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Research Article

Study on Therapeutic Drug Monitoring of Anti-Epileptic Drugs among Epileptic Patients in Silchar Medical College and Hospital, Silchar

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Abstract

Background: Anti-Epileptic Drugs (AEDs) are the mainstay in treatment of epilepsy. They are known to have narrow therapeutic index and complex pharmacokinetic properties resulting in wide fluctuations in their plasma concentration, leading to toxic effects or loss of therapeutic efficacy.

Methodology: This prospective, observational case-series study was carried out in the Medicine and Psychiatry outpatient and inpatient departments of Silchar Medical College and Hospital. A total of 69 patients of either sex between the age group of 18 - 75 years, diagnosed with epilepsy were recruited for the study after procuring due consent. Patients on single AED only were recruited for the study and were assessed for their plasma AED levels.

Results: Out of the 69 patients, 13.04% received carbamazepine, 33.33% received phenytoin and 53.62% received valproic acid monotherapy. Among patients receiving carbamazepine, 77.78% had the drug level is within the therapeutic range and 22.22% patients had the drug levels is above the therapeutic range. Among those receiving phenytoin, 65.22%, 17.39% and 17.39% had drug levels within, above and below therapeutic ranges respectively and for patients receiving valproic acid, 64.86%, 8.11% and 27.03% were found to have drug levels within, above and below the recommended therapeutic ranges respectively. Various adverse effects like break-through seizures, headache, drowsiness, gum hypertrophy, fixed drug eruptions, menstrual irregularities, etc. were observed with these AEDs.

Conclusion: The study found that plasma drug levels of carbamazepine and phenytoin correlated well with their therapeutic range while it did not always correlate with serum levels of valproic acid.

Keywords: Epilepsy; Phenytoin; Carbamazepine; Valproic Acid; Plasma Drug Level

Introduction

Epilepsy is a collection of chronic neurological disorders which is characterized by seizures [1]. A seizure is a paroxysmal event due to abnormal, excessive or asynchronous neuronal activity in the brain. The word seizure is derived from the Latin word sacire which means "to take possession of" [2], while the word epilepsy originates from the Greek verb epilambanein, which means "to seize, possess, or afflict" [3]. Seizure is the symptom of an underlying disorder, whereas epilepsy is a disorder characterized by repeated seizures of cerebral origin due to a chronic underlying process presenting with episodes of sensory, motor or autonomic incident with or without loss of consciousness [2].

Epilepsy is mostly diagnosed during childhood or adolescence, though it can occur in any age. The incidence is highest among young children and the elderly with men being more affected than women in a ratio of 1.5:1 [4].

Epilepsy is a long-term disease requiring chronic therapy [5]. The mainstays in treatment of epilepsy are the group of drugs generally referred to as Anti-Epileptic Drugs (AEDs). Success of anti-epileptic treatment depends upon watchful dosage titration based on pharmacokinetic principles to a preferred patient response, the patient's capability to endure side effects and long-standing patient monitoring to guarantee compliance, prevent drug interaction and reduce toxicity [6].

Anti-epileptic drugs act by enhancement of GABA action (e.g. phenobarbitone, gabapentin, vigabatrin, tiagabine), inhibition of sodium channel function (e.g. phenytoin, carbamazepine, sodium valproate, lamotrigine), inhibition of calcium channel function (e.g. ethosuximide, gabapentine). Apart from these, some drugs act by inhibition of glutamate release and block of glutamate receptors. These drugs have been found to be effective in animal models but are unsuitable for clinical use. Newer antiepileptic drugs such as levetiracetam and zonisamide act by mechanisms which are poorly understood [7].

Antiepileptic drugs are known to have a narrow therapeutic index and complex pharmacokinetic properties, due to which wide fluctuations occur in their plasma concentration which can lead either to toxic effects or loss of therapeutic efficacy [8], and hence, they are ideal candidates for Therapeutic Drug Monitoring. Clinical responses to the drug regimen correlate better with the plasma concentration of the drug than with the prescribed daily dose regimen [9].

