Research Article

Readdressing the role of therapeutic drug monitoring for antiepileptic drugs – A tertiary care hospital experience

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Abstract

Background: Therapeutic drug monitoring is a beneficial tool to supervise patients when they do not respond to a therapeutic dose. Inter individual variability in the concentration of an antiepileptic drug that produces optimal therapeutic response is highly significant. Therefore, this retrospective study was taken up to study the inter relation between antiepileptic drug dosages, serum concentration sand clinical condition in the Indian patients. **Materials and Methods:** This is a retrospective study, in which the data of the samples of adult patients of either gender, analyzed for Phenytoin, Valproate, Carbamazepine and Phenobarbitone were included. The samples were stratified based on dosage prescribed. The endpoints were to estimate the percentage of samples of each stratum having sub therapeutic, therapeutic and supra therapeutic concentrations. **Results:** Of the 134 samples included, 114 (85%) were analyzed for phenytoin, 9 for valproate, 7 for carbamazepine and 4 for phenobarbitone. Of the 114 samples analyzed for phenytoin, 61(53.5%) samples were having sub therapeutic concentrations, 22 samples (19.3%) had therapeutic concentrations and 31 samples (27.2%) had toxic concentrations. Among the 61 samples having sub therapeutic concentrations, 54.1% were prescribed dose of 300-350mg/day, 16.4% were on 350-400 mg/day and 1.6% were taking above 400mg/day. Of the total cases referred, 41.8 % had H/O of seizures and 30.6% presented with toxic symptoms. **Conclusion:** This study demonstrated unpredictable inter individual variability in clinical response based on reference ranges. However, the relevance of individual reference concentrations for predicting outcomes can only be confirmed through adequately controlled randomized studies.

Key words: Therapeutic drug monitoring, individual reference concentrations, Antiepileptic drugs.

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Background

Therapeutic drug monitoring (TDM) is a beneficial tool to supervise patients when they do not respond to a therapeutic dose. Drug levels in biological fluids are used to optimize patient's clinical outcome by altering medication regimen. TDM was initiated for a number of antiepileptic drugs and used in prescribing optimal therapy regimens [1].

TDM in antiepileptic drug (AED) therapy is indicated in the following situations (i) suspected drug toxicity (ii) no response to therapeutic dose (iii) need for assessment of therapy after a change in dosage regimen (iv) change in clinical state of patient v) drug interactions are anticipated (vi) assessment of compliance and (vii) when signs of drug toxicity and progression of disease appear similar [2].

In 1960 Buchtal et al reported a close correlation between serum phenytoin levels, electroencephalographic findings, and clinical status and suggested to adjust dosage to attain a "therapeutic level." Physicians enthusiastically received the concept and by 1975, most authorities believed that

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pharmacokinetic factors explained individual differences in drug response [3].

Generally optimization of therapy in newly diagnosed patients involves prescription of a single drug at therapeutic dose and does not need gradual dose escalation, but some AED' smay require a gradual increase in dosage to minimize toxicity [1].

Inter individual pharmacokinetic and pharmacodynamic variability in the concentration of an AED that produces optimal therapeutic response is highly significant, AED blood levels in a patient who is controlled, may be well above or below the standard therapeutic range without any adverse effects. Conversely, clinically significant toxic adverse effects may develop at sub therapeutic and therapeutic concentrations [4].

So, AED therapy can be best guided by identification of the "individual therapeutic concentration", which is defined as the concentration (or range of concentrations), which has found to have optimal response in the individual patient [1].

Taking into view all these concepts regarding TDM and as these concepts are based on data from other countries, this retrospective study was taken up to study the interrelation between antiepileptic drug dosages, serum drug concentrations and clinical condition in the Indian patients.

Methods

This study was done in compliance with Good Clinical Practice guidelines. This is a retrospective study in which TDM data of samples analyzed for antiepileptic drugs was collected for a period of three years from records maintained at Dept of Clinical Pharmacology & Therapeutics. Demographic details, clinical information and serum concentrations of antiepileptic drugs were recorded.

