

VARIABILITY OF PK INTERACTION BETWEEN PHENYTOIN AND CARBAMAZEPINE IN TERTIARY CARE: A RETROSPECTIVE STUDY OF 25 PATIENTS.

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Drug interaction can occur whenever a patient is administered two or more drugs simultaneously. In this study drug interaction occurs when drug is withdrawn from the patients. The outcome of drug interaction can be beneficial or harmful. A vigilance is needed while prescribing the drugs. In some circumstances the drug interactions are complicated and problematic. No single antiepileptic drug (AED) is appropriate in all clinical situations. Pharmacokinetics has an important role to play in the clinical practice of antiepileptic drug therapy, as it is important in estimating individualized drug dosage regimens necessary to achieve serum concentration without causing unacceptable toxicity. In this study 25 patients on phenytoin and carbamazepine were taking concomitantly with equal doses in equal intervals of time. This was a retrospective study shows that phenytoin level increases significantly after withdrawing the carbamazepine. Therapeutic window of phenytoin is narrow, one has to be vigilant in maintain the concentration of phenytoin within therapeutic range. So dosage regimen is important and TDM is a vital programme which helps to keep the level within therapeutic objective.

Keywords: Phenytoin, Carbamazepine, PK, Polypharmacy.

INTRODUCTION

Phenytoin and Carbamazepine are the two vital drugs to control the epilepsy. Both these drugs are measured easily in the laboratory as a Therapeutic Drug Monitoring programme. A physician knows their drug-drug interaction but the extent of variability of these drugs makes their serum concentration to be measured necessarily after every three months. Once the Carbamazepine is switched off from the drug regimen, the concentration of phenytoin increases slowly with the passage of time as it takes one or two weeks. Data from World Health Organization [WHO] indicates that as many as 1 in 20 people may have an epileptic seizure during their life and that at least 1 in 20 people will have epilepsy (Shorvon, 2009). A single epileptic drug [AED] is appropriate in all clinical situations and epileptologists agrees that proper seizure diagnosis and classification is important in individualizing pharmacotherapy (Sander, 2004). Therapeutic decisions should be made on a variety of specific factors such as seizure types, onset of drug effect, presences of renal or hepatic diseases, possibility of drug disease interaction, possibility of pregnancy, the age of the patients, adherence to therapy issues and prior history of AED use. Many of the new drugs are approved only for adjunctive use; thus polypharmacy and drug interactions should also be considered (Tidwell and Swims, 2004). Although monotherapy remains the mainstay for the treatment of epilepsy, combination of antiepileptic drugs [AEDs] are used frequently in patients not responding to a single medication. AEDs may also be combined with drugs used to treat co morbid or associated conditions. When multiple drug therapy is used, there is possibility of clinically relevant drug interaction, which in patients with epilepsy is particularly common for a variety of reasons (Hachad *et al* 2002, Majkowski *et al* 2005). Pharmacokinetics is the quantitative description of what happens to a drug when it enters the body, and includes the process of drug absorption, distribution, metabolism and elimination [ADME] and how these processes effects the serum concentration obtained. Drug-drug interactions between phenytoin and Carbamazepine are well established but the withdrawal of Carbamazepine as inducers produces the phenytoin toxicity, so the phenytoin level increases after 2 weeks of time. So the optimization of dose regimen of phenytoin is an important step in the therapeutically monitored tools in the successful outcome of the therapy in the seizure or epilepsy control. Retrospective

