



Therapeutic Drug Monitoring of Carbamazepine and Phenytoin: Monotherapy versus Combination Therapy

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ABSTRACT

Objectives: To study serum concentration of carbamazepine and phenytoin, when given singly and together.

Method: This is a non-interventional, cross-sectional, analytical study done in a tertiary care hospital. Consenting epileptics on stable antiepileptic regime for at least past 2 weeks and taking carbamazepine 200mg BD (group I) or phenytoin 100mg BD (group II) or carbamazepine (200)+phenytoin (100)mg BD (group III) were included. There were 20 patients in each group. Blood samples were collected 12 hours after the last dose and serum was analyzed for carbamazepine, phenytoin concentrations using HPLC method and data was compared using unpaired t-test.

Results: Mean serum carbamazepine concentration in group I was (7.37±3.67)mcg/ml and in group III (5.65±2.37) mcg /ml (p=0.09). Mean serum phenytoin in group II was (15.16±6.48) mcg /ml and in group III (12.66±5.5) mcg/ml (p=0.2). When used singly carbamazepine showed 30% subtherapeutic and 20 % toxic concentrations. Whereas in combination group the plasma concentrations of carbamazepine were found to be therapeutic, subtherapeutic and toxic ranges in 55%, 40% and 5% patients, respectively. In phenytoin monotherapy group the concentrations were subtherapeutic in 15%, therapeutic in 65% and in toxic range in 20% patients, whilst in combination group the concentrations obtained were 50%, 40 and 10% respectively.

Conclusion: Co-administration of carbamazepine and phenytoin do not affect the serum concentrations of either group significantly. It's possible that Indian population has different therapeutic range of antiepileptic drugs from that given in standard literature. But larger study needs to be done to confirm the results.

Keywords: Therapeutic drug monitoring, HPLC, Phenytoin, Carbamazepine.

INTRODUCTION

Epilepsy is one of the most common serious chronic neurological disorders. It is a disorder of brain

which is characterized by an enduring predisposition to generate seizures and by its neurobiological, cognitive, psychological, and social consequences. International League Against

Epilepsy (ILAE; 1993) defines epilepsy as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. [Epilepsy_Indian perspective] Antiepileptic medication is the mainstay of treatment of most patients of epilepsy (those without a reversible cause).^[1]

Therapy for an epileptic patient is almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with antiepileptic medications or surgery, and addressing a variety of psychological and social issues.^[2]

Anti-epileptic medication is the mainstay of treatment of most patients of epilepsy (those without a reversible cause). Often, antiepileptic treatment will be long-term and can have major effects on quality of life. Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against various seizure types. However, there is considerable overlap between many antiepileptic drugs, such that choice of therapy is often determined more by specific needs of the patient, especially the patient's assessment of side-effects.^{[3][4]}

Moreover, monotherapy with antiepileptic drugs often fails, requiring polytherapy regimens in an attempt to achieve better seizure control and fewer side effects. Most side effects are mild and dose-related and can often be avoided or minimized by the use of the smallest effective dose. Some examples include mood changes, drowsiness, or unsteadiness in gait. Some antiepileptic medications have idiosyncratic side effects that cannot be predicted by dose. Some examples include drug rashes, liver toxicity (hepatitis), or bone marrow suppression.^{[5][6]}

Unfortunately, it is incontestable that these clinical practices of poly- and add-on therapies frequently lead to complex and unpredictable pharmacokinetic and pharmacodynamic interactions, with possible clinical consequences in terms of toxicity or even therapeutic inefficacy.^{[7][8]} All these short comings

coupled to fact that the pharmacotherapy with antiepileptic drugs is usually prophylactic and lifelong, and the relationship between dose and drug concentrations is unpredictable, the effectiveness of antiepileptic drugs therapy frequently requires therapeutic drug monitoring procedures. Based on the measurement of drug concentrations in plasma, therapeutic drug monitoring is therefore largely employed with the purpose of avoiding the risks of acute and chronic toxicity^{[9][10]} and to optimize the patient's clinical outcome. Indeed, antiepileptic drugs can be used more safely if the clinician is aware of the concentrations the patient is exposed to and adjusts the dose as necessary.^{[11][12]}

Carbamazepine (CBZ) and phenytoin (PHT) are first line antiepileptic drugs. Despite the availability of newer antiepileptic drugs, these first line drugs are commonly used because of their efficacy and low cost. However both the drugs have narrow therapeutic index. Hence, monitoring of their serum concentration is essential in most cases. An overlap between phenytoin and carbamazepine toxicity has also been reported. Both are enzyme inducers and thus affect each other's serum concentrations.^[13]

