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A prospective study to assess the association between genotype, phenotype and *Prakriti* in individuals on phenytoin monotherapy

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ABSTRACT

Background: Genetic polymorphisms in drug metabolizing enzymes (DMEs) impart distinct drug metabolizing capacity and a unique phenotype to an individual. Phenytoin has large inter-individual variability in metabolism due to polymorphisms in CYP2C9 and CYP2C19. As per Ayurveda, *Prakriti* imparts a unique phenotype to an individual.
Objective: To assess whether *Prakriti* can substitute phenotyping [therapeutic drug monitoring (TDM)] and genotyping in individualizing therapy with phenytoin in epilepsy patients.
Methods and materials: This was a cross-sectional study conducted over a period of three years. *Prakriti* was assessed using standardized and validated software. Polymorphisms in CYP2C9 and CYP2C19 were assessed using Polymerase Chain Reaction (PCR)-Restriction fragment length polymorphism (PCR-RFLP). Plasma concentrations of phenytoin (phenotype) were determined using reverse phase-high performance liquid chromatography (RF-HPLC).
Results: Total 351 patients were enrolled for the study. *Kapha vata* (KV) (39%) was the predominantly observed *Prakriti* followed by *vata kapha* (VK) (20.8%) and *vata pitta* (VP) (8.83%) among the patients. The CYP2C9 and CYP2C19 genotype distributions were in accordance with Hardy–Weinberg equilibrium. There was no association between *Prakriti* and genotypes and *Prakriti* and phenotype ($p > 0.05$ each). Patients with CYP2C9 *1/*3 genotype were thrice more likely to have toxic plasma concentrations of phenytoin as compared to those with wild-type genotype (*1/*1) (Adjusted odds ratio – 3.36; 95% C.I. 1.61, 7.01). However, no such association was observed between polymorphisms of CYP2C19 and phenotype.
Conclusions: We did not find any association between *Prakriti* and either phenotype or genotypes suggesting that *Prakriti* assessment would be of limited utility in individualizing phenytoin therapy in epilepsy patients.

1. Introduction

Genetic polymorphisms in drug metabolizing enzymes (DMEs) impart high, moderate or low drug metabolizing capacity and a unique phenotype to an individual [1]. Phenytoin is an antiepileptic drug having large inter-individual variability in metabolism because of polymorphisms in its DMEs CYP2C9 and CYP2C19 which account for approximately 90% and 10% of its metabolism respectively [2,3]. It has a narrow therapeutic window (10–20 μg/ml) and thus plasma concentrations below 10 μg/ml could produce sub-optimal therapeutic effect and levels above 20 μg/ml may result in its toxicity [2]. Mutant alleles of these DMEs can result in poor metabolism of phenytoin, increased plasma drug concentrations and thus toxicity. Although, Therapeutic Drug Monitoring (TDM) remains the standard of care for routine patient management, studies have identified genotyping as a potential tool in individualizing the therapy with phenytoin [4–6].

Ayurveda, the traditional Indian system of medicine describes that individuals may exhibit one of the seven types of *Prakriti* (constitution) according to the predominance of the three different *doshas* (humors): *Vata*, *Pitta* and *Kapha* [7]. Some efforts at linking

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Prakriti with either phenotype and genotype have been attempted [8,9]. On the other hand, there has been a paradigm shift in the focus of the modern medicine from "generalized" to "personalized" with the objective of maximizing benefit and minimizing harms [5]. Therefore, we postulated that identification of *Prakriti* could guide dosing with phenytoin and individualize the therapy in patients with epilepsy. The present study was thus carried out to evaluate association between CYP2C9 and CYP2C19 genotypes, the consequential phenotype as assessed by plasma concentrations and *Prakriti* in Indian patients with epilepsy who were on phenytoin monotherapy.