study of 25 epileptic patients who were on the phenytoin and Carbamazepine taking equal doses for 2-3 years time. After the withdrawal of carbamazepine the level of phenytoin went up significantly, it needs vigilance in such situation. Instead of benefits for the patients harmful effects are stopped. TDM program is required to determine serum drug concentration and in turn the technique is vital to be optimized (Eadie, 2001). There is the need to find out the steady state or trough level to appreciate the relevance of the parameters in AED drug therapy (Fanglur, 2002). An awareness of AED clinical pharmacokinetics will thus aid the choice of an optimal dosage schedule for each patient (Gidal, 2001). The plasma concentrations in multiple doses have to be maintained at steady state when the absorption and elimination remains constant. All patients with chronic epilepsy can be expected to develop during their life time concomitant non-epilepsy related diseases that require additional drug therapy, increasing the potential for drug interactions and toxicity. Thus, it is desirable that the drugs do not cause interactions that can precipitate toxicity (Deckers, 2003). It is important to recognize that interactions are not with only one drug but it occurs when two drugs are given together they influence each other. In addition, another important concept is that drug interactions may occur not only when an inducer or inhibitor is added to a patient's medication regimen, but also when the inducing [i.e carbamazepine] or inhibiting [i.e valproate] agents is removed.

METHODOLOGY

The aim and objective of the study was to determine drug-drug interaction between carbamazepine and phenytoin. The study was carried out at SKIMS University, Srinagar, JK India, a tertiary care hospital where Neurology department is well established. It was a retrospective study on 25 patients. They were routinely received from OPD neurology and the trough level was taken for the serum drug concentration [SDC]. Almost equal male and female were included in this study. All the patients were on two drug regimen i.e carbamazepine and phenytoin. Patients were on equal doses with equal interval of time. Same sample was used to estimate carbamazepine and phenytoin level at first attempt. Second sample of phenytoin was taken at an interval of 2 weeks after withdrawal of carbamazepine. The data included in the study was of four years from Jan 2009 to Dec 2013. Only those patients were included who were on equal doses of carbamazepine and phenytoin with same brands. Patients were advised to withdraw carbamazepine and report after 2 weeks without taking carbamazepine with the consent of the neurologist of tertiary care hospital.

The same patients were received after interval of 2 weeks who were on both drugs. Serum carbamazepine and phenytoin was estimated by EMIT system using semi-automated analyzer. The EMIT [Enzyme Multiplied Immunoassay Technique] is a homogenous enzyme immunoassay. It is a versatile methodology desired to measure the concentration in microgram from the serum matrix. Serum was used for the estimation and the samples were drawn exactly at 12 hours after the last dose as the drug was taken twice a day. Calibrators for phenytoin were used from 2.5,5,10,20 and 40 $\mu\text{g/ml}$. with 3 controls. Carbamazepine calibrators 2,4,8, 12 and 20 $\mu\text{g/ml}$ each were used with 3 controls of lyphocheck. The EMIT technology is based on competition for the target analyte antibody binding sites. Analyte antibody competes with the drug in the enzyme reagents that is labeled with $G_6\text{PDH}$. Active enzyme $G_6\text{PDH}$ converts the co-enzyme [NAD] in the antibody reagent to NADH, resulting in a kinetic absorbance change that is measured on semi-automatic analyzer [ERBA].

RESULTS

25 patients were included in the study. Male female ratio was 12:13. Their age range was from 12 to 70 years. Weight and height of the studied patients were 23-65 kg and 155-172.5cm. The BMI of the included patients in the study ranges from 8.47-25.39. The mean of the BMI is 16.55 and the standard deviation is ± 4.75415 [figure 1].