METHODS

This was an observational, cross-sectional, analytical, single center study done in 6 months (June 2016 to November 2016) duration. The study protocol was approved by Institutional Ethics committee. It was conducted in tertiary care hospital in Pune, Maharashtra. Diagnosed epileptics, coming to Neurology OPD in the Medicine Department, who were on regular stable antiepileptic regime for at least past 2 weeks and taking either carbamazepine 200mg BD or phenytoin 100mg BD or carbamazepine + phenytoin (200+100) mg BD, were included. Twenty patients from each category were selected for the study. To minimize batch inconsistency, it was ensured that patients were taking drugs belonging to same batch. Drug details were as follow- Tablet carbamazepine (Ciron drugs & pharmaceuticals Pvt. Ltd., batch 601013, Mfg. date 01/2016 and Exp. date 12/2017) and Tablet

phenytoin (Unicare India Ltd., batch PST03-35, Mfg. date 12/2015 and Exp. date 11/2017). Patients with other concurrent diseases that are known to interact with the above mentioned drugs, patients receiving any drug other than folic acid and calcium supplements were excluded. The study protocol was explained in detail to the patients in their own language. Patients willing to participate in the study were asked to fill and sign an informed consent form. They were asked to maintain a daily drug diary for 2 weeks mentioning time of drug administration and adverse drug effect, if any, to ensure complete adherence to the therapy. Basic information like demographic data, detailed medical history, drug details including batch number, manufacturing date, expiry date, manufacturing company were recorded on a study specific Case Record Form. Patients were examined for adverse effects, if any. Fasting blood samples were collected in the morning 12 hours after the last night dose. Blood was allowed to clot at room temperature. Serum thus obtained on centrifugation was stored at -20°C. Chromatographic analysis was carried out using an HPLC system (Hitachi Elite La Chrom). ClinRep® complete kit for antiepileptics in serum was used. All instrumental parts were automatically controlled by Agilent Chem Station software (Agilent Technologies). Temperature was set to 55°C. Flow rate was set at 1.0 mL/min. The injection volume was 10µL and the wavelength of 205nm was selected for the detection of both compounds as per instructions in the kit manual.

Method of HPLC

EXTRACTION

100µl sample (calibrator, control, patient)	150µl Precipitant P (contains internal standard)
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- ↓ Mix for 30 sec using cyclomixer.
- ↓ Centrifuge for 5 min at 10000 x g

DILUTION

50µl Supernatant	50µl Diluting Solution D
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HPLC analysis

Inject 10µl of diluted supernatant into HPLC system and read at 205 nm

Inject 10µl of diluted supernatant into HPLC system and read at 205 nm

Serum concentration was calculated using internal standard method. Reference Therapeutic serum concentration of phenytoin was taken as 10-20mcg/ml and that of carbamazepine 5-12mcg/ml. [4]

Analysis of variance

(ANOVA) was used to comparedemographic characteristics among the three groups of patients. Unpaired t-test was applied to compare serum concentrations of each drug (carbamazepine and phenytoin) in both mono and combination groups. Linear regressionand correlation coefficient were used to test the associations between serum concentrations and seizure frequency.

Table no. 1: Demographic data of patients in all three groups (mean ± SD)

	CBZ monotherapy	CBZ+PHT combitherapy	PHT monotherapy
n	20	20	20
M/F ratio	12/8	9/11	13/7
Age (Yrs)	35.1±12.89	35.6±13.23	34.2±14.18
Weight (Kg)	64.6±15.16	60.1±13.24	63.85±12.38
Dose (mg/Kg/d)	CBZ	6.98±1.87	6.42±2.39
	PHT	-	3.5±0.86
			3.26±0.72

RESULTS

A total of 60 patients were included in study during 6 months data collection period. Out of which 56.66% were male population and 43.33% were female population. The clinical details of the patients like age, gender distribution, daily dose of carbamazepine and phenytoin, are shown in Table 1. All three groups were compared using ANOVA test and unpaired t-test. The Baseline characteristics - Age, gender, weight were comparable in all the Groups (p>0.05).

Table no. 2: Serum levels of carbamazepine and phenytoin in all three groups (mean ± SD)

	CBZ (mcg/ml)	PHT (mcg/ml)
CBZ monotherapy	7.37±3.67	-
CBZ+PHT combitherapy	5.65±2.37	12.66±5.5
PHT monotherapy	-	15.16±6.48
P Value	0.08#	0.195#

#Means were not significantly different by analysis of unpaired t-test.