2. Methods

2.1. Ethics

The study was initiated after obtaining Institutional Ethics Committee approval and written informed consent from participants. The study is registered with the Clinical Trial Registry of India (CTRI/2011/06/0011782).

2.2. Study duration and design

This was a proof of concept, cross sectional study conducted between February 2011 and June 2014 in prospective patients.

2.3. Key eligibility criteria

Male and female patients over the age of 18 years who were receiving phenytoin monotherapy for any indication and who attended the TDM Outdoor Patient Department (OPD) were recruited. Patients with hepatic/renal dysfunction, psychiatric disorders or patients on drugs which induce or inhibit CYP2C9/19 were excluded.

2.4. Study methodology

2.4.1. Assessment of Prakriti

Prakriti assessment was performed by a qualified Ayurvedic physician (BAMS graduate with two years of experience) using AyuSoft software and by traditional method involving patient's detailed interview and physical examination as per Ayurvedic texts [9]. However, eventually, the *Prakriti* assessed using AyuSoft was considered for the final analysis because AyuSoft is a standardized, validated and more comprehensive tool for *Prakriti* assessment. Moreover, a good agreement has been observed between AyuSoft and traditional methods in various studies [10]. The software calculated *Prakriti* with built- in weightage configuration. It had 85 questions pertaining to the anatomy, physiology, and psychology with weightage ranging from 1 to 10 to ascertain the *dosha* (Expression of each trait in a given *Prakriti*) Traits corresponding to physical or anatomical characteristics were assigned higher weightage whereas those pertaining to physiological had lesser weightage. The resultant output from the software displayed an individual's final *Prakriti* as the combination of predominant *doshas (dvandvaja)* and the *Prakriti* was presented as *vata pitta* (VP), *pitta kapha* (PK), *kapha vata* (KV), *kapha pitta* (KP), *vata kapha* (VK), *pitta vata* (PV) and *sama* (combination of *vata, pitta* and *kapha*) [11–13]. The scores of $\geq$ 50% and 25%–35% were considered as cut-offs to classify each individual into primary and secondary *doshas*, respectively. The software classified patients' *Prakriti* as *dvandvaja* on the premise that individuals with *ekdoshaja* are very rare and every person may have some traits corresponding to each of the three major *doshas* [9,13].

2.4.2. Determination of the genotype

5 ml of venous blood was collected in 100 μl of 10% disodium EDTA for genotyping. Genotyping was done using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. DNA was extracted from whole blood using the phenol chloroform method and PCR was carried out for CYP2C9 *2, CYP2C9 *3, CYP2C19 *2 and CYP2C19 *3 alleles. All the digested samples were run on 3% agarose gel electrophoresis and visualized under UV detector using ethidium bromide [14,15]. Allele frequencies were measured and Hardy–Weinberg equilibrium was assessed [16].

2.4.3. Measurement of plasma concentration of phenytoin (phenotype)

Plasma concentrations of phenytoin were assessed as the phenotype consequential to genotype and *Prakriti*. 5 ml of blood was collected in heparinized bulb for assessment of plasma concentration of phenytoin. Steady state concentrations (trough levels) were assessed using Reverse Phase-High Performance Liquid Chromatography (RP-HPLC) using the method of Joshi et al. [17]. In brief, the drug was extracted from plasma by liquid–liquid extraction using chloroform and acetonitrile. Separation was achieved with a C18 column and detection was done using a UV detector at wavelength 255 nm. Dose adjusted plasma concentration of phenytoin was also derived. Odds of developing plasma phenytoin concentrations above > 20 μg/ml (toxicity is more likely to occur above this concentration) was assessed between different genotypes and *Prakriti* [2].

2.5. Statistical analysis

2.5.1. Sample size calculation

As this was a proof of concept study, no formal sample size calculation was done.