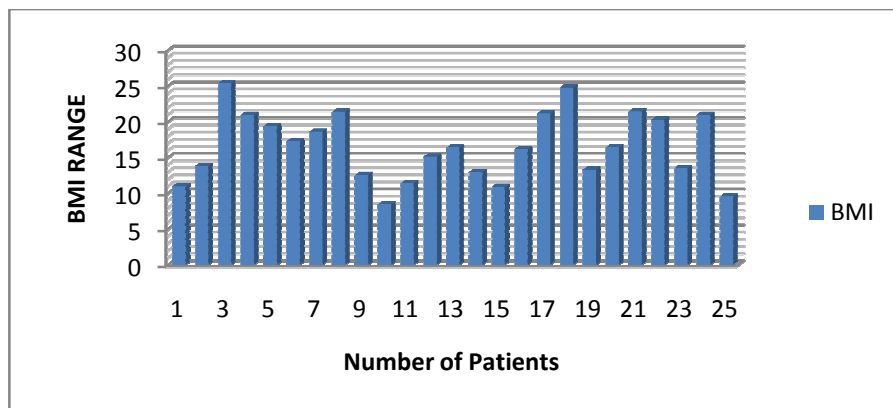


Figure 1: BMI Value of Patients

Phenytoin level with carbamazepine is given in the figure 2. Phenytoin level estimated by EMIT was 8.7µg/ml [minimum] and 25.3 µg/ml [maximum] with mean value 15.024 µg/ml and Standard deviation ±3.78 µg/ml.

