

Analysis of phenytoin drug concentration for evaluation of clinical response, uncontrolled seizures and toxicity

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Abstract: The narrow therapeutic index, non-linear pharmacokinetics and unpredictable absorption require regular therapeutic monitoring of phenytoin. The influence of genetic differences, sex, age and race on the phenytoin plasma levels and its metabolites is well recognized. This study is aimed at evaluating phenytoin plasma drug concentration and its relationship with clinical response, persistent seizures and toxicity in different gender and various age groups of Chinese epileptic patients. This knowledge will help the clinicians in adjusting the drug dosages of phenytoin in various sub-groups of epileptic patients for enhancing the safety, efficacy and minimizing the toxicity of phenytoin. A total of 48 plasma samples of epileptic patients for measuring the plasma phenytoin concentration were received. Only patients displaying persistent seizures or suspected of adverse effects were requested for drug monitoring. All these samples were analyzed for therapeutic drug monitoring with Enzyme-multiplied immunoassay technique. Surprisingly, it was found that majorities (85.5%) of samples were out of the reference range, of which 69% of samples were in sub-therapeutic levels and 16.5% of samples were above therapeutic levels. Only 14.5% of all samples had phenytoin levels in the therapeutic range. The difference in plasma concentration of phenytoin was notably altered in gender and various age groups. Careful attention must be applied to specific gender and particular age group on an individual basis in the interpretation of plasma concentration results, in order to facilitate the modification of doses and develop the best approach in treatment and to obtain the desired clinical response because multiple factors can affect the phenytoin plasma concentration. Through these results, it can be concluded that a good correlation exists between phenytoin plasma concentration and clinical response. Therefore, regular therapeutic monitoring of phenytoin and screening of HLA-A, B, C and DRB1 genotypes before prescribing phenytoin in epileptic patients is essentially required to achieve maximum clinical response and prevent the serious toxicity.

Keywords: Analysis, clinical response, phenytoin, toxicity.

INTRODUCTION

Phenytoin (PHT) is chemically known as 5, 5-diphenylhydantoin. Phenytoin is an antiepileptic drug having large inter-individual inconsistency in metabolism. PHT has a narrow therapeutic range (10-20µg/ml) and thus plasma concentrations below 10µg/ml could produce sub-optimal therapeutic effect and levels above 20µg/ml may result in its toxicity (Thaker *et al.*, 2017). It has been noted that only in a narrow window of plasma concentration, phenytoin is mostly found safe and efficient. Keeping the plasma levels of phenytoin in therapeutic range optimizes the efficacy and minimizes the deadly toxicity in majority of the individuals. The blood plasma concentration of phenytoin corresponds better with pharmacological action than the dosage due to the individual's alteration in metabolism, comorbidities, absorption, polytherapy, and compliance. Monitoring of the serum concentration of phenytoin aids physicians to provide rational treatment (Sivasankari *et al.*, 2012). The plasma drug concentration quantification and interpretation can be beneficial in the management of seizures which are not controlled and in suspected cases

of toxic effects; the adjustment for inconstant or nonlinear pharmacokinetics, individual therapy and correction of doses in particular cases like pregnancy, children or elderly can be assisted with therapeutic drug monitoring (TDM) (Jacob and Nair, 2016). Distinguishing the capacity among inadequate seizures controls due to insufficient dosing or overdose is important. Pharmacologists and physicians have for a long time been trying to understand why the same dose works in some patients but not in others. It has been noted generally within a reference range of plasma concentrations, the therapeutic effect of most of the antiepileptic drugs accomplished; while too low concentrations are more likely to produce an inadequate effect, too high plasma concentrations are commonly related to serious side effects. Therapeutic drug monitoring (TDM) helps us to evaluate non-compliance and variation in pharmacokinetics which arises among and between the individuals and the elements accountable for these type of variation can be examined (Patsalos *et al.*, 2008). Therapeutic drug monitoring is a harmless and efficient way of a therapeutic regimen for patients (Sivasankari *et al.*, 2012). The present study is a quantification of phenytoin plasma concentration for identifying their

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possible relationship with clinical response, uncontrolled seizures and toxicity in different gender and age groups of epileptic patients.

MATERIALS AND METHODS

The Neurologists in the Neurology Department of Qilu Hospital advised 48 epileptic patients to do routine therapeutic drug monitoring of phenytoin. Only patients displaying uncontrolled seizures, suspected of adverse effects or overdose were counseled for therapeutic drug monitoring of PHT. We performed TDM with Enzyme-multiplied immunoassay technique (EMIT) assay.

