

Original Article

Evaluate Clinical Impact of Therapeutic Drug Monitoring of Phenytoin Monotherapy in Patient of Generalized Tonic Clonic Seizures

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ABSTRACT

Background: Epilepsy is one of the most common serious disorders of the brain, affecting about 50 million people worldwide, 80% of the burden of epilepsy is in the developing world. Therapeutic drug monitoring (TDM) is one of the major arms to maximize efficacy and minimize risk of overdosing. **AIM:** To compare clinical outcome between monitored and unmonitored dose of Phenytoin in patient of generalized tonic clonic seizure. **Methods:** Comparative study of 40 patients on phenytoin with therapeutic drug monitoring verses 40 patients on phenytoin without therapeutic drug monitoring of Generalized tonic clonic seizure were undertaken. For therapeutic drug monitoring, early morning sample (before taking morning dose) was collected, centrifuged, plasma separated and after that therapeutic level are monitored using HPLC. Sampling was done twice a month for one month than once a month for third and sixth month; samples were also taken abruptly in case of poor or no response to therapy, any adverse effect if noted or if any patient taking other medication in between. Evaluation of Efficacy is done by mean Seizure frequency reduction and comparison of side effect profile of the two groups. **Results:** Statistically significant difference is seen in TDM and non-TDM Group at 3 and 6 months; with percent reduction of mean seizure frequency 85.44% in TDM group compared to 43.81% in non- TDM group. **Conclusions:** The results of this comparative evaluation after the collection of data and its analysis confirms clinical impact of therapeutic drug monitoring of phenytoin monotherapy in patients of generalized tonic clonic seizures.

Key words: Therapeutic Drug Monitoring, Phenytoin, Seizures.

Section – Pharmacology

INTRODUCTION

Epilepsy is one of the most common serious disorders of the brain, affecting about 50 million people worldwide, 80% of the burden of epilepsy is in the developing world. Epilepsy encompasses a number of different syndromes for which the predominant feature is recurrent, periodic,

unpredictable and unprovoked seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons.^[1-3]

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.^[4]

TDM is one of the major arms to maximize efficacy and minimize risk of overdosing. 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.^[5]

Phenytoin sodium is widely used in the clinics for treatment of epilepsy and the drugs have close connection with concentration of drug in plasma so monitoring of plasma levels of phenytoin plays an important role in the management of epilepsy.^[6] The optimal therapeutic

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concentration of phenytoin is 10-20 µg/mL, most patients will show a marked reduction or complete control of seizures when phenytoin plasma concentrations are in this range.

AIM AND OBJECTIVES

- 1) To compare clinical outcome between monitored and unmonitored dose of phenytoin in patient of generalized tonic clonic seizure
- 2) To maximize the efficacy and minimize toxic effect profile of phenytoin therapy.
- 3) To correlate the therapeutic level of phenytoin with optimal seizure control.

METHODS

Study area: The study was conducted in the department of Pharmacology and Neurology at J.A. Group of Hospital and G.R Medical College, Gwalior (M.P) during academic session 2013 to 2015.

Study Design: This was a prospective open label comparative study between clinical outcome of patient with generalized tonic clonic seizure on phenytoin therapy with and without therapeutic drug monitoring.

Inclusion Criteria:

1. Patient ages above 15 years and below 50 years were included.
2. Patient could be of either sex.
3. Patient must be medically stable.
4. Patient or family member must be willing to give written informed consent.
5. Patient must be able to communicate in Hindi/English.
6. Determined to have had at least two episodes of seizures by an epilepsy specialist, or to have had a single episode of seizure with abnormal EEG.

Exclusion Criteria:

1. Clinical suspicion of non-epileptic psychogenic seizures.
2. Pregnant, child-bearing age using contraception, or breast feeding
3. Presence of a vagus nerve stimulator
4. Creatinine clearance of less than 50mL/min
5. Blood pressure instability: pulse <50 or >100, SBP <50 or >180, clinically significant EKG abnormality
6. History of diabetes mellitus.
7. History of hepatic insufficiency.
8. History of hematological disorder.
9. History of significant drug rash or anaphylactic reaction with antiepileptic drug
10. Patients with progressive lesions (e.g. brain tumors).

Procedure of the study:

Comparative study of 40 patients on phenytoin with therapeutic drug monitoring verses 40 patients on phenytoin without therapeutic drug monitoring of Generalized tonic clonic seizure were undertaken.

For therapeutic drug monitoring, early morning sample (before taking morning dose) was collected, centrifuged, plasma separated and after that therapeutic level are monitored using HPLC. Sampling was done twice a month for one month than once a month for third and sixth month; samples were also taken abruptly in case of poor or no response to therapy, any adverse effect if noted or if any patient taking other medication in between.

Evaluation of Efficacy is done by mean Seizure frequency reduction and comparison of side effect profile of the two groups.