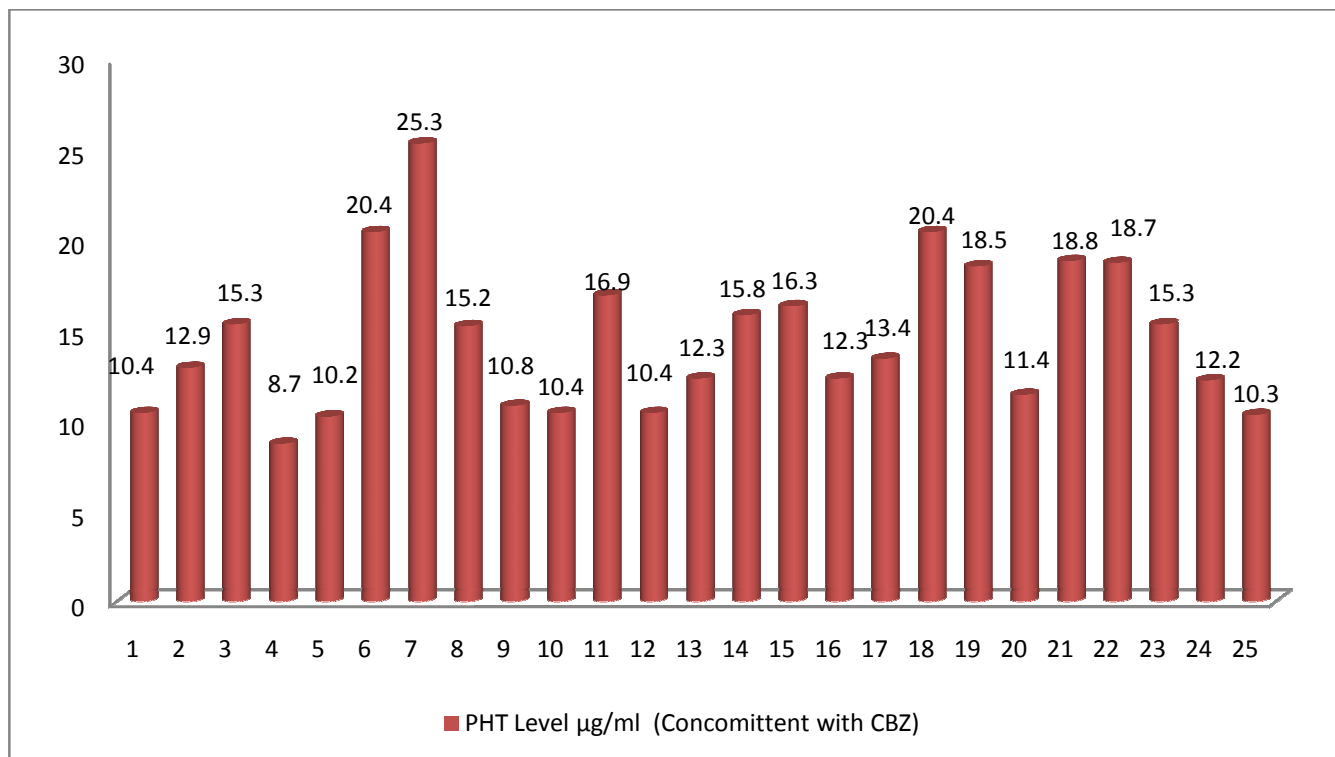


Figure 2: Phenytoin Levels In Patients Concomittent With CBZ

Carbamazepine level estimated was 4.4 µg/ml [minimum] and 12.0 µg/ml [maximum] with mean value 7.96 µg/ml and Standard deviation ±2.43 µg/ml figure 3. Both the levels were estimated from same sample of serum.

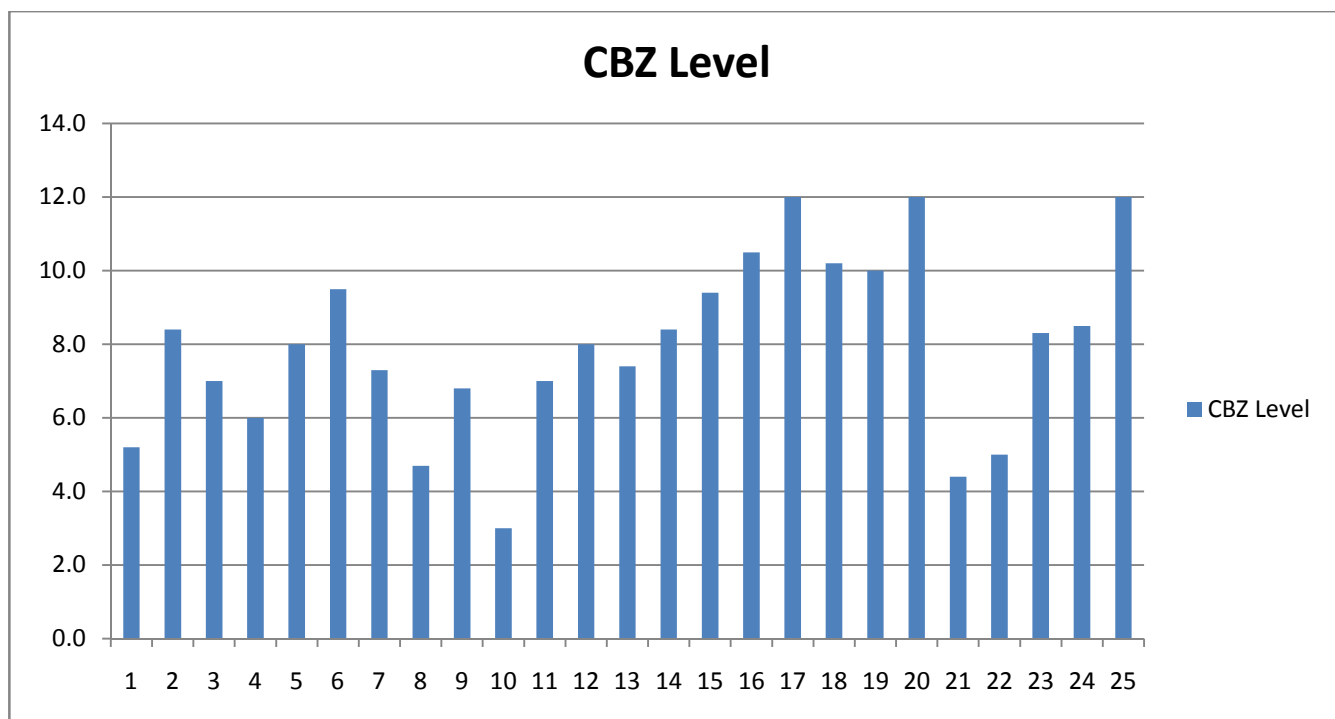


Figure 3: Carbamazepine Levels In Patients

Phenytoin level after withdrawal of carbamazepine is specified in the figure 4. It represent the minimum value of 12.7µg/ml and maximum value of 27.4 µg/ml with mean value 17.88 µg/ml and Standard deviation ±3.75 µg/ml.