2.5.2. Detailed analysis

Categorical data was presented as actual numbers and proportions and continuous data as mean ± S.D./median [range]. Normality of the continuous data was checked using Kolmogorov-Smirnov test. Categorical variables were analyzed using Chi-square test/Fischer's exact test. Continuous variables between two groups were compared using Mann–Whitney U test/unpaired t test (depending upon the distribution). Logistic regression models were developed for predicting phenytoin toxicity based on plasma concentration. Univariate analysis was performed using age, gender, phenytoin dose, genotypes and *Prakriti* as independent variables and plasma concentration (above >20 μg/ml vs. $\leq$ 20 μg/ml) as dependent variable. The independent variables which had significance of <0.20 in univariate analysis were assessed further in multivariate analysis adjusting with the other variables. All analyses were done at 5% significance using SPSS 20.0 (Chicago, IL) for Windows.

3. Results

3.1. Demographic details

Total 351 patients were enrolled for the study. The demographic characteristics of the patients are as described in Table 1. Both CYP2C9 and CYP2C19 genotype distributions were in accordance with Hardy–Weinberg equilibrium. *Prakriti* assessed by AyuSoft was in agreement with the physician's assessment in ~70% of the patients.

Table 1
Demographic characteristics.

Sr. No.	Characteristics	N = 351
1.	Age (years), Median [range]	35 [18–77]
2.	Gender, n (%)	Males – 249 (71%) Females – 102 (29%)
3.	Phenytoin dose (mg/kg) Median [range]	4.80 [1.10–10.50]
4.	Plasma concentration (μg/ml) Median [range]	8.39 [BDL, 76.80]
5.	Dose adjusted plasma concentration (μg/ml/mg/kg)	1.99 [BDL, 35.60]
6.	*Prakriti*, n (%)	KV – 137 (39%) KP – 82 (23.4%) VK – 73 (20.8%) VP – 31 (8.8%) PV – 15 (4.3%) PK – 13 (3.7%)
7.	CYP2C9 genotype, n (%)	*1/*1–261 (74.4%) *1/*2–39 (11.1%) *1/*3–49 (14%) *2/*3–01 *3/*3–01
8.	CYP2C19 genotype, n (%)	*1/*1–134 (38.2%) *1/*2–174 (49.6%) *2/*2–42 (12%) *3/*3–1
9.	Plasma phenytoin concentrations, n (%)	>20 μg/ml – 56 (16%) <20 μg/ml – 295 (84%)

BDL = Below detection levels, KV – *kapaha vata*, KP – *kapha pitta*, VK – *vata kapha*, VP – *vata pitta*, PV – *pitta vata*, PK – *pitta kapha*.

3.2. Univariate analysis

3.2.1. Association between genotype and phenotype

Patients with CYP2C9 *1/*3 genotype were thrice more likely to have toxic plasma concentrations of phenytoin as compared to those with wild-type genotype (Crude OR = 3.54; 95% C.I. 1.78, 7.07). Patients with *3/*3 genotype were found to have twice the odds of having toxic plasma concentrations of phenytoin as compared to those with wild-type genotype. However, the statistical significance was not achieved (Crude OR-2.22; 95% C.I. 0.22, 22.01). In addition, on combining the mutant genotypes, we observed a crude odds ratio of 2.16 (95% C.I-1.18, 3.94, p = 0.02) suggesting that patients who had mutant genotypes for CYP2C9 (*1/*2, *1/*3, *2/*2 and *3/*3 combined) were twice more likely to develop toxic plasma concentrations of phenytoin as compared to those having wild type genotype (*1/*1). However, we did not find any such association with the mutant alleles of CYP2C19 (p = 0.33) (Table 2).

3.2.2. Association between Prakriti and phenotype and Prakriti and genotype

We did not find any association between *Prakriti* and phenotype (p = 0.81) and *Prakriti* and genotypes (p = 0.66 and 0.99 for CYP2C9 and 19, respectively) (Tables 2 and 3).

