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Original Research Article

VARIABILITY OF PHENYTOIN INDUCED GUM HYPERPLASIA IN PATIENTS OF EPILEPSY IN A TERTIARY CARE: THERAPEUTIC DRUG MONITORING OF PHENYTOIN NEEDS VERSATILE AND SPECIFIC METHODOLOGY

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Abstract:
Phenytoin is still used as the first choice in epilepsy. It is a well studied drug and due to its ADRs and side effects, TDM is a well defined technique, used in tertiary care centers. It optimizes dosage regimens in patients on phenytoin as it has a narrow therapeutic window. Its use needs vigilance as it has many drug-drug interactions, CNS side effects and gum hyperplasia. Serum drug concentrations guides us that the therapeutic levels be maintained during the course of treatment. Its therapeutic range is 10-20 micrograms/ml. Study was carried in tertiary centre where Neurology department is well established. A total of 1450 patients were enrolled in the study in 5 years period. Patients of (21-30)years of age group attend maximally, maximum gum hyperplasia was in this age group who were in therapeutic range of phenytoin and patients in the study were taking equal doses in equal intervals of time. Patients had variable response in gum hyperplasia and it was a retrospective study. Serum concentration was estimated by EMIT System. Out of 1450 patients, only 190 (13.1%) patients developed gum hyperplasia in heterogeneous population viz therapeutic, subtherapeutic or toxic groups. Therapeutic drug monitoring of phenytoin is carried out to ensure effective and safe levels.

Keywords: Gum hyperplasia, Therapeutic Drug Monitoring, Enzyme Multiplied Immuno Technique, Therapeutic range

Introduction:

Control of seizures is generally obtained at the total concentration above 10 microgram/ml, while toxic effects like nystagmus develop at concentration around 20 microgram/ml [1]. Gingival enlargement has been described as the most frequent adverse effects associated with long term Phenytoin therapy. Drug induced gingival enlargement (DIGE) associated with chronic use of anti-epileptic drug Phenytoin was first reported in 1939 by Kimball [2]. Fifty four outpatients with epilepsy who had been taking Phenytoin for more than one year

were examined for gingival hyperplasia. Approximately 76% of patients showed either mild or no gingival hyperplasia. The duration of Phenytoin is main factor to get the hyperplasia. A free level of Phenytoin estimation is very important in this regard. Carbamezepine can be considered a safe drug in the children to gingival overgrowth. Sodium valproate has the potential to cause gingival overgrowth in a significant level. It is recommended that newer drugs may be evaluated for gingival hyperplasia in children [3]. There are conflicting reports regarding incidence of Phenytoin induced gingival hyperplasia. a study estimated that about 30-50% of the patients taking Phenytoin develop significant gingival alteration [4]. It is postulated that PHT is a Folic acid antagonist, interfere with normal metabolism of these tissues and may decrease PHT metabolite production although not active metabolites. It was postulated that administration of folic acid with PHT to cats, markedly decreased the occurrences of PIGO (PHT induced gingival overgrowth) when to a group administered PHT alone [5].

The reported incidence of gingival overgrowth varies widely from 0-100 percent and these variations can be attributed in part too medically versus dentally trained personal and indicates of overgrowth. Clinically significant overgrowth is estimated to occur in half of the patients taking PHT. However, the most recent study found clinically significant overgrowth in only 13% of epileptic patients in a general medical practice [6]. While it is observed that some minimal concentration (or dose) of PHT is required to cause gingival overgrowth. The incidence and severity do not appears to be directly related to the pharmacodynamics of the drug. Even sub therapeutic serum levels of PHT have been associated with gingival overgrowth [7]. The situation is further complicated as many patients receive more than one anti-convulsant drug and this usually alters the pharmacodynamics of PHT making elucidation of dosages more complex. There are conflicting results with regards to the relationship between severity of overgrowth and daily dose. Some authors related this to a positive correlation [8]. Most theories of pathogenesis of developing gingival enlargement have centered on the gingival fibroblast and its interaction with Phenytoin and its metabolites [9]. Despite the tremendous advances in the management of epilepsy in the recent decades, the anti-epileptic drug Phenytoin still remains the prime drug of choice in the management of epileptic patients in India. Gingival enlargement is the most often reported adverse drug consequences of long term Phenytoin usage [10]. Numerous reported suggested that Phenytoin gingival enlargement is more commonly seen in the younger age group. This is in coordination with the observation of several epidemiological studies. Also, both genders have been reported to be equally susceptible to Phenytoin induced gingival enlargement [11].