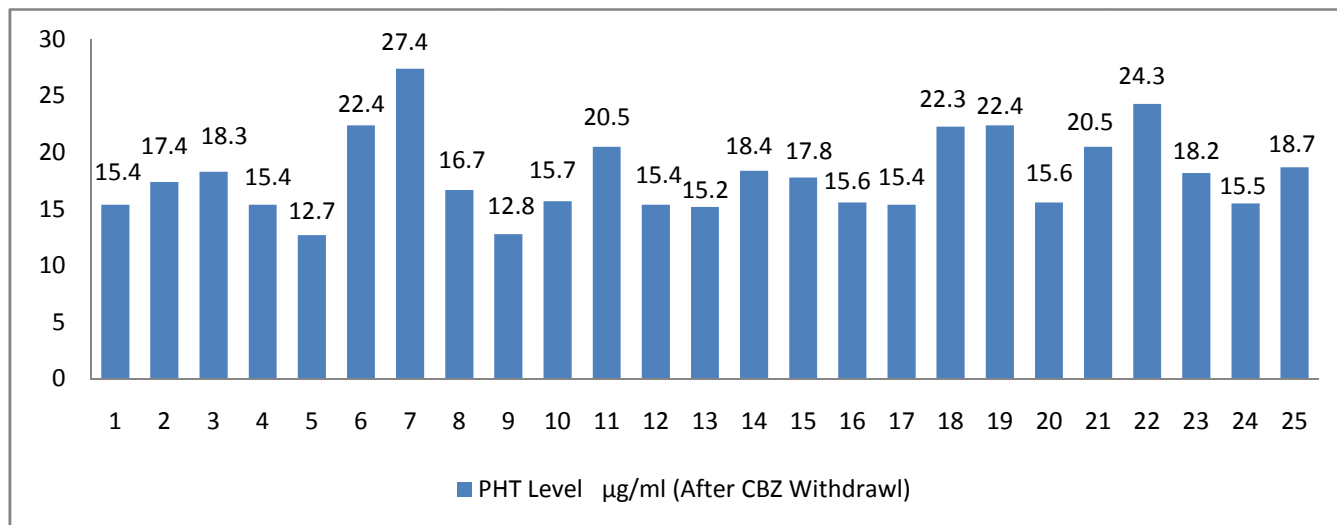


Figure 4: Phenytoin Level After Withdrawal Of Carbamazepine

The figure 5 presents the difference between the increases of Phenytoin concentration in the serum of the patients under observation.