Statistical Analysis

The statistical analysis of this comparative study was done by using suitable statistical methods.

Statistical analysis was performed by using software Epicalc 2000ec2v102. Reduction in seizure frequency was compared by Student's t-test. All means were expressed as mean ± Standard error of mean (SEM). The critical level of significance of the results was considered at 0.05 i.e. $P \leq 0.05$ was considered significant.

RESULTS

The present study is a prospective; open labeled, comparative study conducted in the Department of Pharmacology and Department of Neurology, J.A. Group of Hospitals, G.R. Medical College, Gwalior (M.P.) and included 80 patients who fulfilled the selection criteria. Number of patients enrolled and dropout were as follows.

Total No. of cases	= 82
Therapeutic drug monitoring Group	= 41
Non-Therapeutic drug monitoring Group	= 41
Total Dropouts	= 19
Therapeutic drug monitoring Group	= 11
Non-Therapeutic drug monitoring Group	= 08

Mean seizure frequency in TDM group was found to be 3.16 ± 1.08 at 0 month. It came down to 1.46 ± 0.77 , 0.46 ± 0.77 at 3 and 6 months respectively with percent reduction of 85.44%.

Mean seizure frequency in non-TDM group was found to be 3.72 ± 1.25 at 0 month. It came down to 2.48 ± 1.00 , 2.09 ± 0.87 at 3 and 6 months respectively with percent reduction of 43.81%.

Statistically significant difference is seen in TDM and non-TDM Group at 3 and 6 months.

In TDM group the most common adverse effect at 3 month was dizziness, which was seen in 12 (40%) patients. Next common adverse effect was drowsiness in 10(33%) patients; followed by fatigue, irritability, weight gain, hypersensitivity reaction, and acne in 8(26%), 8 (26%), 3(10%), 3(10%) and 2(%) patients respectively.

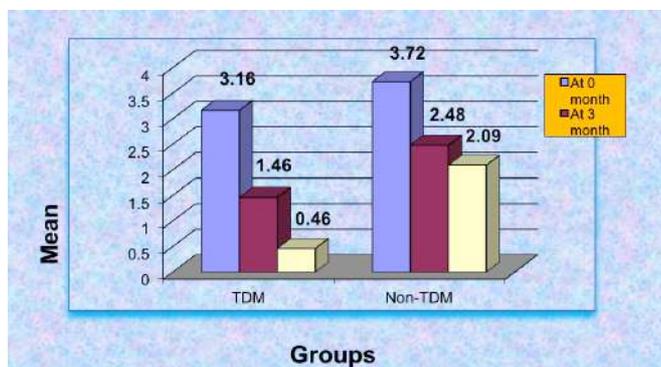
In non-TDM group the most common adverse effect at 3 month was again dizziness, which was seen in 19 (57.5%) patients. Next common adverse effect was drowsiness in 15(45%) patients; followed by fatigue, irritability, weight gain, hypersensitivity reaction, acne and gum hypertrophy

in13(39%), 13 (39%), 6(18%), 2(6%), 5(15%) and 1(3%) patients respectively. Statistically difference between two groups was not significant at 3 months. In TDM group, the most common adverse effect at 6 month was drowsiness, which was seen in 6 (20%) patients. Next common adverse effect was fatigue in 10(16%) patients; followed by dizziness, irritability, weight gain and hypersensitivity reaction in 4(13%), 2 (6%), 1(3%) and 1(3%) patients respectively. In non-TDM group, the most common adverse effect at 6 month was again drowsiness, which was seen in 12 (36%) patients. Next common adverse effect was dizziness in 11(33%) patients; followed by irritability, fatigue, weight gain, acne, hypersensitivity reaction and gum hypertrophy in10(30%), 7 (21%), 4(12%), 3(9%), 2(6%) and 1(3%) patients respectively. Statistically difference between two groups was not found significant at 6 months.

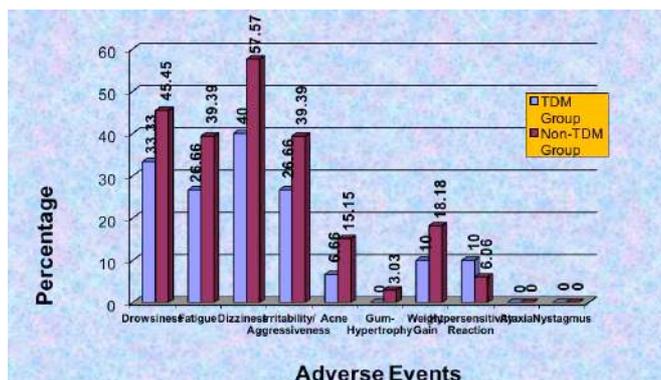
Table 1: Mean seizure frequency in TDM and non-TDM groups at different time interval.