Therapeutic drug monitoring (TDM) has been defined by the International Association for Therapeutic Drug Monitoring and Clinical Toxicology as "the measurement made in the laboratory of a parameter that, with appropriate interpretation, will directly influence prescribing procedures. Commonly, the measurement is in a biological matrix of a prescribed xenobiotic, but it may also be of an endogenous compound prescribed as a replacement therapy in an individual who is physiologically or pathologically deficient in that compound" [10].

The goal of therapeutic drug monitoring is to optimize pharmacological responses of a drug while preventing adverse effects. Usually for drugs that are routinely monitored in clinical laboratories, serum concentrations are a better predictor of desired pharmacological effects than the dose. Moreover, therapeutic drug monitoring is also utilized to monitor a patient's compliance with a drug regimen and to identify potential drug-drug or food-drug interactions. Therapeutic drug monitoring not only consists of measuring the concentration of a drug in a biological matrix, but it also involves the proper interpretation of the value using pharmacokinetic parameters, drawing appropriate conclusion regarding the drug concentration and dose adjustment [11].

Patients can gain both medically and economically from therapeutic drug monitoring. Many reports in the literature indicate that therapeutic drug monitoring can decrease hospital stay and have important implications on the cost of medical care. Reduced drug-related toxicities are beneficial for patients and also diminish the liability of physicians.

Thus, monitoring the serum levels of the anti-epileptic drugs plays a vital role in the management of epilepsy. 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 [12]. TDM of the anti-epileptic drugs thereby can benefit the patient by reducing the number of seizures, reducing the adverse drug reactions and increasing their scholastic performance [13]. However, the facilities for Therapeutic Drug Monitoring are still not available in many hospitals in India. Only limited information is available in the literature about the clinical utility of TDM in India.

Objectives

1. To observe whether the plasma level of Anti-Epileptic Drugs is within the therapeutic range.
2. To assess whether individualization of the therapeutic concentration of Anti-Epileptic Drugs in patients are required.

Materials and Methods

This non-interventional and observational study was carried out in the Medicine and Psychiatry outpatient and inpatient departments of Silchar Medical College and Hospital, the hospital being the only referral hospital located in the southern part of Assam. Prior approval from the Institutional Ethical Committee was obtained before initiating the study. This study was carried out after for a period of 12 months commencing from 1st September 2016 to 31st August 2017.

Patients of either sex, aged between 18-75 years, attending the outpatient departments or admitted in the indoor departments of Psychiatry and Medicine in Silchar Medical College and Hospital, Silchar, and diagnosed with epilepsy were screened and recruited for the study after satisfaction of the inclusion and exclusion criteria, and after obtaining due consent from the patients.

Inclusion Criteria

Patients of either sex between 18 - 75 years of age, who were diagnosed with epilepsy and undergoing treatment with monotherapy with a single AED, and having parameters of blood haemogram, blood sugar level, lipid profile, liver function test, renal function test and ECG within the normal range.

Exclusion criteria

Those patients who were diagnosed with epilepsy but were below 18 years and above 75 years age or receiving more than one AED or with deranged liver and renal function or suffering from any co-existing diseases requiring prolonged medications or with history of alcohol or substance abuse were excluded from the study. Pregnant and lactating woman and those who were unable or not willing to give consent were also excluded.

Detailed medical histories of the subjects were taken followed by a thorough clinical examination. Subjects were screened by residents from respective departments and the diagnosis was confirmed by senior physicians. After that the selection criteria were checked and written informed consent signed from the patient after explaining the purpose of the study to them. Blood for estimation of serum levels of antiepileptic drugs were collected in empty stomach at the morning before the next due dose (trough concentration). Serum levels were then analysed using a drug auto-analyser.

Any medication (other than those permitted by protocol), that could affect the pharmacological effects of the drugs under investigation, was strictly discouraged and the possible effects were described to the family members accompanying the patients. Other medication needed by the patient for any existing co-morbid clinical conditions were allowed to be taken by the patient.