The samples of adult patients of either gender, with complete demographic and relevant clinical information, analyzed for the antiepileptic drugs, Phenytoin, Valproate, Carbamazepine and Phenobarbitone were included in the study. The samples of patients on combination therapy and for whom AED were prescribed for indications other than seizures were excluded.

All the samples of patients analyzed for routine monitoring were collected for estimation of trough levels at steady state. Those analyzed for emergency purposes were collected for estimation of peak levels.

The samples were stratified based on dosage prescribed as follows:

1. Phenytoin dosages were analyzed by dividing into four groups: below 300mg/day; 300-350mg/day; 350-400 mg/day and above 400 mg/day.
2. Valproate into three groups, below 750 mg/day; 750-1250 mg/day; above 1250 mg/day.

3. Carbamazepine into three groups, below 600 mg/day; 600-1200 mg/day; 1200-1800 mg/day.

4. Phenobarbitone into two groups, 60-120 mg/day & 120-180 mg/day.

The reference ranges of serum drug concentrations were, for Phenytoin -10 - 20 µg/ml; Valproate- 50 -100 µg/ml; Carbamazepine- 4 -12 µg/ml and Phenobarbitone - 15 - 25 µg/ml. Concentrations that are below the lower limit of reference range were considered as sub therapeutic, those in the reference range considered as therapeutic and above the upper limit of reference range as supra therapeutic.

The objective was to study the inter relation between antiepileptic drug dosages, serum drug concentrations and clinical condition of the patients. The endpoints were to estimate the percentage of samples having sub therapeutic concentrations, therapeutic concentrations and supra therapeutic concentrations. Across all the three concentration ranges, estimation of the percentage of samples in each dose group and the percentage of the samples with H/O seizures or adverse effects.

Results

Total number of samples analyzed was 290, of which data of 134 samples was included whereas data of rest of the 156 samples were excluded, as they did not meet eligibility criteria.

Of the 134 samples included, 114 (85%) were analyzed for phenytoin, 9 for valproate, 7 for carbamazepine and 4 for phenobarbitone.

The characteristics of the patients whose samples were analyzed are tabulated in Table No 1.

Patient Characteristics	**Number (%)**
Total number of samples	134
Males	87 (64.9%)
Females	47 (35.1%)
Reported seizures in last 3 months	56 (41.8%)
Reported toxic symptoms	41 (30.6%)
Sent for Routine monitoring	93 (69.4%)
Sent for Emergency reasons	41 (30.6%)

Ninety two (92) samples were analyzed using HPLC (Shimadzu) and forty two (42) samples by FPIA (Axsym). Cross validation was done between the two methods.

Of the 114 samples analyzed for phenytoin, 61(53.5%) samples were found to have sub therapeutic concentrations, 22 samples (19.3%) had therapeutic concentrations and 31 samples (27.2%) had toxic concentrations.

Analysis of 61 samples having sub therapeutic concentrations of phenytoin:
Concentrations vs. Dosage details: Of the 61 samples, 54.1% were on 300-350mg/day, 16.4 % on 350-400 mg/day and 1.6% were on above 400mg/day.

Concentrations, Efficacy vs. Dosage details: In the samples, 52.4% of cases referred had H/O of seizures, of which only 25% of patients were on below 300mg/day rest of the patients were on either optimal dose or higher dose.

Concentration, Toxicity vs. Dosage details: In the samples, 24.6% of cases referred had presented with toxic symptoms, of which only 6.7% on higher dose, 350-400 mg/day.

Analysis of 22 samples having therapeutic concentrations of phenytoin:
Concentrations vs. Dosage details: Among the 22 samples, 54.5% on 300-350mg/day and 31.9% on 350-400 mg/day. Rest of them were on either less than 300mg/day or more than 400 mg/day.