Table no. 3 Concentration ranges of carbamazepine and phenytoin in all three groups(N and %)

	CBZ		PHT	
	Monothera py	Combithera py	Monotherap y	Combithera y
Subtherapeutic	6 (30%)	8 (40%)	3 (15%)	8 (40%)
Therapeutic	10(50%)	11 (55%)	13 (65%)	10 (50%)
Toxic	4 (20%)	1(5%)	4 (20%)	2(10%)

As depicted in table no. 2, mean serum carbamazepine concentration in monotherapy group was 7.37 ± 3.67 mcg/ml and in combination therapy group, it was found to be 5.65 ± 2.37 mcg/ml ($p=0.08$).

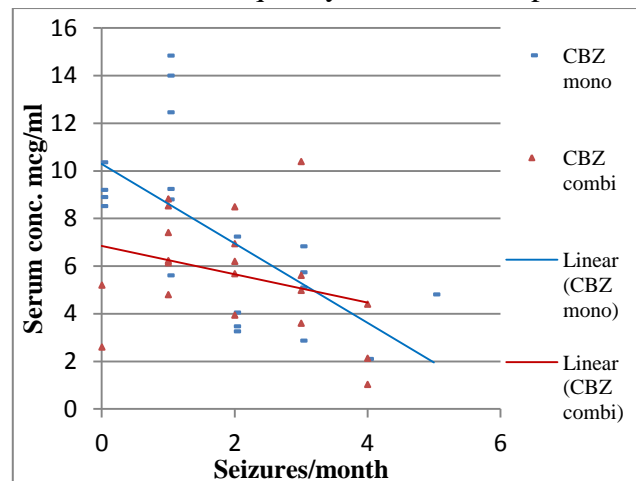
Mean serum phenytoin in monotherapy group was 15.16 ± 6.48 mcg/ml and in combination therapy group, it was around 12.66 ± 5.5 mcg/ml ($p=0.195$).It was observed that, although the patients receiving carbamazepine + phenytoin tended to have lower carbamazepine and phenytoin levels than the other two groups of patients, the differences did not reach statistical significance.

As shown in Table no.3, when used singly carbamazepine produced therapeutic concentration in 50% patients while concentration was subtherapeutic in 30% and toxic in 20 % subjects.

Table no. 4: Adverse effects seen in all three groups.
(N and %)

	CBZ monothera py	CBZ+PHT combithera py	PHT monotherapy
Nausea/Vomiting	2 (10%)	3 (15%)	3 (15%)
Gingival hypertrophy	-	3 (15%)	4 (60%)
Tremors	-	2 (10%)	1 (5%)
Ataxia	1 (5%)	-	1 (5%)
Nystagmus	-	-	1 (5%)
Vertigo	1 (5%)	-	

Figure no. 1: Linear correlations between serum conc. and seizure frequency for carbamazepine.



CBZ monotherapy: $y = -1.666x + 10.285$; $R^2 = 0.4091$
 CBZ combitherapy: $y = -0.5943x + 6.8447$; $R^2 = 0.0985$

In combination group 55% patients showed therapeutic, 40% showed subtherapeutic and 5% showed toxic concentrations. In phenytoin monotherapy group the serum concentrations were therapeutic in 65%, subtherapeutic in 15% and toxic in 20%. Whilstphenytoin when given in combination with carbamazepine resulted in plasma concentration that was therapeutic in 50%, subtherapeutic in 40 % patients and 10%patients' values were in toxicrange.

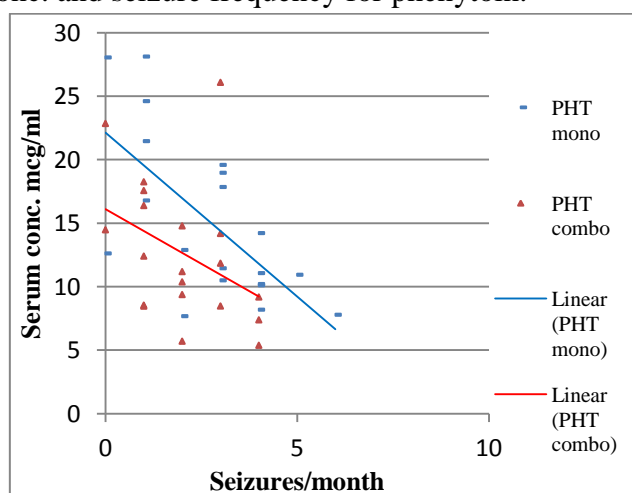
Regarding idiosyncratic side effects, out of 40 patients on phenytoin, four had coarse facial appearance. Other side effects of phenytoin were as follows: six had nausea and vomiting, twelve had gingival hypertrophy, four had drowsiness and one had ataxia. While, out of 40 patients taking carbamazepine; five had nausea and vomiting, three had gingival hypertrophy, two had tremors, and one had ataxia.