Data were entered in computer database with the help of Microsoft excel-2007 and analysis was done in the Department of Pharmacology, Silchar Medical College and Hospital, Silchar.

Results

A total of 69 patients were selected for the study, out of which 44 (63.77%) were males and 25 (36.23%) were females. The mean age of the patients was found to be 37.74 ± 13.99; the mean age of male patients being 40.23 ± 15.8 while that of female patients being 33.36 ± 8.49.

Department	Male	Female	Total
Psychiatry	8 (11.59%)	5 (7.25%)	13 (18.84%)
Medicine	36 (52.17%)	20 (28.89%)	56 (81.16%)
Total	44 (63.77%)	25 (36.14%)	69 (100%)

Table 1: Distribution of patients according to sex and departments.

The patients were divided into 5 groups according to their age: 18-30 years, 31-40 years, 41-50 years, 51-60 years and 61-75 years, which is shown in table 2 below. Thus, it was observed that majority of patients suffering from epilepsy were from the age group of 31-40 years, closely followed by the age group of 18-30 years.

Age group	Number (n)	% age
18 - 30yrs	20	28.99
31 - 40yrs	26	37.68
41 - 50yrs	10	14.49
51 - 60yrs	9	13.04
60 - 75yrs	4	5.80
Total	69	100

Table 2: Distribution of patients according to age group.

In this study only, those patients were considered who were receiving only one AED. Subsequently it was found that only three AEDs viz., Carbamazepine, Phenytoin and Valproic Acid were being used as monotherapy in epileptic patients. Table 3 shows the distribution of AEDs in patients as follows:

Anti-Epileptic Drug Used	No. of patients	% age
Carbamazepine	9	13.04
Phenytoin	23	33.33
Valproic Acid	37	53.62
Total = 69		

Table 3: Distribution of patients according to the AED prescribed.

Table 4 shows the distribution of AEDs according to the sex of the patient. Thus, it was observed that Phenytoin and Valproic Acid were the most common AEDs prescribed to male and female patients respectively.

AED	Male	Female	Total
Carbamazepine	5 (7.25%)	4 (5.80%)	9 (13.04%)
Phenytoin	20 (28.99%)	3 (4.35%)	23 (33.33 %)
Valproic Acid	19 (27.54%)	18 (26.09%)	37 (53.62%)
Total	44 (63.77%)	25 (36.23%)	69 (100%)

Table 4: Distribution of AEDs according to the sex of patients.

Table 5 shows the details of AEDs drugs prescribed in the various age groups.

Age group	Prescribed Anti-Epileptic Drugs			Total
	Carbamazepine	Phenytoin	Valproic Acid	
18 - 30yrs	2 (2.90%)	5 (7.25%)	13 (18.84%)	20 (28.99%)
31 - 40yrs	3 (4.35%)	9 (13.04%)	14 (20.29%)	26 (37.68%)
41 - 50yrs	2 (2.90%)	4 (5.80%)	4 (5.80%)	10 (14.49%)
51 - 60yrs	2 (2.90%)	4 (5.80%)	3 (4.35%)	9 (13.04%)
60 - 75yrs	0 (0%)	1 (1.45%)	3 (4.35%)	4 (5.80%)
Total	9 (13.04%)	23 (33.33%)	37 (53.62%)	69 (100%)

Table 5: Distribution of AEDs according to age groups.

Carbamazepine was found to be the least prescribed among the three AEDs found in the study. Only 9 patients were prescribed carbamazepine. Table 6 summarizes the findings with Carbamazepine monotherapy.

Number of patients prescribed with Carbamazepine	09
Normal therapeutic range of Carbamazepine	4 -12 µg/mL
Number of patients with serum level of Carbamazepine	
a) Below therapeutic range	Nil
b) Within therapeutic range	07 (77.78%)
c) Above therapeutic range	02 (22.22%)
Number of patients with adverse effects due to Carbamazepine therapy	03 (33.33%)
Adverse effects observed due to Carbamazepine therapy	
a) Break-through seizures	01 patient
b) Headache and Vomiting	01 patient
c) Vomiting and Drowsiness	01 patient

Table 6: Summary of results with Carbamazepine therapy.