Concentrations, Efficacy vs. Dosage details: In the samples, 50% of cases referred had H/O of seizures, of which only 9.1% of patients were on below 300mg/day.

Concentration, Toxicity vs. Dosage details: In the samples with therapeutic concentrations, 31.8% of cases had presented with toxic symptoms, none of the patients were on more than 400mg/day. But they were on either 300-350 mg/day or 350-400 mg/day.

Analysis of 31 samples having toxic concentrations of phenytoin:
Concentrations vs. Dosage details: Among the 31 samples, 16.1% of samples were prescribed a dose below 300mg/day and16.1% on 350-400 mg/day.

Concentrations, Efficacy vs. Dosage details: In the samples, 41.9% of cases referred had H/O of seizures, of which only 7.7% of patients were on below 300mg/day, rest of them were on either on 300-350mg/day or 350-400mg/day.

Concentration, Toxicity vs. Dosage details: In the samples, 61.3% of cases referred had presented with toxic symptoms, of which 15.8% were prescribed a dose of below 300mg/day, rest were on 300-350 mg/day or 350-400 mg/day but none of them received more than 400mg/day.

Dosage range wise distribution of sub therapeutic, therapeutic and toxic concentrations of phenytoin in the samples has been depicted in Fig No.1. A pie diagram representation of percentage of samples, which were referred with H/O seizures

across different concentrations, and percentage of samples, which were referred with adverse effects across different concentrations, is made in Fig No. 2.

Patients on phenytoin, reported sixty-three adverse events. The most common adverse effect reported was drowsiness by 19 patients, followed by ataxia by 14 and headache by 13 patients as shown in the Fig No 3.

Figure No. 1 depicting dosage range wise distribution of sub therapeutic, therapeutic and toxic concentrations of phenytoin.

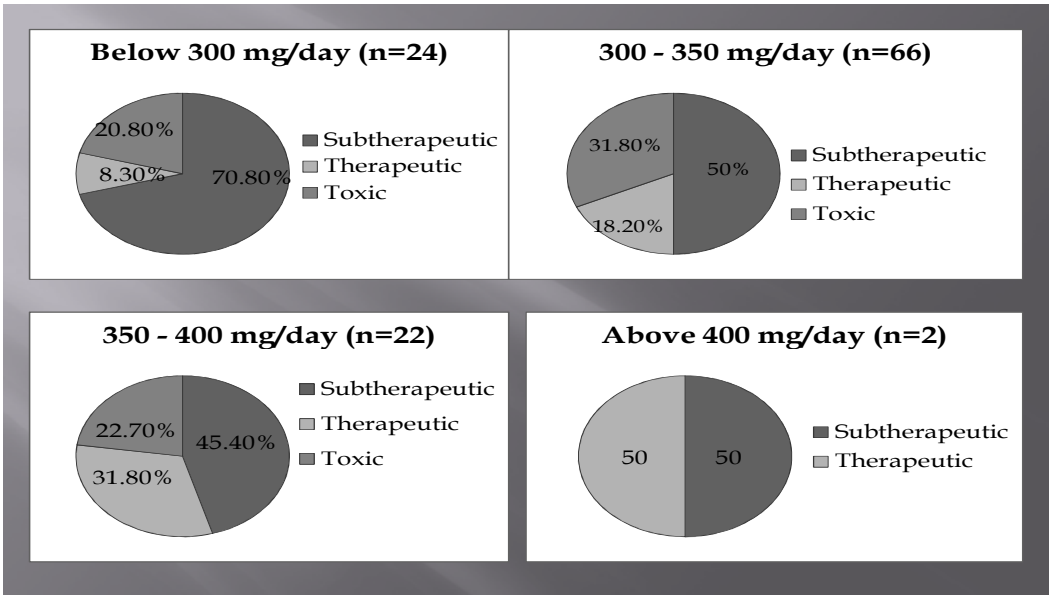


Figure No 2. depicting percentage of samples with H/O seizures across different concentrations and percentage of samples with adverse effects across different concentrations of phenytoin.