Blood sampling

The samples of blood from epileptic patients that were receiving PHT were drawn at Qilu Hospital of Shandong University. The protocol of this study was approved by the ethics committee of Shandong University Jinan China and this work was performed with the agreement of Declaration of Helsinki (2013). The therapeutic drug monitoring results of PHT plasma levels of all patients were compiled in Microsoft Excel and data was recorded and evaluated by a registered pharmacist using Excel and SPSS. The results were further characterized as per plasma concentrations levels of PHT into (Sub therapeutic range, therapeutic range, and toxic range). The samples of female patients were (25) and samples of male patients were (23).

RESULTS

In our study, majority of samples (85.5%) were out of reference range. Only 14.5% of Chinese patients taking PHT had the drug in therapeutic level. The plasma PHT levels were found in sub-therapeutic level in 69% of patients and 16.5% samples found in toxic levels. Females had 92% of samples in out of therapeutic range while males had 78% samples in out of therapeutic range. The females also had high number (72%) of samples in sub-therapeutic range while males had (65 %) samples in sub-therapeutic range. As compared to adults both male and female children had an increased number of samples within sub-therapeutic levels.

DISCUSSION

The samples of PHT users of 48 epileptic patients displaying uncontrolled seizures or toxicity have been received. Plasma concentrations of phenytoin were quantified with EMIT assay in all these patients for identifying their possible relationship with clinical response, uncontrolled seizures, and toxicity in different gender and age groups of epileptic patients. Kutt and his coworkers (Kutt *et al.*, 1964) suggest that TDM is valuable but no study has evaluated at what plasma concentration of PHT, ataxia or nystagmus occur in

children are lower, higher or same. TDM helps in optimizing the patient outcome by dealing their medication regimen with the support of result of plasma concentration (Patsalos *et al.*, 2008). Numerous drugs influence plasma concentrations of phenytoin, various interactions of drugs with phenytoin are clinically significant (Patsalos and Perucca, 2003). Our results of samples in therapeutic levels were lower than Shakya and his coworkers (Shakya *et al.*, 2008) who reported 38.8% patients having concentration levels of PHT in therapeutic levels. Our results of sub-therapeutic levels were in agreement with Davis and his team workers (Davis *et al.*, 1976), who found a sub-therapeutic level in 65% of patients. Shakya *et al* reported that (38.8% and 28.4%) specimens were in sub-therapeutic levels (below therapeutic range) and toxic levels (above therapeutic range) respectively. Results of concentration levels of phenytoin in all patients including both genders and various age groups are presented in table 1. Compared to males and compared to adult patients, females and children patient samples had an increased number of out of reference range.

Houghton *et al* (Houghton *et al.*, 1975) and Travers *et al* (Travers *et al.*, 1972) also reported that compared to males, females had low phenytoin concentration levels. Houghton *et al* also stated that phenytoin concentration and age are positively correlated. Eadie *et al* (Eadie *et al.*, 1973) did not find any difference in children or adults. Lai ML (Lai, 1985) conducted a study in a Chinese population in Taiwan and stated that steady-state plasma level of phenytoin is not affected by the age and sex or use of phenobarbital in combination in Chinese patients. He stated that the important causative factor affecting phenytoin concentration is the dosage. Davis *et al* stated that sub-therapeutic levels were due to inadequate dosage. We speculate that uncontrolled seizures or toxicity and unfavorable clinical response in most of these patients may be most probably because of out of therapeutic range of phenytoin. The difference in plasma concentration of phenytoin is also remarkably altered in gender and different age groups. This difference may be due to many factors such as genetic factors, inter- and intra-individual variations in pharmacokinetics parameters, pathological conditions, pharmacokinetics interactions and special conditions such as pregnancy and age-related body response to the drugs. Genetic polymorphisms in cytochrome P450 (CYP) 2C9 and CYP2C19 are predictable to play a vital role in influencing the phenytoin concentration.