Among the study population, 23 patients were on Phenytoin therapy. Table 7 summarizes the findings with Phenytoin monotherapy. Among the patients on Phenytoin monotherapy and in whom the serum levels were found to be above the recommended therapeutic range, one male and one female patient were suffering from serious adverse reactions - Fixed Drug Eruption and Toxic Epidermal Necrolysis, respectively.

Number of patients prescribed with Phenytoin	23
Normal therapeutic range of Phenytoin	10 - 20 µg/mL
Number of patients with serum level of Phenytoin	
a) Below therapeutic range	04 (17.39%)
b) Within therapeutic range	15 (65.22%)
c) Above therapeutic range	04 (17.39%)
Number of patients with adverse effects due to Phenytoin therapy	08 (34.78%)
Adverse effects observed due to Phenytoin therapy	
a) Break-through seizures	04 patients
b) Abdominal pain, Vomiting and Gum hypertrophy	01 patient
c) Abdominal pain, Vomiting, Vertigo and Dizziness	01 patient
d) Fixed Drug Eruption	01 patient
e) Toxic Epidermal Necrolysis	01 patient

Table 7: Summary of results with Phenytoin therapy.

In this study, it was observed that the most commonly used anti-epileptic drug was Valproic acid. 37 patients out of the study population of 69 patients were undergoing therapy with Valproic acid. Table 8 summarizes the findings with Valproic Acid monotherapy.

Discussion

Epilepsy is a disorder of the brain which is characterized by a continuous tendency to generate epileptic seizures. Currently employed antiepileptic drugs can suppress these seizures but may be unsuccessful in treating the underlying cause of the seizures and are effective in 60-70% of individuals. Pharmacogenetic studies involving the anti-epileptic drugs gives an assurance of being able to individualize treatment for each patient, while providing maximum possibility of benefit and minimum risk of adverse effects [14].

Number of patients prescribed with Valproic acid	37
Normal therapeutic range of Valproic acid	50 – 100 µg/mL
Number of patients with serum level of Valproic acid	
a) Below therapeutic range	10 (27.03%)
b) Within therapeutic range	24 (64.86%)
c) Above therapeutic range	03 (8.11%)
Number of patients with adverse effects due to Valproic acid therapy	16 (43.24%)
Adverse effects observed due to Valproic acid therapy	
a) Break-through seizures	11 patients
b) Vomiting, Tremors and Menstrual irregularities	01 patient
c) Weight gain and tremor	01 patient
d) Vomiting and Tremor	01 patient
e) Vomiting and Menstrual Irregularities	01 patient
f) Weight gain and Alopecia	01 patient

Table 8: Summary of results with valproic acid therapy.

Antiepileptic drugs are known to have a distinct association between their blood concentration and pharmacodynamic effects, but they are known to lack a good correlation between the dose and the blood concentration in a patient. R.G. Feldman and C.E. Pippenger, in 1976, observed that that several patients who underwent treatment for epilepsy surprisingly remained free from episodes of seizure in spite having serum levels of anti-epileptic drugs well below the "optimal therapeutic interval" established at that time [15].

For many antiepileptic drugs, lack of seizure control can occur when blood concentrations are either above or below the recommended therapeutic range. Hence these drugs invariably fit the "profile" of drugs which should be monitored in therapeutic settings. Therapeutic drug monitoring for anti-epileptic drugs in treatment of epilepsy are useful in establishing a baseline effective concentration, evaluating causes for toxicity or lack of efficacy, evaluating non-compliance versus loss of efficacy, minimization of side effects, and evaluation of serum levels when the therapeutic regimen is changed. Moreover, it also becomes useful wherever individualization of drug dosing is required for effectively controlling of epilepsy [16].

From the present study, it was found that majority of the patients were males and also that epilepsy was more prevalent in the younger age group (i.e., between 18-40 years of age) which indicated that the prevalence of epilepsy in this region is more among the younger age group and males. Almost similar findings were found in the study conducted by Shakya., *et al.* [17], where they found that majority of the patients suffering from epilepsy were from the age group of 16-30 years.