Currently more than 15 drugs have been identified as possible causative agents, including oral contraceptives. However, there are 3 classes of drugs that are well established causes of gingival enlargement being responsible for most cases viz anti-epileptic, anti-hypertensive, calcium antagonist and immunosuppressant cyclosporine. One property that is common to these three classes of drugs is that they all directly affects cellular calcium metabolism. Since cellular production of collagenase is modulated by calcium influx. Fibroblasts from patients treated with these drugs may produce an inactive form of collagenase being responsible for an increase in extra-cellular matrix [11]. Dose dependent correlations with the severity of gingival overgrowth are weak, but decreased drug use in general results in reduced severity of gingival pathology. Phenytoin was reported to effuse into cervicular fluid without any

correlation to the incidence of overgrowth. While, no direct link was shown between overgrowth and concentration of Phenytoin and its metabolites. A more recent study supports a correlation between diminished metabolites of Phenytoin in affected individuals and overgrowth but this has not been confirmed.

Age gender concomittent medications with multi-drugs, local factors such as plaque accumulation and genetic disposition are additional complicating risk factors in drug induced gingival overgrowth. There is a high incidence and increase severity of gingival enlargement in epileptic patients on Phenytoin therapy. There is the positive correlation between gingival enlargement and average serum level before and after Phenytoin administration. A significant drop in serum level after 6 months of Phenytoin treatment was observed [12]. High correlation between serum and salivary Phenytoin levels supports the use of saliva instead of blood for Phenytoin monitoring in the children, which were difficult to collect and had psychological trauma. Salivary levels could be used to detect the gum hyperplasia [13]. There may be a wide interpatient variability in phenytoin serum levels with equivalent dosages. A number of Phenytoin side effects, such as gingival hyperplasia, folate deficiency and peripheral neuropathy do not appear to be directly related to serum Phenytoin concentration. Conversely CNS side effects do correlate with plasma concentration [12].

Phenytoin is still given as monotherapy in epilepsy. Approximately 60-70% of newly diagnosed patients will have their seizures controlled effectively by one AED and switching to an alternate AED will offer effective seizure control in half of the remaining 30-40% of patients. AED polytherapy may be helpful for a small population of patients. Who do not respond to monotherapy, but careful consideration should be given to the consequences of any drug interaction between the various AEDs that are co-administered. Indeed it has been estimated that in 6% of the patients experiencing AED intoxication and the drug interaction was the cause. About 50% of the patients taking Phenytoin use have been well studied. The medication develops gingival hyperplasia within 12-24 months of initiation of treatment. As PHT is the most commonly used drug.

While, it is obvious that some minimal concentration of Phenytoin is required to cause gingival outgrowth. The incidence and severity doesn't appear to be directly related to pharmacodynamics of the drug. Even sub-therapeutic serum levels of the Phenytoin have been associated with gingival outgrowth [7]. The situation is further complicated as many patients receive more than one anti-convulsant Drug and this usually alters the pharmacodynamics of Phenytoin. This makes the elucidation of the dosages more complex. There are conflicting results with regards to the relationship between severity of overgrowth and daily dose [14]. The aim and objective of the study was to determine that gum hyperplasia response of Phenytoin was variable. The estimation was carried over by simple and accurate method of EMIT SYSTEM. Levels were checked by calibration curve along with the three levels of external quality control.

Material and Methods:

A retrospective observational study was conducted in the department of Clinical Pharmacology SKIMS, Soura J&K India, a tertiary care. Patients were received from the department of Neurology on OPD/ IPD basis. Randomized levels of the patients, who were on this drug, from Jan 2008 to Dec 2012, were assessed. Only those patients were included who were on usual therapeutic doses of phenytoin for 12 months to 24 months , taking same dose with equal intervals of time. Both male and females were included from the age group of (10-70 years) Serum levels of these

phenytoin samples were analyzed by EMIT system using Semi-Automatic Analyser. The EMIT (Enzyme Multiplied Immunoassay Technique), homogeneous enzyme immunoassay is a versatile methodology designed to measure micro amounts of drugs in human biological fluid (serum). The EMIT technology is based on competition for the target analyte antibody binding sites. Analyte in the sample competes with the drug in the enzyme reagent that is labeled with G6PDH. Active enzyme G6PDH converts the co-enzyme (NAD) in the antibody reagent to NADH, resulting in a kinetic absorbance change that is measured spectrophotometrically. Calibrators 5 to 40 µg/ml, were used to validate the levels so that minimum 5 µg/ml can be also be detected taken as sensitivity of the study. Linearity was evaluated over this analytical range and lyphocheck controls of all the three levels (low, medium, high) were used to validate the method to quantitate the levels accurately.

Results:

The study was carried in the department of clinical pharmacology from January 2008 to December 2012. A total number of 1450 patients were included in the study. Maximum numbers of patients were 325 in year 2012. A total number of 808 (55.72%) were males and 642 (44.28%) were females Table 1.

Table 1: Yearly distribution of patients on Phenytoin

Year	Number of Patients	Male	Male (%age)	Female	Female (%age)
2008	230	140	60.86	90	39.14
2009	285	133	46.66	152	53.34
2010	300	180	60	120	40
2011	310	195	62.9	115	37.1
2012	325	160	49.23	165	50.77
Total	**1450**	**808**	**55.72**	**642**	**44.28**

Patients were in the age group of 10-70 years. Maximum patients comprise of 455 were from the age group of 21-30yrs i.e 31.2%. The minimum patients 34 were from the age group of 61-70 years i.e 2.3%. Table 2.

