role in the management of epilepsy<sup>8</sup>.

Therapeutic drug monitoring refers to the measurement of drug concentration in biological fluids with the purpose of optimizing a patient's drug therapy, while minimizing its risk for side effects or toxicity<sup>7</sup>. Knowledge of drug levels can provide clinicians with important information for making quantitative therapeutic decisions i.e. titration of drug doses to the individual patient, thus avoiding adverse reactions which are a direct

consequence of patient variability in drug disposition<sup>9</sup>.

The Neurology Department of Madras Medical College, Chennai, runs exclusive epilepsy out-patient clinic, which is attended by approximately 350 patients per day, and they revisit the clinic every fortnight. On an average about 5000-5500 patients attend the epileptic clinic every month between the age group of 16-55 years. About 55% are male, while 45% are female patients. To state further, though a correlation between the plasma drug concentrations and optimum anticonvulsant effect with minimum adverse effects is known, there is very little data on Indian population. So, a decision was made to conduct a study to evaluate the clinical impact of therapeutic drug monitoring of phenytoin monotherapy in epileptic patients.

## MATERIALS AND METHODS

### STUDY POPULATION

A randomized, open label, comparative study was conducted in 60 epileptic patients who attend Epilepsy clinic, Institute of Neurology, Government General Hospital, Madras Medical College, Chennai. The study was carried out from April 2006 to September 2007. Institutional Ethical Committee Approval was obtained.

### INCLUSION AND EXCLUSION CRITERIA:

A total of 320 patients screened, 60 of both genders and aged between 18 to 50 yrs with a confirmed diagnosis of partial or idiopathic generalized epilepsy on 200mg / day of phenytoin monotherapy, for at least six months duration with a history of more than two seizure episodes in the past four months,

those with sub therapeutic plasma concentration of phenytoin ( $< 10\mu\text{g}/\text{mL}$ ) were included in the study. Subjects with neurological deficits, history of drug /alcohol abuse, evidence of gastrointestinal tract, renal, endocrine, cardiovascular diseases were excluded from the study.

During enrollment visit, written informed consent was obtained from all the patients after explaining the study protocol and a screening identification number with screening dates were allotted to them. Patients were instructed to come on an empty stomach at 8.00am on the day of screening to the Out Patient Department of Epilepsy clinic. In the first screening visit, a baseline demographic characteristics, detailed medical history, clinical information regarding seizure frequency with physical and systemic examination, hematological and serum biochemical tests and urine analysis were done. All the patients were instructed to take the drug for a minimum of 28 days to measure the steady state levels i.e. after the completion of 4 to 5 half lives of an unchanged dose regimen. In the second screening visit, the trough samples were collected at the end of the dosing interval. The blood samples were collected into the blood collection tubes by venepuncture of the contralateral arm. At each sampling 3ml of blood was drawn. Serum concentration of phenytoin was analyzed and those patients with subtherapeutic concentration of phenytoin ( $<10\mu\text{g}/\text{ml}$ ) were recruited for the study.

#### **RANDOMIZATION:**

Patients were randomized into two groups of 30 each as **Group I** -Therapeutic Drug Monitoring (TDM) Group and **Group II** - Non Therapeutic Drug Monitoring (Non TDM) Group. For Group I patients the serum phenytoin concentration values were provided to the Neurologist for adjusting the dosage to optimum level within a target range for control of seizure rate with minimum drug related

adverse events. In Group I patients who were on 200mg / day of phenytoin monotherapy, whose plasma concentration is  $< 7\mu\text{g}/\text{ml}$  were incremented with additional 100 mg / day and those with concentration between 7 to  $10\mu\text{g}/\text{ml}$  were incremented with 50 mg / day. After dosage modification, Group I patients were advised to follow the new dosage schedule for 3 months. They were instructed to review at the end of 3<sup>rd</sup> and 6<sup>th</sup> month to obtain the trough sample collection and were asked to report to the Neurologist if there was any adverse effect noted at any point of the study period.