Valproic acid was found to be the most common antiepileptic drug in the present study; the finding of which is similar to the study by Nicholas *et al*.[18], but are quite different from that found in the studies by Karaalp., *et al.* [19], Shakya., *et al*. and Garg., *et al*. [20], where the most commonly prescribed drug was Carbamazepine, and in studies conducted by Lertsinudom., *et al*. [21], Dahiya., *et al*. [22], Taur., *et al*. [23] and Harivenkatesh., *et al*. [24] where Phenytoin found to be the most commonly used AED. The reason of preferential use of Valproic acid as anti-epileptic monotherapy in our institute may either be due to personal preference of the physician concerned or due to the fact that it is generally considered as a broad-spectrum antiepileptic and can be used in almost all types of epilepsy and also in cases where the epileptic disorder cannot be classified.

In the present study phenytoin was found to be the most commonly prescribed AED among the male population, but it was less preferred among females, which may be attributed to phenytoin's propensity to cause hirsuitism and birth defects (in fetus of pregnant women taking phenytoin). Also, another reason may be that concomitant use of Phenytoin and oral contraceptive pills can lead to contraceptive failure by decreasing the efficacy of the latter. Even one of the female patients who were prescribed phenytoin reported with a serious adverse effect, Toxic Epidermal Necrolysis (TEN) and was found to have toxic level of phenytoin in her blood. All these reasons may be the reason for avoiding phenytoin in females, in general, by the physicians.

The most commonly prescribed anti-epileptic among the female population was found to be Valproic acid. Though Valproic Acid is known to cause hirsuitism, but it was not reported by any female patients on Valproic Acid monotherapy in the present study. The teratogenic property of Valproic acid was also not studied as pregnant women were excluded from the present study.

In the present study, it was found that the serum level of Carbamazepine correlated well with its pharmacological profile; breakthrough seizures were reported by one patient who had serum level of the drug below the therapeutic range, inspite of taking the drug regularly in the prescribed dose, while adverse effects were observed in those who had their serum levels above therapeutic range. These findings were well in accordance to other studies conducted on serum levels of Carbamazepine by Shakya., *et al*. [17], Karaalp., *et al*. [19], Garg., *et al*. [20], Dahiya., *et al*. [22], Taur., *et al*. [23], Harivenkatesh., *et al*. [24], Sharpe., *et al*. [25] and Radeef., *et al*. [26]. Almost all the authors had opinion that Carbamazepine is an ideal drug for TDM owing to its large inter-individual differences in plasma half-life due to its auto-inducing properties and its narrow therapeutic range.

Phenytoin is also an ideal drug for TDM as it follows dose-dependent pharmacokinetics and its hepatic metabolism can become saturated which indicates a non-linear relation between the dose and plasma concentration with variation in saturation levels between individuals. This was well reflected in studies conducted by Shakya., *et al.* [17], Garg., *et al*. [20], Dahiya., *et al.* [22], Taur., *et al*. [23], Harivenkatesh., *et al.* [24] and Sharpe., *et al*. [25] and in the present study too. Patients who were found to have serum levels of phenytoin below the therapeutic range complained of recurrence of episodes of seizure, while those who had higher serum levels of Phenytoin, suffered from various adverse effects including Toxic Epidermal Necrolysis and Fixed Drug Eruption. Out of the 4 patients who complained of breakthrough seizures, three patients were regularly taking the drug in the prescribed dose while the other one gave history of irregular intake of the medication.