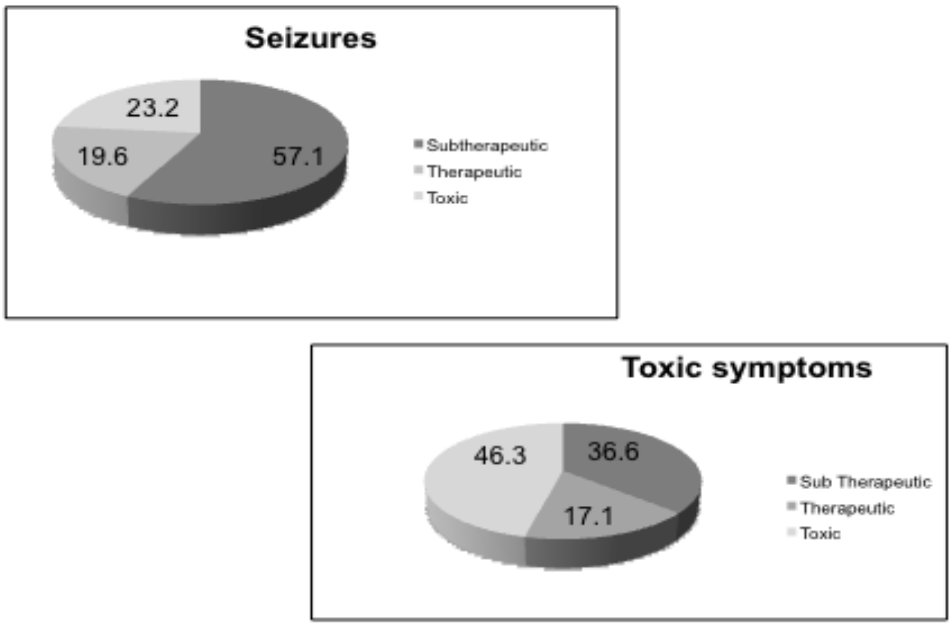
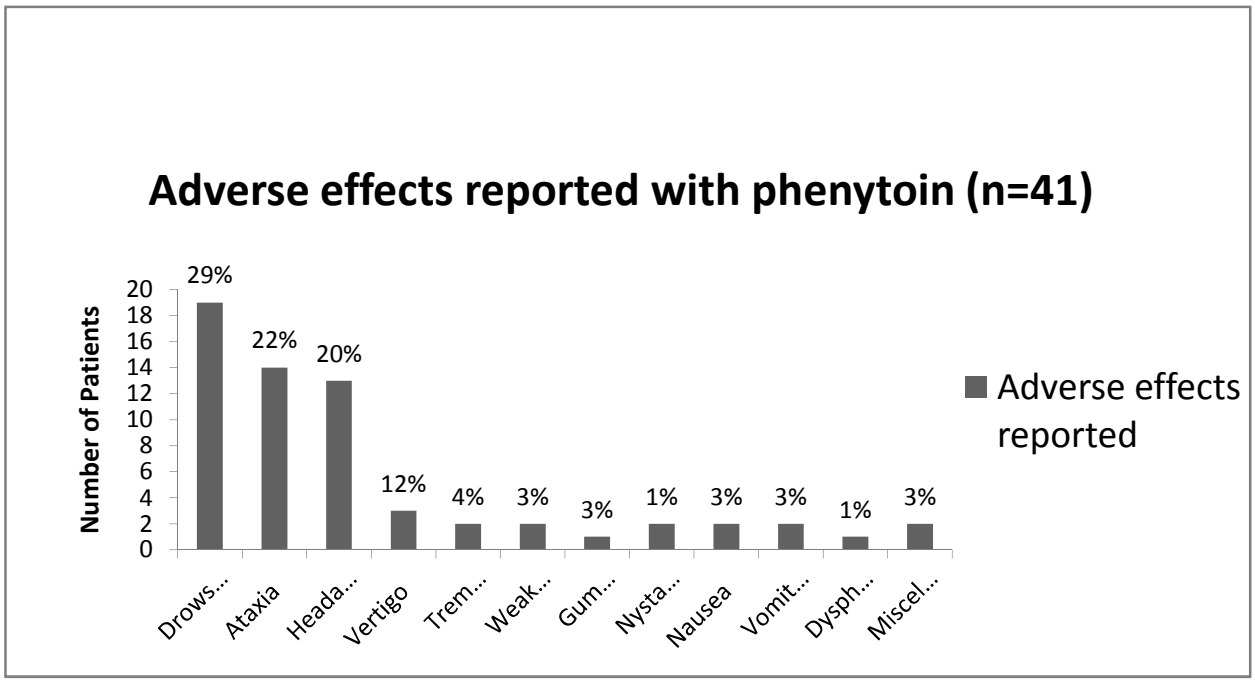


