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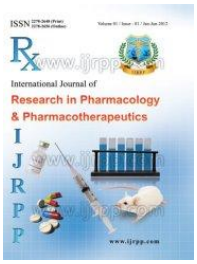

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Research Article ***Open Access***

Therapeutic drug monitoring of phenytoin needs vigilance: An individualized PD response is variable

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ABSTRACT

Therapeutic drug monitoring of Phenytoin is carried out to ensure effective and safe levels. Some of the factors complicating Phenytoin dosing include a narrow therapeutic window, high degree of protein binding, and non-linear pharmacokinetics. However, serum drug levels should only be taken when there is a clear indication to guide patient management. Scenarios where monitoring levels may be clinically useful include 1; establish an individual therapeutic concentration 2, aiding in diagnosis of clinical toxicity 3, assisting patient compliance and 4, guiding dosage adjustment in patients likely to have greater pharmacokinetic variability. The therapeutic range of Phenytoin is 10-20 microgram/ml. The study was carried out at a tertiary care where Neurology dept is well developed. This was a retrospective study a total number of samples of 2239 were included. Patients were taking only on monotherapy, Phenytoin. Samples were of trough levels and were taking the same dosage regimen. Patients were in the age range from 10 yrs. to 70 yrs. comprised 52.38% males and 46.62% females. 75% samples were in therapeutic range.

Keywords: Phenytoin, Therapeutic drug monitoring, Out patients department, Enzyme Multiplied Immuno Technique, Glucose 6 phosphodehydrogenase.

INTRODUCTION

Epilepsy is the second most common neurological disorder after stroke (1). It affects about 50 million people in the world (2). In India approximately 5.5 million people are suffering from epilepsy (3). Epilepsy a chronic disorder characterized by recurrent seizures are convulsions (4). The chronicity of the disease, the drug therapy and associated psychosocial impact significantly affects the quality of life of epileptic patients (5). The factors influencing the quality of life include seizure severity, unpredictability, stigma, fear, anxiety and cognitive and psychiatric problems (6).

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 and ensure compliance, prevent drug interaction and minimize toxicity (5). Antiepileptic drugs are ideal candidates for therapeutic drug monitoring (TDM) because they have narrow therapeutic index and clinical responses correlate better with serum concentration of the drug than with prescribed daily dose regimen (7). Monitoring of serum levels of Phenytoin plays an important role in the management of epilepsy (8). Therapeutic drug monitoring refers to the

measurement of drug concentration in biological fluids with the purpose of optimizing a patient's drug therapy, while minimizing its risk for side effects or toxicity [(7)]. 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[(9)].

MATERIAL & METHODS

The aim and objective of the study was to determine that pharmacodynamic response of Phenytoin was variable. The estimation was carried over by simple and accurate method of EMIT. Levels were checked by calibration cure along with the three levels of external quality control. A retrospective observational study was conducted in the department of Clinical Pharmacology SKIMS, Soura J&K India, and 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 2003 to Dec 2012, were assessed. Only those patients were included who were on usual therapeutic doses of Phenytoin for 3-4 months, taking same dose with equal intervals. 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 Analyzer. 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- 40 microgram were used to validate the levels. Linearity was evaluated over this analytical range and lypho check controls of all the three levels (low, medium, high) were used to validate the method to quantitate the levels accurately. The levels were total estimated by this EMIT system.

RESULTS

2239 levels of blood samples were tested, out of them 1173 (52.38%) samples of Phenytoin were from males and 46.62% (1066) were from females. Maximum patients were received in 2012 (325) and the minimum patients were in the year 2003 (100). There was a progressive increase of patients on yearly basis because of the awareness of physicians in particular and the patients in general (Table.1).

Table-1: Year wise distribution of patients

Year	No. of patients	Male	Female
2003	100	30	70
2004	120	70	50
2005	160	85	75
2006	210	100	110
2007	199	80	119
2008	230	140	90
2009	285	133	152
2010	300	180	120
2011	310	195	115
2012	325	160	165
Total	**2239**	**1173 (52.38%)**	**1066 (47.62%)**

Samples were drawn from patients in the age range of 10-70 yrs. Maximum levels comprised of 763 (34.12%) in the age range of 21-30. The least levels were detected in the age group of 61-70 (3.04%). The samples in this group were only 68 (Table.2).