Two patients taking phenytoin alone showed tremors as adverse effect even though their serum phenytoin concentration was in therapeutic range. Two patients taking carbamazepine alone complained of ataxia and vertigo had toxic levels of serum carbamazepine. In combination group, two patients showed signs of tremors had therapeutic levels of carbamazepine and phenytoin. One patient in the same group exhibited nystagmus had his

phenytoin in therapeutic range whereas his carbamazepine was in toxic range.

In phenytoin alone group, out of thirteen patients twelve had convulsions and two had adverse drug reaction, despite therapeutic concentration. In the same group three out of four patients had convulsions despite toxic concentrations. In carbamazepine alone group, out of ten patients seven had convulsions despite therapeutic concentration. In the same group three out of four patients had convulsions despite toxic concentrations. Whereas in combination group, all six patients with therapeutic concentration gave history of convulsions. Two out of them had adverse drug reaction. So, it can be said that most of the patients who showed some evidence of side effects due to the antiepileptic drugs had normal serum levels of the antiepileptic drugs. Thus, it's possible that Indian population has different therapeutic range of antiepileptic drugs from that given in standard literature. But larger study needs to be done to confirm the results.

Figure no. 2: Linear correlations between serum conc. and seizure frequency for phenytoin.



PHT monotherapy: $y = -2.5777x + 22.125$; $R^2 = 0.4344$

PHT combitherapy: $y = -1.7253x + 16.111$; $R^2 = 0.1552$

The study showed only 8 patients (13.33%) became seizure-free during the study period while 52 patients (86.67%) still experienced convulsions. There is a negative correlation between seizure frequency and serum concentrations for both the drugs, as depicted in Figure no. 1 and Figure no. 2.

Number of seizures reduced as serum level increased for both the drugs irrespective of given singly or in combination.

DISCUSSION

The statistical comparison of carbamazepine and phenytoin when given singly and in combination in a given population is determined mainly by the homogeneity of that population. In the present study, there were no significant differences in age, body weight, male/female ratio or sampling time among the three groups of patients.

In the present study, the time of sampling was standardized at -12 h after the last carbamazepine and phenytoin dose, and patients had BD dosing schedule. Therefore, time interval between last dose and sample collection in carbamazepine and phenytoin levels probably did not contribute to any great extent to the observed variation. Patients with hepatic or renal disease were not included in this study to avoid the interference of drug protein binding and metabolism of the drug by these diseases.

Though majority of the patients were within the therapeutic range, all the patients did not show the same clinical outcome. Some patients can achieve therapeutic benefit at serum drug concentrations outside the reference ranges or at higher than routine doses.

Numerous studies demonstrated that carbamazepine metabolism is highly inducible by phenytoin and vice versa. Johannessen and Strandjord, observed that patients receiving carbamazepine and phenytoin are required in larger doses when given together. Because carbamazepine concentration and carbamazepine level/dose ratio were lower than those in patients receiving carbamazepine alone. Wang et al., in their study found that clearance of carbamazepine was increased by phenytoin comedication.^{[14] [15]} Hua L and Delgado, 1995; had also studied interactions between phenytoin and carbamazepine. They observed that, patients receiving polytherapy were treated with larger carbamazepine doses than were patients treated with carbamazepine alone. Because the doses of

carbamazepine in these patients were based on clinical response rather than serum carbamazepine level, this result may reflect the fact that these patients required a relatively larger carbamazepine dose than patients receiving carbamazepine monotherapy to maintain an adequate therapeutic effect.^[16]

Chapron et al., in their study suggested- when epileptic patients receiving monotherapy require a second antiepileptic drug, and especially if comedication of phenytoin and carbamazepine is required, their larger doses may be needed to compensate for the increased elimination caused by the drug interactions. Chapron et al., on the other hand, enhance that in the process of tapering and discontinuing comedications, more frequent serum concentration monitoring is recommended during the ensuing deinducing phase to avoid sudden change in drug concentration and their toxicity.^[17]

The main limitation of this study is that it is based on a small sample size of only 60 epileptic patients from one single tertiary care hospital. The study included those patients who were prescribed phenytoin and carbamazepine for treating epilepsy only. Thus, a study of a bigger magnitude would prove useful in the future.

CONCLUSION

We tried to systematically investigate the effect of carbamazepine and phenytoin comedication on their concentrations in the Indian population. Our results suggest that despite concentration being in sub-therapeutic or toxic range, subjects may not necessarily have toxicity of failure. Therefore, we recommend that, though it is necessary to determine the serum levels of carbamazepine and phenytoin for dose adjustment and in avoidance of clinical problems owing to interactions of drug combinations, Dose titration should be done by correlating the serum drug levels with both; clinical outcome and the safety profile.

ACKNOWLEDGEMENT

We would like to thank the patients who participated in the study.

FUNDING: There was no funding source.

CONFLICT OF INTEREST

No conflict of interest.

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