Figure No. 3 depicts adverse effects reported with phenytoin.



The concentrations vs dosage details of the samples analyzed for antiepileptic drugs valproate, carbamazepine and phenobarbitone are presented in Table No 2.

Table No: 2 shows the concentrations vs dosage details of the samples analyzed for valproate, carbamazepine and phenobarbitone.

S. No	Antiepileptic Drug	Total No. of samples	Concentration range	Dosage prescribed
1	Valproate	9	Sub therapeutic	Below 750 mg/day 750-1250 mg/day 1250-2000mg/day
			Therapeutic	750-1250 mg/day
2	Carbamazepine	7	Therapeutic	Below 600mg/day 600-1200mg/day 1200-1800 mg/day
3	Phenobarbitone	4	Sub therapeutic	60-120 mg/day
			Therapeutic	60-120 mg/day 120-180 mg/day

As the number of samples analyzed for valproate, carbamazepine and phenolbarbitone were meager, further analysis with respect to H/O seizure and adverse effects was not done.

Discussion

Generally, from the TDM reports if one finds any medication in sub therapeutic range, it is suspected that the patient might be on a sub therapeutic dose and that the patient might have presented with seizures and one will never expect that the case will present with adverse effects/toxicity, but in our study it was observed that a proportion of samples with sub therapeutic concentrations were on optimal dose and there were cases which did not report seizures and surprisingly a proportion of cases presented with toxic symptoms

which are in contrary to this general trend. Similar contrary findings were found with samples in therapeutic range and those with toxic range.

Similar findings were seen in a retrospective analysis of Veterans Administration Cooperative Study conducted to examine the relationship between serum phenytoin concentration (SPC) and various measures of patient response, no statistically significant association was noted between SPC and any of the response measures. The study suggested that the range of SPC values in successfully treated patients is quite broad; and the value of the commonly accepted SPC therapeutic range in predicting various measures of patient response is quite limited. Therefore, patient response should be the ultimate end point in monitoring patients on phenytoin [3]. In a study done by Schumacher, it was reported that there was no correlation between phenytoin levels and seizure control or adverse effects [5].

In an article by EranKozer et al., the authors opined that some patients receiving phenytoin may achieve seizure control with sub therapeutic levels, and others may need supra therapeutic levels [6]. In a study, Froscher reported that measuring levels did not improve patient outcome [3].

In a prospective study done by Babaei and Eslamai in Iranian epileptic patients, they observed that seizure control in patients with serum phenytoin concentration in the therapeutic range was the same as that in patients with serum concentration below the therapeutic range [7].

In a prospective study done by Forooghipour et al., to evaluate the possible relationship between serum levels and the clinical response of valproic acid, they observed that in 33% of patient's plasma levels were within the therapeutic range and in 67% they were in sub therapeutic range. Of the patients with sub-therapeutic levels, 75% achieved complete control[8].