The scenario with Valproic acid monotherapy was found to be quite complex in the present study as its plasma level did not correlate well with its effects and adverse event profile. Out of the 37 patients who were prescribed the drug, 11 patients reported with breakthrough seizures while 5 patients reported with various adverse events while its serum level was found to be above therapeutic range in only 3 patients and below the therapeutic range in 10 patients. Out of the patients who reported with breakthrough seizures, only 4 patients had history of irregular intake of the drug. So, the therapeutic profile did not always correlate with its serum level. Similar opinion was given in other studies conducted by Shakya., *et al*. [17], Taur., *et al.* [23], Harivenkatesh., *et al.* [24] and Sharpe., *et al.* [25]. This complex scenario is attributed to its complex pharmacokinetic profile, slower elimination of active metabolites and wide concentration variation across the dosage interval and concentration-dependent protein binding property. Some of the authors opined that monitoring of Valproic acid can be misleading as it offered very little reliable information regarding the possible clinical outcome but concluded that interpretation of the plasma concentration of this drug must be done wisely.

Thus, the present study indicates that therapeutic drug monitoring of anti-epileptic drugs can be a beneficial tool for regulating anti-epileptic therapy and optimal control of seizures in patients as these drugs have a narrow therapeutic index and the clinical response may have a better correlation with the plasma concentration of the drug than with the prescribed daily dose regimen.

In-spite of all the meticulous efforts taken in conducting the present study, it has got its own limitations. Firstly, as the sample size was small, and the duration of the study was short it did not have a greater reflection of the population in general. Secondly, the natures of the present study as a prospective observational study with a closed environment, itself limited its scope. Thirdly, as the present study only included patients who were on monotherapy with a single AED and without any co-morbid conditions, the effect of AED polytherapy and that of various drugs on the AEDs and their reflection in the serum levels and the resultant clinical outcome could not be studied. Fourthly, lack of proper instruments and infrastructure, especially the absence of a TDM unit in our hospital, has also been a big hindrance to the proper conduction of a study of such nature. And, finally, as with various other studies conducted in our country, the socio-economic status, hygiene and literacy status of majority of the patients attending a government hospital, is generally skewed towards the lower side and it directly affects the compliance of the patient, both towards the treatment and the study.

Conclusion

The present study on "therapeutic drug monitoring of anti-epileptic drugs among epileptic patients in Silchar Medical College and Hospital, Silchar" was conducted with an aim to relate the importance of monitoring serum levels of the AEDs in aiding anti-epileptic therapy.

The present study showed that the older generation AEDs were the most preferable agents for monotherapy in epileptic patients in our hospital. The study found that out of the older generation AEDs, three drugs viz., carbamazepine, phenytoin and valproic acid were the most commonly used anti-epileptic drugs in our hospital, with the latter being the most commonly preferred drug.

The study indicated that among these three AEDs, monitoring of serum levels of carbamazepine and phenytoin were found to be very useful in aiding anti-epileptic drug therapy. In relation to valproic acid the same statement cannot be emphasized upon as it has been found that the clinical picture in its case may not always correlate with its serum level.

Nonetheless, the importance of therapeutic drug monitoring of AEDs in aiding anti-epileptic therapy cannot be totally ignored due to the complex pharmacokinetic properties of these drugs and their huge inter-individual variations. Moreover, the narrow therapeutic range of these drugs makes them an ideal candidate for monitoring their serum levels.

Thus, it can be concluded that therapeutic drug monitoring of anti-epileptic drugs can not only aid in modulating anti-epileptic therapy, but also can help in individualization of therapy while achieving optimal clinical outcome and preventing adverse events and thereby improving the social, economic and occupational outcomes of the epileptic patients with an increase in the chance of disease remission.

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Nil

Conflicts of Interest

None

Bibliography

1. Leppik IE. "Contemporary diagnosis and management of the patient with epilepsy". 2nd edition. Newtown, PA: Handbooks in health care. (1996).

2. Kasper DL., *et al*. "Harrison's Principle of Internal Medicine". 19th Edition. USA: McGraw Hill education (2015).

3. Magiorkinis E., *et al*. "Hallmarks in the history of epilepsy: epilepsy in antiquity". *Epilepsy and behaviour* 17 (2010): 103-108.

4. Robert GC. "Cecils Essential of medicine. 6th ed". Philadelphia: Elsevier (2004): 1051-1052.

5. Sridharan R and Murthy BN. "Prevalence and pattern of epilepsy in India". *Epilepsia* 40.5 (1999): 631-636.

6. Garnett WR., *et al*. "Pharmacotherapy - A Pathophysiological Approach". 3rd *edition* Stamford. Appleton and Lange (1997).