Table-2: Age distribution

Age (yrs.)	No.	Percentage
10-20	356	15.90
21-30	764	34.12
31-40	570	25.46
41-50	250	11.16
51-60	231	10.32
61-70	68	3.04
Total	**2239**	**100**

In this study 1675 (75.0%) were in therapeutic range 10-20 microgram/ml. Sub-therapeutic range <20µg/ml was in 360 (16.10%) and toxic level >20µg/ml estimated in 199 (8.90%) (Table 3)

Table 3: Distribution of levels

Level	Concentration (µg/ml)	Total	Percentage
Therapeutic	10-20	1675	75.00
Sub-therapeutic	<20	360	16.10
Toxic	>20	199	8.90

Out of 199 samples of toxic levels 36-40 µg/ml were detected in 65 (32.66%). 40 patients were without toxicities, where levels above 20µg/ml, were detected. This behavior of the drug confirmed that the levels are altogether variable so was important to employ the therapeutic drug monitoring programme in individualizing the dosage in such patients. The trend of therapeutic drug monitoring from 2003 to 2012 is increasing as it is maximum in 2012 and only 100 in 2003. The toxic concentration above 20µg/ml shows variable toxicity profile. Adverse reaction profile of above 15µg to 20µg was observed in 20 patients. They developed drowsiness. The toxic level picture of 199 patients was - level 21-25µg/ml was observed in 60 (30.15%) and only 40 patients developed nystagmus. Level 26-30µg/ml was quantified in 39 patients (19.60%). Only 19 developed nystagmus and rest developed ataxia. Level 31-35µg/ml was quantified in 35 patients (17.59%), ataxia developed in 30 and rest developed slurred speech (Table. 4).

Table 4: Distribution of toxic levels

Concentration (µg/ml)	Total	Percentage
15-20	20	10.05
21-25	60	30.15
26-30	39	19.60
31-35	35	17.59
36-40	65	32.66

Maximum patients 65 (32.60%) were admitted in hospital whose levels were from 36 microgram to 40µg/ml. They developed severe confusion, lethargy. Only five persons were in coma. The drug was withdrawn in all the 65 patients the concentration was assumed to be in zero order kinetics till the level regressed to below 20 micrograms. It was suggested that the TDM programme is not to quantitate the levels but it is essential element to stop the drug in those patients whose level is above the therapeutic range like Phenytoin.

CONCLUSION

Phenytoin is still a drug of choice to be prescribed to control the tonic clonic seizures and maximum numbers of patients are being maintained on

monotherapy. Studies show that the use of total Phenytoin level is adequate in most clinical cases (10). Various antiepileptic drugs are prescribed to control the epilepsy and Phenytoin is an important armamentarium to control general tonic clonic as a monotherapy. This study included the routine samples and the information required to allow interpretation of the results and it should include the time of the last dose, dosage regimen and there was an appropriate indication for drug monitoring (11). In this study the trough levels were used as it is preferable to draw the Phenytoin level just prior to the next dose (trough level) or at least eight hours after the last dose (12). For rational prescribing requires an understanding of the factors affecting its pharmacokinetics and keeping in view its narrow therapeutic index, Michaelis-Menten kinetics and its close relationship between serum concentration and clinical effect (13). Two of the enzymes that catalyze the metabolism of Phenytoin (CYP 2C9 and CYP 2C19) shows pharmacogenetic variation. Individuals with lower catalytic activity (poor metabolicers) are at risk for developing supra-therapeutic concentrations (14). Phenytoin demonstrates non-linear pharmacokinetics even within the therapeutic range. The enzyme system involved in Phenytoin metabolism gradually becomes saturated, resulting in a decrease in the rate of elimination of Phenytoin as the dose is increased (15). The approximate half-life of lithium is 24 hrs in adults, 36 hrs in elderly and 40-50 hrs in patients with impaired renal failure (16). Thus arises need to be vigilant in prescribing the drug in these sub-sets of patients. Important consideration is how the body handles lithium are three fold: water balance, sodium balance and renal function (17). In Kashmir the temperature does not remains high as compared to other tropical regions so the concentration throughout the year is almost uniform. In this study, there were 8.90% comprising of almost 199 samples could be from slow metabolizers and pharmacodynmic response in determining CNS effects were altogether variable too. The metabolite of Phenytoin is pharmacologically inert. There is a need to use newer methods to estimate the drug levels of Phenytoin on a routine basis so as to validate the levels individually to lessen the adverse drug reactions and maximize the efficacy of such drugs having narrow therapeutic index and the cause of levels having inconclusive interpretation were sorted out. One of the major causes is that Phenytoin is metabolized by CYP 450 so there is a need to estimate the metabolite which but phenotypically it is important to estimate the parent as well as its metabolite to be estimated on HPLC which estimates both the compounds on the same run. Thus there is a warning that the level above therapeutic range means to be vigilant in those drugs which have a narrow therapeutic range. EMIT system is not a specific method to estimate the drug like Phenytoin because it is metabolized by CYP 450 although its metabolite is not pharmacologically active but this metabolite may interfere in the process of estimation in EMIT system. Most of the patients having same dose for prophylactic have different serum concentrations and their frequency of epileptic episodes also differ so there is a need to optimize newer techniques to find out PK/PD models to validate the Pharmacogenetic techniques in TDM.

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