Samples were collected in the same way for Group II patients but the results were not provided to the Neurologist, as he has to adjust the entire dose adjustments based on clinical knowledge, experience and judgment to achieve seizure free interval. After dosage modification, Group II patients were instructed regarding the drug intake. They were asked to bring the empty foils at the end of 2 weeks to check the patient's compliance. They were briefed about the clinical assessment at the end of 3<sup>rd</sup> month and trough sample collection again at the end 6<sup>th</sup> month.

At the end of 3<sup>rd</sup> month trough samples were collected to assess the new serum phenytoin levels for Group I patients. For those whose seizures were inadequately controlled, the dosage was increased according to the serum plasma concentration. Patients those who achieved better seizure control were instructed to be on the same dosage schedule for another 3 months. For Group II patients details regarding seizure frequency were noted and dose modification was done based on the clinical assessment by the Neurologist.

At the end of 6<sup>th</sup> month trough blood samples were taken and analyzed for the phenytoin concentration level in both groups. Dosages were altered according to the disease process. The patients were advised to attend epilepsy clinic regularly and follow the instructions given by the Neurophysician.

All the patients were followed up for next 6 months.

### **SAMPLE ANALYSIS:**

Serum phenytoin drug levels were determined by High Performance Liquid Chromatography. The results were reported on a fortnightly basis, so that the Neurologist could decide about making any suitable dose adjustments by the time the patient arrived for the subsequent follow-up visit for group I patients.

### **STATISTICAL ANALYSIS:**

Statistical analysis was done by SPSS (Version 11.2) software. Student independent t-test was used for comparing mean age distribution, serum phenytoin concentration and seizure frequency between TDM and Non TDM Groups. Sex distribution and seizure type distribution were analyzed by Chi-square test. A P value <0.05 was considered as statistically significant.

## **RESULTS**

Out of 320 patients screened, 60 were recruited for the study. They were randomly allocated into 2 groups of 30 each. Clinical and laboratory parameters were assessed at baseline, at the end of 3<sup>rd</sup> month and 6<sup>th</sup>

month. Only 51 out of 60 subjects completed the study. There were 5 dropouts in TDM group and 4 dropouts in Non TDM group. Three patients in the TDM group and two patients in the Non TDM group did not report after first month. Two patients in the TDM group and two patients in the Non TDM group were lost in follow-up due to noncompliance at the end of 2<sup>nd</sup> month.

Demographic features like age and sex of the study groups given in Table -1, 2 and 3. The mean age was 29.24 for TDM group and 27.54 for Non TDM group with no statistical significant ( $p=0.41$ ). There were 31 male and 20 female patients with no statistical significance. ( $p=0.63$ ). Table-4 shows the distribution of the type of seizure in two groups and the difference was not significant. ( $p=0.87$ ). Table-5 shows the comparison of mean serum phenytoin concentration. The difference between the two groups was not significant at baseline ( $p=0.27$ ) but at the end of 6<sup>th</sup> month the TDM group patients showed significant increase in the mean serum phenytoin concentration ( $p=0.001$ ). Table-6 shows the comparison of mean seizure frequency. At baseline, statistically there was no difference ( $p=0.48$ ) but at the end of 3<sup>rd</sup> and 6<sup>th</sup> month there was significant reduction in mean seizure frequency between two groups. ( $p=0.001$ )

**Table 1**  
**Age distribution**

Age in years	Groups		Total
	TDM	Non TDM	
< 20	7	4	11
21-30	5	16	21
31-40	13	4	17
41-50	-	2	2
Total	25	26	51

**Table 2**  
**Mean age Distribution**

Group	N	Mean	SD	Student independent t-test
TDM	25	29.24	7.991	<b>t=0.83 p=0.41 not significant</b>
NonTDM	26	27.54	6.592	