A prospective study of AED blood level monitoring with older AEDs found no difference in outcomes of reported seizure control or adverse effects between patients randomized to AED adjustment by clinical practice, or those who received AED therapy directed to achieve target blood levels [4].

In a study done in India by, Garg et al., to assess the utility of TDM in management of the epileptic patients, a necessary action in terms of dose adjustment was initiated in most of the cases. As knowledge of plasma levels of phenytoin and carbamazepine was put to use for better management of epileptic patients, authors concluded that the study revealed the wide inter patient variation of plasma drug levels and the usefulness of carrying out TDM [9].

In a open label, prospective study done by G. Jannuzzi et al., to assess the clinical impact of TDM in patients with epilepsy, in one group, dosage was adjusted to achieve serum AED concentration whereas in the other group, dosage was adjusted on clinical grounds. There was no significant difference between the monitored group and the control group in achieving 12-month remission (60% vs. 61 %). Frequency of adverse effects did not differ between the groups. Authors concluded that early implementation of TDM did not improve therapeutic outcome, and the majority of patients could be satisfactorily treated by adjusting dose on clinical grounds [10].

In another study done in India by Kiran Dahiyaet al. it was observed that, of the samples of 100 patients on phenytoin who were having good seizure control and no adverse effects, 46% were found to be in therapeutic range, 31%were in sub therapeutic range and 23% were found to be in toxic range. Authors felt it was difficult to speculate on the reason behind this good response and role of dosage adjustment to attain the levels in the therapeutic range even when epilepsy is well controlled is still controversial [11].

According to best practice guidelines for therapeutic drug monitoring, the "reference range" can be defined as a range of drug concentrations, which is quoted by a laboratory. Clinicians using reference ranges should remember that, many patients can achieve therapeutic benefit at serum drug concentrations outside these ranges and defined therapeutic range as the range of drug concentrations which are associated with the best achievable response in a given person, so can only be determined on the individual basis [1].

Though it is well accepted that TDM plays a vital role in management of epileptic patients, there is still confusion with reference range concept. In this study unpredictable inter individual variability in clinical response based on reference ranges was observed.

Therefore, it was recommended that dosage should not be modified in patients who achieved good clinical response at serum drug concentrations either below the

lower limit of the reference range or above this range [1].

Our study results are in agreement with the above recommendation, and this study highlights the concept of utilization of 'individual reference concentration' based on intra-individual changes in serum drug concentrations as stated in the review article by Johannessenand Tomson [12].

The "individual reference concentration" concept can help clinical management. Specht*etal.* in a study, found that serum AED levels measured shortly after a breakthrough seizure in 52 patients treated with carbamazepine, valproic acid orlamotrigine, were, in 44% of the cases, less than one-half the "individual reference concentration" measured in each patient during periods of good seizure control [13].

The Cochrane review done by Tomson et al., in 2007 demonstrated the lack of relevant randomized studies assessing the impact of therapeutic drug monitoring to optimize the drug treatment of newly diagnosed epilepsy [14]. However, the relevance of individual therapeutic concentration in predicting clinical outcomes in epileptic patients can only be confirmed by conducting adequately powered studies in this regard.

Conclusion

In this retrospective study, some of the patients on phenytoin whose samples had sub therapeutic concentrations have presented with toxic symptoms, some of those whose samples had therapeutic concentrations have presented either with H/O seizure or toxic symptoms and some in whom concentrations were supra therapeutic, presented with H/O seizure, demonstrating unpredictable inter individual variability in clinical response based on reference ranges in Indian patients. Therefore, this study emphasizes the utilization of individual reference concentration. However, the relevance of individual reference concentration for predicting outcomes can only be confirmed through adequately controlled randomized studies.

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Permission of IRB: Yes

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