3.3. Multivariate logistic regression analysis

We found only CYP2C9 genotype to be the significant predictor for achieving toxic plasma concentration of phenytoin (p = 0.01). This model depicted that the patients with CYP2C9 (*1/*3) genotype were thrice more likely to develop toxic plasma concentrations of phenytoin as compared to those having CYP2C9 (*1/*1) genotype (Adjusted odds ratio-3.36; 95% C.I. = 1.61, 7.01). None of the other variables could predict the development of toxic plasma concentration of phenytoin ($p > 0.05$).

The following equation was formulated using binary logistic regression model:

Toxic plasma concentrations of phenytoin (No/Yes) = −2.47 + 0 (CYP2C9 *1/*1) + 0.89 (CYP2C9 *1/*2) + 3.36 (CYP2C9 *1/*3).

However, this model could predict only 13% of variability in developing toxic plasma concentration of phenytoin.

4. Discussion

We observed a significant association between CYP2C9 genotype and phenotype. However, no similar association could be observed between *Prakriti* and phenotype as well as *Prakriti* and genotype indicating that only CYP2C9 genotype could significantly predict the probability of developing phenytoin toxicity.

As per Ayurveda, the constitution of an individual (*Prakriti*) is based on differences in physical, physiological and psychological characteristics and is independent of racial, ethnic or geographical considerations. *Prakriti* also forms an important basis for treatment in Ayurveda. As per this science, *Prakriti* can be correlated with drug metabolism as follows: *kapha*, *vata* and *pitta* each imparting slow, intermediate and fast metabolizing capacity respectively to an individual [9]. Similarly, the science of pharmacogenomics classifies individuals as slow, fast or intermediate metabolizers to individualize the treatment [18]. However, lack of association between *Prakriti* and CYP2C19 genotype observed in our study is different from that seen by Ghodke et al. who assessed the correlation between polymorphisms of CYP2C19 and *Prakriti* in 132 healthy individuals using an identical genotyping methodology. They found

Table 2
Association between CYP2C9 and CYP2C19 genotypes and *Prakriti* with phenotype.

		Toxic plasma concentrations of phenytoin (N = 351)		Odds ratio and 95% C.I.	p value
		Yes	No		
CYP2C9 genotype	*1/*1	34	227	–	**0.002***
	*1/*2	5	34	0.98 [0.36,2.68]	
	*1/*3	17	32	3.54 [1.78,7.07]	
	*3/*3	0	2	2.22[0.22,22.01]	
CYP2C19 genotype	*1/*1	17	117	–	0.33
	*1/*2	34	140	1.67[0.89,3.14]	
	*2/*2	5	37	0.93[0.32, 2.69]	
	*3/*3	0	1	3.44[0.30,40.00]	
Prakriti	KV	24	113	–	0.81
	KP	14	68	0.96[0.46,2.00]	
	PK	2	11	0.86[0.18,4.11]	
	PV	1	14	0.34[0.04, 2.68]	
	VK	9	64	0.66 [0.29,1.51]	
	VP	6	25	1.13 [0.42, 3.05]	

*$p < 0.05$.

Table 3
Association between *Prakriti* and genotypes.

		KV	KP	PK	PV	VK	VP	p value
CYP2C9 genotype (N = 351)	*1/*1	97	62	10	12	59	21	0.66
	*1/*2	13	10	1	3	8	4	
	*1/*3	25	10	2	0	6	6	
	*3/*3	2	0	0	0	0	0	
CYP2C19 genotype (N = 351)	*1/*1	53	28	4	6	30	13	0.99
	*1/*2	66	44	7	7	35	15	
	*2/*2	17	10	2	2	8	3	
	*3/*3	1	0	0	0	0	0	

*$p < 0.05$.