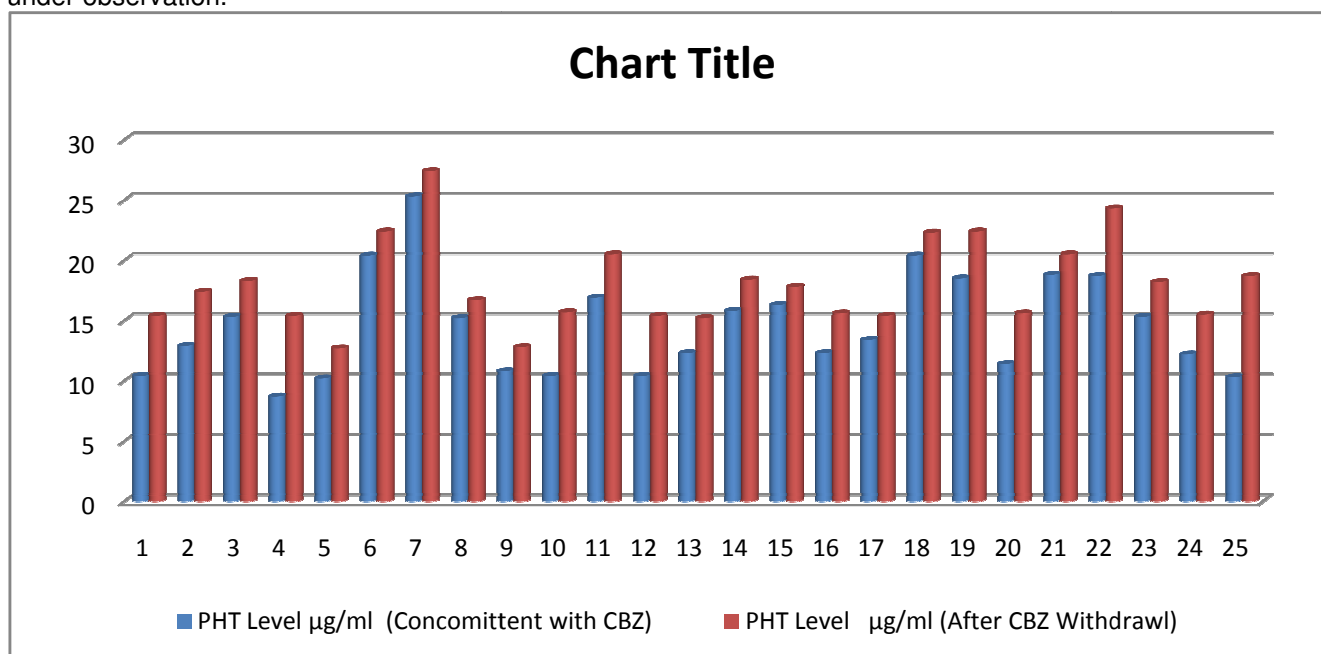


Figure 5: Differences Between Concomittent And Withdrawl Phenytoin Level

The %age increase in the level of Phenytoin before and after the withdrawal of CBZ. The obtainable data suggested the mean value of percentage increase 20.40 $\mu\text{g/ml}$ with standard deviation of $\pm 9.93 \mu\text{g/ml}$.

DISCUSSION

Phenytoin serum concentration should be measured in most patients because epilepsy is an epidemic disease state, patients do not experience seizures on the continuous basis. Thus during the doses interaction it is difficult to predict if the patient is responding to drug therapy or not. Control of seizures is gradually obtained at total concentration above 10 $\mu\text{g/ml}$, while toxic effect like nystagmus develop at total concentration around 20 $\mu\text{g/ml}$ (Brunton *et al* 2011). Removal of enzyme inducing drug will result in reinduction and if the dose is not adjusted, serum concentration of many metabolites concomittent drugs may increase. Loss of enzyme induction can occur with days to several weeks following discontinuation of the inducing drug. It will take about five half lives for the previously induced medication to reach to

new steady state level, these reinduction interactions may have insidious onset. The present study indicates the t-test significance of 0.0074 when the comparison of two levels of phenytoin is made that is with carbamazepine and after withdrawal of carbamazepine. The level needs to be detected by HPLC method. Our method EMIT is not sensitive. Carbamazepine levels with its metabolites 10,11-epoxide is to be estimated. Its metabolites are also anti-epileptic. The clear picture of drug-drug interaction comes once the metabolic ratio of carbamazepine and its metabolites is estimated.

CONCLUSION

Clinically important AED interactions are frequently observed in clinical practice, and often they can be anticipated by knowledge of the underlying mechanism. Whenever possible, these interactions should be prevented by avoiding the unnecessary use of poly-pharmacy, and by selecting co medications which are less likely to interact. If the use of potentially interacting drugs cannot be avoided, adverse clinical consequences may be minimized, as appropriate, by individualized dose adjustments guided by careful monitoring of clinical response and measurement of serum drug concentrations. There is a need to estimate the phenytoin and carbamazepine levels through HPLC method. That can resolve the metabolite status of the patients. Particularly metabolite of carbamazepine, 10-11 epoxide which is pharmacologically active and can give us the real picture of drug-drug interaction in future studies.

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