**Table-3**  
**Sex Distribution**

Groups	Sex				Chi-square test
	Male		Female		
	N	%	N	%	
TDM	16	64.0%	9	36.0%	<b>x<sup>2</sup> = 0.21 p = 0.63 Not significant</b>
Non TDM	15	57.7%	11	42.3%	
Total	31	60.8%	20	39.2%	

**Table 4**  
**Seizure type**

Group	Seizure type				Chi-square test
	Generalized tonic clonic seizure		Partial seizure		
	No. of patients	%	No. of patients	%	
TDM	15	60.0%	10	40.0%	<b>x<sup>2</sup> = 0.02 p= 0.87 not significant</b>
Non TDM	15	57.7%	11	42.3%	
Total	30	58.8%	21	41.2%	

**Table- 5**  
**Comparison of mean serum phenytoin concentration at baseline and at the end of 6<sup>th</sup> month**

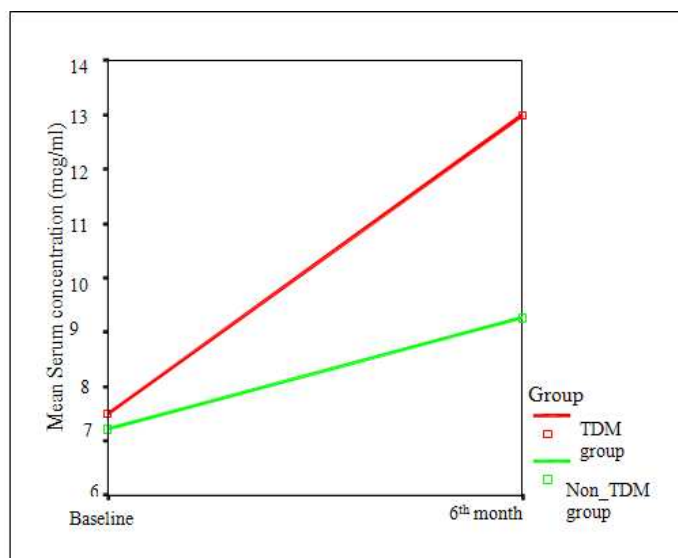
Groups	Baseline Mean $\pm$ SD	6 <sup>th</sup> month Mean $\pm$ SD	% of increase in the mean serum concentration
TDM	7.50 $\pm$ 1.02	13.00 $\pm$ 1.58	73.33%
Non TDM	7.22 $\pm$ 0.77	9.27 $\pm$ 1.36	28.39%
Student independent t-test	t = 1.10 p= 0.27 not significant	t = 9.05 p= 0.001 significant	

**Table- 6**  
**Comparison of mean seizure frequency in both groups at baseline and at the end of 6<sup>th</sup> month**

Groups	Baseline Mean $\pm$ SD	3 <sup>rd</sup> month Mean $\pm$ SD	6 <sup>th</sup> month Mean $\pm$ SD	% of reduction
TDM	3.60 $\pm$ 0.50	1.96 $\pm$ 0.73	0.60 $\pm$ 0.50	83.34%
Non TDM	3.50 $\pm$ 0.51	2.08 $\pm$ 0.63	1.62 $\pm$ 0.64	53.72%
Student independent t-test	t = 0.70 p= 0.48 not significant	t = 19.51 p= 0.001 significant	t = 39.85 p= 0.001 significant	