We also speculate that pregnancy may be a contributing factor which can cause the differences in weight, changing plasma constituents, hemodynamic variations, hormonal factors, and contribution of the fetoplacental unit to drug distribution and disposition resulting in a decrease in total concentration of phenytoin. Children and

Table 1: Phenytoin plasma concentration levels in all patients

Groups	Therapeutic Range N (%)		Sub-therapeutic Range N (%)		Toxic Range N (%)		Total no of samples	
	Males	Females	Males	Females	Males	Females	Males	Females
Children	0 (0)	0 (0)	5 (100)	8 (100)	0 (0)	0 (0)	5	8
Adults	5 (28)	2 (12)	10 (55)	10 (59)	3 (17)	5 (29)	18	17
Total	5 (22)	2 (8)	15 (65)	18 (72)	3 (13)	5 (20)	23	25

infants are unique groups because of the rapid metabolic rate and rapid elimination time and larger volume of distribution values which may cause the sub-therapeutic levels. Poor compliance, use of inappropriate dose by patients themselves, co-medication of enzyme-inducing drugs may also alter the concentration of phenytoin. The rational reason for starting low doses of phenytoin in Chinese epileptic patients is that because there are many reports published on toxic effects associated with iatrogenic phenytoin toxicity (Sivathanu *et al.*, 2014). Toxic epidermal necrolysis and Stevens-Johnson syndrome are toxic adverse effects also frequently reported with phenytoin-induced toxicity (Schneider and Cohen, 2017; Sweileh, 2017; Thong, 2013). One new study currently published that HLA-A*24:02 is an often genetic risk factor for cutaneous adverse reactions caused by aromatic antiepileptic drugs including phenytoin in the southern Han Chinese and probably in other ethnic populations (Shi *et al.*, 2017). A strong link also reported between HLA-B*15:02 and phenytoin induced Stevens-Johnson syndrome in Chinese patients (Shi *et al.*, 2017). In another study, it is reported that HLA-B*1301, HLA-B*1502, Cw*0801 and DRB1*1602 showed a link with phenytoin-induced Stevens-Johnson syndrome/ Toxic epidermal necrolysis in Chinese patients (Hung *et al.*, 2010). Recently it is reported that CYP2C9 and CYP2C19 polymorphisms are related to lower phenytoin maintenance dosage in Asian epileptic patients. Ethnic variations can affect phenytoin maintenance dosage. However, dosage adjustment is necessary (Liao *et al.*, 2018). One of the ways of improving the compliance can be restricting these patients to take a limited number of appropriate daily doses and besides that, all patients' especially non-compliant patients should be regularly monitored for PHT plasma concentrations to ensure that these patients are observing full compliance. Very low phenytoin concentration may not produce an adequate effect and very high concentration may produce harmful toxic effects. The narrow therapeutic index of phenytoin, the unpredictable link between dose and concentration of phenytoin concentration and noteworthy clinical drug interactions support the need of therapeutic drug monitoring in epileptic patients to individualize and sustain therapy. Most probably the reason for some of the samples within toxic range was an increased dose by patients themselves because they feel that their uncontrolled seizures can be controlled by an increased dose of phenytoin. Quantifying plasma concentrations are very helpful. Results of very low concentration may be

due to poor recent compliance or insufficient dose. Poor compliance is suspected when recommended dose to the patient is not related to the measured low concentrations or earlier concentration levels that guide the plasma concentration levels and should be greater for the certain dose (Kang and Lee, 2009). Because of alterations in the metabolism of the drug, and genetic differences, there is a poor association between dose of phenytoin and concentration, especially in patients who also use other antiepileptic drugs. TDM may deliver significant evidence for modifications of doses in most of antiepileptics patients with unforeseen treatment outcomes or in circumstances related with pharmacokinetic variations, such as in different disease states, in pregnancy, in combination with drug interactions and in particular age groups (children and the elderly) in which evaluation of clinical outcome is very hard.

CONCLUSION

Phenytoin plasma concentration results in most of the patients displaying persistent seizures or toxicity were out of reference range. We speculate that persistent seizures or toxicity and unfavorable clinical response in most of these patients may be most probably because of out of therapeutic range of phenytoin. As mentioned above, there could be so many factors which may cause the out of therapeutic range of phenytoin. However, this requires further evaluation. Vigilant care must be applied to specific gender and particular age group on an individual basis in the interpretation of plasma concentration results, in order to facilitate the modification of doses and develop the best approach in treatment and to obtain the desired clinical response because multiple factors can affect the phenytoin plasma concentration. TDM is also useful in order to assess the compliance, optimize the safety, efficacy, clinical outcome and minimize the toxicity. The present findings are very helpful for neurologists and as well as epileptic patients especially in adjusting the daily dosages for maximizing the efficacy, safety and minimizing the toxicity of phenytoin. It is suggested that regular monitoring of plasma phenytoin should be performed in order to get desired clinical response.

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