Groups	Mean seizure frequency (per month)			% of Reduction
	At 0 month	At 3 month	At 6 month	
TDM	3.16 ± 1.08	1.46 ± 0.77	0.46 ± 0.77	85.44
Non-TDM	3.72 ± 1.25	2.48 ± 1.00	2.09 ± 0.87	43.81
'p' value (CI 95%)	0.0630 (-1.15 to 0.031)	0.0001* (-1.47 to -0.56)	0.0001** (-2.045 to -1.21)	

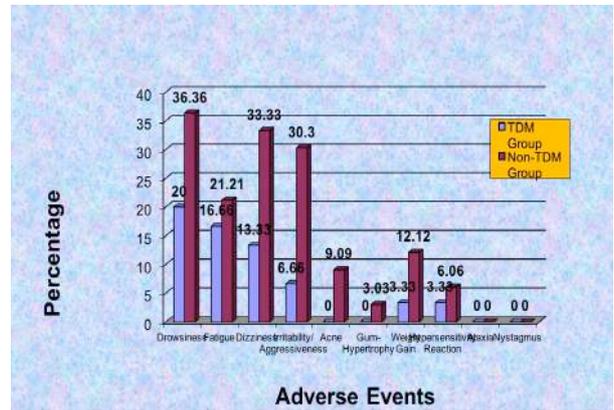
* Significant, ** Highly significant



Graph 1: Mean seizure frequency in TDM and Non-TDM groups at different time interval.



Graph 2: Comparison of adverse events reported by the patients at 3rd month



Graph 3: Comparison of adverse events reported by the patients at 6 month

DISCUSSION

Therapeutic drug monitoring has impact on improving the effectiveness and safety of anticonvulsant therapy. For this study, 82 patients were enrolled who fulfilled the selection criteria but 63 patients completed the study. 30 patients in TDM group taking phenytoin, doses are adjusted according to plasma level obtained after therapeutic drug monitoring, 33 patients in Non-TDM group phenytoin doses are adjusted according to clinical response and without monitoring of therapeutic level. They were assessed for efficacy at 3rd and 6th months by comparing Seizure frequency reduction and tolerability by recording & comparing the frequency of adverse effects at 3rd and 6th month.

Regarding seizure frequency in comparison between 2 groups TDM patients showed a decrease in seizure frequency by 85.44% as compared to non-TDM group where it was only 43.81%, the results are comparable with the study conducted by V. Sivasankari *et al* where they found 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%.^[7] G. Jannuzzi *et al* found that the proportion of patients achieving 12-month remission in seizure frequency were 60% in the TDM group and 61% in the control group, proportion of patients achieving remission nor rates at which remission was achieved differed between the TDM and the control groups.^[8] C. T. Rane *et al* found that TDM showed far greater benefit in terms of reduction in number of seizures (16% vs 48%) as compared to non TDM group.^[9]

In our study, we found that at 3 month in TDM group the most common adverse effect was Dizziness, which was seen in 12 (40%) patients compared to 19 (57.5%) patients in non-TDM group. Next common adverse effect was drowsiness in 10(33%) patients and 15(45%) patients in TDM and non-TDM groups. Other side effect like fatigue, irritability, weight gain, hypersensitivity reaction, and acne are also more in non-TDM group compared to TDM group; but difference was not significant for any adverse effect.

Similarly, at 6 month in TDM group the most common adverse effect was drowsiness, which was seen in 6 (20%) patients compared to 12 (36%) patients in non-TDM group. Next common adverse effect was fatigue in 10(16%)

patients in TDM group and Dizziness in 11(33%) patients in non-TDM group. Other side effect like irritability, weight gain, hypersensitivity reaction, and acne are also more in non-TDM group compared to TDM group; but again, difference was not significant for any adverse effect.

So, we don't get statistically significant difference on adverse effect profile in between two groups; may be due to small sample size. C. T. Rane *et al* found that number of adverse effects (8% vs 40%) between TDM and non TDM group, with a significant difference.⁹ G. Jannuzzi *et al* found that adverse effects were reported in 45 (48%) of patients in the TDM group and in 41 (47%) of those in the control group.^[8] None of these effects was considered serious. Somnolence or sedation was the most commonly reported adverse experience, being observed in one fourth of patients in both groups. The frequency of the most common adverse effects was similar in the two groups. V. Sivasankari *et al* in their study, reported adverse effects 4% in the TDM group and 15.38% in Non TDM group patients. The common 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.^[7]

CONCLUSION

The results of this comparative evaluation after the collection of data and its analysis confirms clinical impact of therapeutic drug monitoring of phenytoin monotherapy in patients of generalized tonic clonic seizures. Statistically significant reduction in seizure frequency is seen in TDM at 3 and 6 months when compared to non-TDM group at same time-period. Though therapeutic drug monitoring did not show any significant effect on adverse effect profile of the phenytoin when compared to non-TDM group, reason may be due to small sample size.

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