**Figure-1**

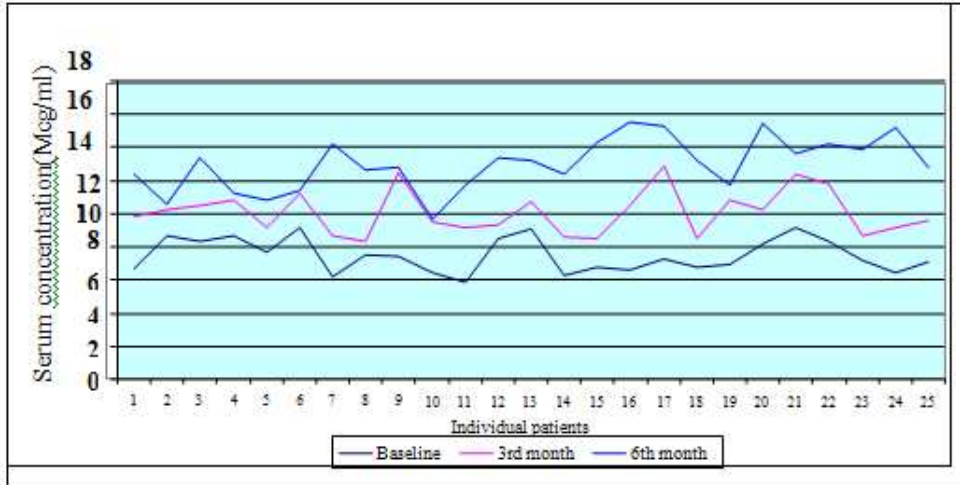
**Graphical representation of mean serum phenytoin concentration at baseline and at the end of 6<sup>th</sup> month**



**Student independent t-test - At baseline p value = 0.27 (not significant), at the end of 6<sup>th</sup> month p value = 0.001 (statistically significant).**

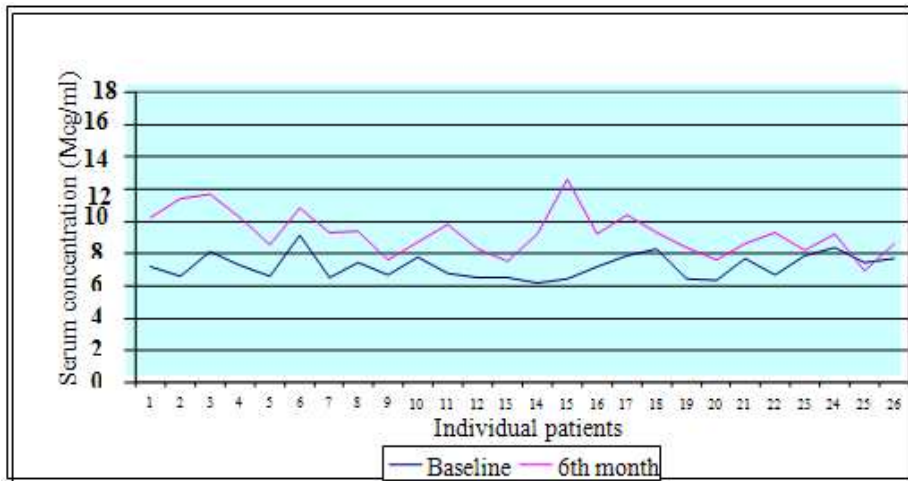
**Figure-2**

**Graphical representation of the serum phenytoin concentrations of individual patients in TDM group.**



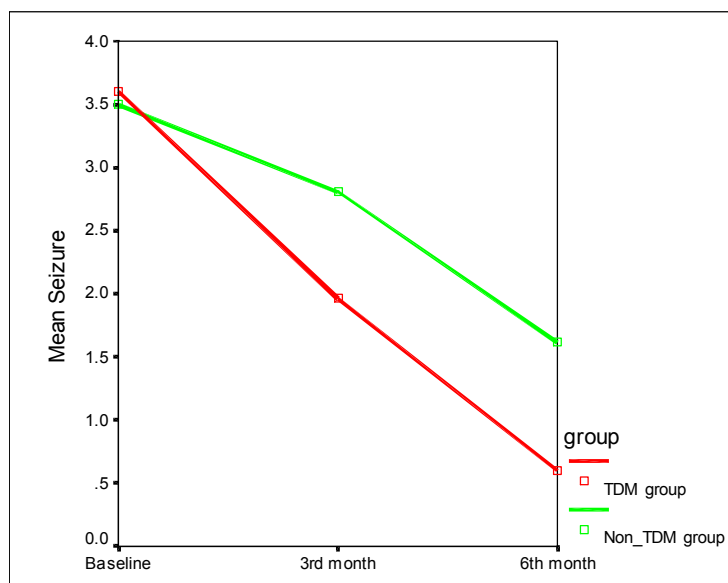
**Figure-3**

**Graphical representation of the serum phenytoin concentrations of individual patients in Non TDM group**



**Figure- 4**

**Graphical representation of comparison of mean seizure reduction between TDM and Non TDM groups. It shows more reduction in the mean seizure frequency at the end of 3<sup>rd</sup> and 6<sup>th</sup> month in TDM group.**