that extensive metabolizer (EM) genotype of CYP2C19 (*1/*1) was predominantly distributed in the individuals having *pitta Prakriti* (91%) while; poor metabolizer (PM) genotype (*2/*2, *2/*3, *3/*3) was majorly (31%) distributed in *kapha Prakriti* individuals. On the contrary, we observed both extensive (23%) and poor metabolizer genotypes (39%) predominantly distributed in *kapha pradhan* individuals. This could be explained by the fact that Ghodke et al. chose a healthy population where all *Prakritis* are expected to be uniformly distributed whereas we chose an epileptic population on phenytoin monotherapy [8]. As per *Prakriti* classification, majority of our patients were slow metabolizers (kapha *Prakriti*) followed by intermediate metabolizers (*vata Prakriti*). However, as per genotype, we had more number of extensive metabolizers (*1/*1) as compared to intermediate and slow metabolizers (*1/*2, *1/*3, *2/*2, *2/*3 & *3/*3) and this discordance could explain the lack of association between *Prakriti* and both the genotypes. In addition, as CYP2C19 contributes only 10% towards the metabolism of phenytoin, the lack of association between *Prakriti* and genotype distribution could be justified [2,3].

We could not observe any association between *Prakriti* and phenotype. This is in contrast with Bhalerao et al. who observed that variation in platelet aggregation and response to anti-platelet drugs differs between the individuals belonging to different *Prakriti* in healthy participants [9]. However, lack of such association in our study could be because of the involvement of different study population or the subjective nature of *Prakriti* assessment [9].

We found mutant CYP2C9 *1/*3 genotype to be the significant predictor of toxic levels of phenytoin in plasma. Thakkar et al. in the same population, also found that individuals with CYP2C9 *1/*3 polymorphism had an increased risk of toxic concentrations of phenytoin as compared to those having wild type alleles. [Adjusted OR-4.80; 95% C.I.-1.89, 12.17] [19].

We observed no association between polymorphisms of CYP2C19 and an individual phenotype which corroborates with Kerb et al. [4].

Our CYP2C9 allele distribution correlates with Thakkar et al. [19]. However, our CYP2C19 allele distribution did not match with Kesavan et al. or Kerb et al. who assessed them in South Indian patients and Turkish volunteers respectively [4,20].

5. Limitations of the study

Although a case control or a prospective cohort study would have been better-suited study designs, ours was a cross-sectional study. Secondly, we did not exclude patients whose *Prakriti* assessment did not match by both AyuSoft and clinical assessment. However, the impact of this would be very limited because AyuSoft is considered as an objective, robust and comprehensive tool (although not a "gold standard" – there is no accepted objective method described as yet, and the most reliable method is considered clinical judgment which has inherent subjective biases) for *Prakriti* assessment. Moreover, an acceptable agreement has been observed in *Prakriti* assessment between AyuSoft and other questionnaire-based tools as well as the traditional methods [10]. Thirdly, we did not use the recommendations proposed by Bhalerao and Patwardhan for reporting studies on *Prakriti*-based observations [13] as our study was conceived, implemented and transcribed before this publication.

6. Conclusion and future directions

Although we found that patients with CYP2C9 mutations were more likely to have toxic plasma concentrations of phenytoin as compared to those with wild-type genotype, we did not find any association between *Prakriti* and either phenotype or genotypes suggesting that *Prakriti* assessment would be of limited utility in individualizing phenytoin therapy in epilepsy patients. However, a more rigorously tested *Prakriti* assessment tool needs to be developed that will have better specificity, sensitivity and reproducibility than the one we used. Additionally, a prospective study with the same objectives in a larger number of patients is needed. Likewise, the present concept can be studied further in a holistic manner by incorporating other parameters (i.e. *Dhātu Sāratva*) along with the *Prakriti* assessment. Notwithstanding to only genomics, an opportunity can be explored to assess the association between various *Prakriti* subtypes and other biological variables influencing a target phenotype. Eventually, this may help in establishing the concept of "personalized medicine" in the Ayurveda in its true sense.

Source of support

Nil.

Conflict of interest

None declared.

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