7. Rang HP., *et al*. "Rang and Dale's Pharmacology". 6th *edition* Edinburgh: Elsevier, Churchill Livingstone (2007): 579-84.

8. Reynolds EH. "Chronic Antiepileptic Toxicity: A Review". *Epilepsia* 16.2 (1975): 319-352.

9. Brunton LL., *et al*. "The Pharmacological Basis of Therapeutics. 12th edition China: The McGraw-Hill Companies Chapter 2, Pharmacokinetics: The Dynamics of Absorption, Distribution, Metabolism and Elimination (2011).

10. Watson I., *et al*. "Therapeutic Drug Monitoring. 19.2 (1997): 125.

11. Dasgupta A. "Introduction to Therapeutic Drug Monitoring. In: Dasgupta A, editor. Handbook of Drug Monitoring Methods Therapeutics and Drugs of abuse. Totowa, New Jersey. Humana Press Inc. (2008).

12. Harden CL. "Therapeutic Safety Monitoring: What to Look for and When to Look for It". *Epilepsi*a 41 (2000): 37-44.

13. Gogtay NJ., *et al*. "Therapeutic drug monitoring in a developing country: an overview". *British Journal of Clinical Pharmacology* 52 (2001): 103-108.

14. Duncan JS., *et al*. "Adult Epilepsy". *The Lancet* 367 (2006): 1087-1100.

15. Feldman RG., *et al*. "The Relation of Anticonvulsant Drug Levels to Complete Seizure Control". *The Journal of Clinical Pharmacology* 16 (1976): 51-59.

16. Clarke W. "Interferences with Measurement of Anticonvulsants. In: Dasgupta A, editor. Handbook of Drug Monitoring Methods Therapeutics and Drugs of abuse. Totowa, New Jersey. Humana Press Inc. (2008).

17. Shakya G., *et al*. "Therapeutic drug monitoring of antiepileptic drugs". *Journal of Nepal Medical Association* 47 (2008): 94-97.

18. Nicholas D., *et al*. "Evaluation of therapeutic drug monitoring (TDM) on older antiepileptic medications". *Der Pharmacia Lettre* 7 (2015): 243-250.

19. Karaalp A., *et al*. "Therapeutic Drug Monitoring of Antiepileptic Drugs in Marmara University Hospital: A Three-Year Follow-Up". *Pharmacology Online* 2 (2006): 22-32.

20. Garg SK., *et al*. "Therapeutic Drug Monitoring of Antiepileptic Drugs - A Preliminary Experience". *Indian Journal of Pharmacology* 32 (2000): 28-30.

21. Lertsinudom S., *et al*. "Integrated Epilepsy Research Group. Therapeutic drug monitoring in epilepsy clinic: a multi-disciplinary approach". *Neurology International* 6 (2014): 83-85.

22. Dahiya K., *et al*. "Therapeutic drug monitoring for antiepileptic drugs using HPLC: An experience at a tertiary care hospital in India". *Neurology Asia* 15 (2010): 233 - 237.

23. Taur SR., *et al*. "An Audit of Therapeutic Drug Monitoring Services of Anticonvulsants at a Tertiary Care Hospital in India". *Therapeutic Drug Monitoring* 35 (2013): 183-187.

24. Harivenkatesh N., *et al.* "Therapeutic Drug Monitoring of Antiepileptic Drugs in a Tertiary Care Hospital in India". *Clinical Neuropharmacology* 38 (2015): 1-5.

25. Sharpe PC., *et al.* "An audit of therapeutic drug monitoring of anticonvulsants". *The Ulster Medical Journal* 64 (1995): 151-156.

26. Radeef MY., *et al.* "Therapeutic Drug Monitoring and Evaluation of Therapeutic Effectiveness and Adverse Effects of Antiepileptic Drugs in Iraqi Epileptic Patients". *Global Journal of Medical Research* 12 (2012): 10-34.

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