**Student independent t-test - At baseline p value= 0.48 (not significant), at the end of 6<sup>th</sup> month p value= 0.001 (statistically significant), at the end of 6<sup>th</sup> month p value= 0.001 (statistically significant)**

In our study, 4% in the TDM group and 15.38% in Non TDM group patients reported adverse effects. The reported adverse effect in TDM group was drowsiness (n=1). In non TDM group headache (n=1), drowsiness (n=1) and somnolence (n=2) were reported. But this did not require discontinuation of the drug.

## DISCUSSION

Therapeutic drug monitoring is the science that combines the measurements of serum drug concentrations with clinical pharmacokinetics and pharmacodynamics<sup>10, 11</sup>. In epileptic patients on phenytoin monotherapy, TDM is required for patients having phenytoin

toxicity or those having poor control on seizures or even in well controlled epileptic patient to determine baseline concentration<sup>12</sup>. This study compared the clinical outcomes of phenytoin monotherapy guided by therapeutic drug monitoring with treatment without the aid of therapeutic drug monitoring of epileptic patients and provided better seizure control in TDM group.

There was a significant increase in mean serum phenytoin concentration with reduction in the seizure frequency within 6 months of duration in TDM group and was statistically significant when compared to Non TDM group (p= 0.001). The percentage increase in serum phenytoin concentration for TDM group was 73.33% and for Non TDM group was only 28.29% (Table-5). This has been compared with Jannuzzi G et al study



which showed that the measurement of serum phenytoin concentration provided beneficial results<sup>13</sup>.

Regarding seizure frequency in comparison between 2 groups TDM patients showed a decrease in seizure frequency and was statistically significant ( $p=0.001$ ) and this has been compared with a study conducted in Mumbai on therapeutic drug monitoring with 25 patients, which also reflected the reduction of seizures in TDM group<sup>14</sup>. It is also very heartening to observe that the mean seizure frequency among the TDM group patients decreased by 83.34% and in Non TDM group the reduction was only 53.72% (Table-6). A total of 40% in TDM group and 7.8% in Non TDM group were seizure free during the last 6 months of follow-up.

Adverse effects were reported by 4% in the TDM group and 15.38% in the Non TDM group patients. This was relatively lower when compared to a study conducted by Jannuzzi G et al. which showed that the adverse effect reported in TDM group was 8% and in Non TDM group was 40%<sup>13</sup>. Among the TDM group one patient had drowsiness at the end of 4<sup>th</sup> month and in Non TDM group one patient had headache, another had drowsiness and two patients had somnolence at the end of 2<sup>nd</sup> month. But

this did not require discontinuation of the drug. Similarly, in a retrospective study conducted by S.K. Grag and M.C Gupta in Chandigarh also reported less number of adverse effects in TDM group when compared to Non TDM group<sup>15</sup>.

Hence, TDM service provides better seizure control to the patients who had better quality of life as by social, occupational and economical outcomes. The advantages collectively lead to better control of epilepsy and probably result in greater chances of the disease going into remission.

## CONCLUSION

From our study we conclude that therapeutic drug monitoring group patients had better seizure control with fewer adverse effects when compared with the group that had not undergone TDM. Therapeutic drug monitoring of phenytoin and other drugs with narrow therapeutic index helps the clinician to provide rational therapy. Thus, effective management of chronic diseases relies on both clinicians and pharmacologists who work on pharmacokinetic aspects and drug clearance of individual drugs with low margin of safety

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