Table 2: Age wise distribution of patients on Phenytoin

Age (years)	Number (n)	Percentage of Patients (%)
10-20	**268**	**18.5**
21-30	**455**	**31.2**
31-40	**342**	**24.2**
41-50	**186**	**12.6**
51-60	**165**	**11.2**
61-70	**34**	**2.3**
Total	**1450**	**100**

Phenytoin level were categorized into three groups viz Therapeutic (10-20 µg/ml), Sub-therapeutic (≤ 20 µg/ml), Toxic (≥ 20 µg/ml). 84.41% patients were in therapeutic range, 11.65% were in Sub-therapeutic range and 3.94% patients were detected in toxic range. 162 (85.26%) patients in therapeutic range were hyperplasic, while 23 (12.10%) patients in sub therapeutic range and 5 (2.64%) patients in toxic level were detected with gum hyperplasia Table 3.

Table 3: Distribution of Phenytoin Levels With Gum Hyperplasia

Phenytoin Levels	Number (n) of Patients	Gum Hyperplasic Patients
Therapeutic (10-20 µg/ml)	1224 (84.41%)	162 (85.26%)
Sub-therapeutic (≤ 20 µg/ml)	169 (11.65%)	23 (12.10%)
Toxic (≥ 20 µg/ml)	57 (3.94%)	5 (2.64%)
Total	**1450**	**190 (13.10%)**

A total of 190 patients out of 1450 were having gum hyperplasia i.e 66 (34.74%) comprises of males and 124 (65.26%) were female. Out of total 162 therapeutic range patients 60 were males 102 were females. In sub therapeutic 18 females and 5 males (out of 23) and least in toxic level with 4 female and 1 male (out of 5 totals). Table 4.

Table 4: Distribution of Phenytoin Levels With Gender Having Gum Hyperplasia

Phenytoin Levels	Number (n) of Patients	Male	Female
Therapeutic	162	60	102
Sub-therapeutic	23	5	18
Toxic	5	1	4
Total	**190**	**66 (34.74%)**	**124 (65.26%)**

Table 5 represents the Comparative Distribution of Phenytoin Levels with Gum hyperplasic Patients. 107 patients were in the age group of 21-30years, having 93.46% therapeutic, 4.67% were sub-therapeutic and 1.87% were toxic. The least patients with gum hyperplasia belongs to the age group of 61-70years i.e 100% therapeutic, 00% were sub-therapeutic and 00% were toxic.

Table 5: Comparative Distribution Of Phenytoin Levels With Gum hyperplasic Patients

Age	Gum Hyperplasic Patients	Therapeutic level	Sub-therapeutic level	Toxic Level
10-20	**61**	**50 (81.96%)**	**10 (16.40%)**	**1 (1.64%)**
21-30	**107**	**100 (93.46%)**	**5 (4.67%)**	**2 (1.87%)**
31-40	**83**	**80 (96.35%)**	**2 (2.50%)**	**1 (1.15%)**
41-50	**26**	**20 (76.93%)**	**5 (19.23%)**	**1 (3.84%)**
51-60	**9**	**8 (88.88)**	**1 (11.12%)**	**00**
61-70	**4**	**4 (100%)**	**00**	**00**
Total	**190**	**162**	**23**	**5**

Discussion:

This study depicts that TDM monitoring keeps vigilance on maximum patients in therapeutic ranges. Dose optimization is carried out routinely so the TDM program is essential element for monitoring the serum drug concentration. Maximum numbers of patients 84.41% are in therapeutic range and least number of patients in toxic level. There is a need to increase dose in sub-therapeutic levels where as dose need to be decreased in toxic level. A vigilance program in ADR monitoring is very important in age group 21-30years with maximum gum hyperplasia. There is a total biological variation of gum hyperplasia with no clear indication that only toxic level is having gum hyperplasia. The females (102) are more prone to gum hyperplasia even in therapeutic range. They require cosmetic surgery as the remedial

measure because of social stigma. Most of the previous work suggested that Phenytoin induced gingival enlargement is most in younger age groups. This is in accordance with the present research work.

Conclusion:

Patients on chronic use of Phenytoin cannot leave out gum hyperplasia. Still measurement of plasma concentration can give us an estimate of pharmacokinetics variables so that adjustment in dose can be made and adverse events can be avoided. Adult in the age group of 21-30 yrs are at higher risk of gum hyperplasia because of development phase of life. Supplementations of Ca, vitamins are needed to explore the further studies to avoid gum hyperplasia. Females are more susceptible to this problem hence endocrine studies are essential for further evaluation. Moreover, newer AEDs are to be fully screened for chronic studies.

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